HJOG
An Obstetrics and Gynecology International Journal

Review Article

Management of women with cytological glandular lesions of uterine cervix: new literature data

Nikolaou Marinos[1], Papadimitriou Ifigenia[2], Michail George[2], Androutsopoulos George[2], Adonakis George[2], Relakis Konstantinos[3], Decavalas George[2]

1Department of Obstetrics-Gynecology, General Hospital of Agios Nikolaos, Crete, Greece
[2]Department of Obstetrics-Gynecology, University of Patras, Medical School, Patras, Greece
[3]Department of Obstetrics-Gynecology, University of Crete, Medical School, Herakleio, Crete, Greece

Corresponding Author: Marinos Nikolaou, MD Dept. of Obstetrics & Gynecology General Hospital of Agios Nikolaos Lasithi, Crete 72100 Greece
Tel: +302841343578/ +306972897699 - **Fax:** +302841100839 - **Email:** nikolaoumarinos@yahoo.gr

Submitted 20/3/2014, Accepted 27/3/2014

Abstract

The incidence of cervical glandular lesions has significantly increased during the past two decades especially among young women. This rise in registered cases is predominantly attributed to this entity's rising prevalence as well as recent advances in cytology. Atypical glandular cells (AGC) identified by secondary cervical screening (Papanicolaou) might actually harbor significant underlying pathology. The natural history and progression of cervical glandular lesions comparing to that of their squamous counterparts is less well-understood. High-risk HPV's (HPV16, 18 and 45) have been identified in glandular lesions with high frequency. Cytology and colposcopy illustrate poor sensitivity in the diagnosis of glandular lesions.

Diagnostic excisional procedures are of paramount importance in the management of high-grade glandular lesions. Treatment options are conservative surgery, predominantly conization or definitive therapy (mainly hysterectomy). Cervical conization appears to give satisfactory results especially in young women with high grade glandular lesions who strongly wish to preserve their fertility potential. However, adequate counseling should be provided to patients before therapeutic decisions. Long-term follow-up is mandatory for women treated for glandular lesions to detect any possible residual disease and early signs of recurrence.

Key words: cervical glandular lesions, diagnostic investigations, treatment options.

Introduction

Cervical cancer (CxCa) is presented to be the 3rd most common type of cancer among women worldwide, with 500,000 new cases and 273,000 deaths annually.[1] CxCa originates predominantly from the squamous cervical epithelium (85-90%), the remainder emanating either purely from the columnar endocervical epithelium, or representing mixed types (10-15%). Despite the reduction in squamous CxCa over the last few decades in the western world, mainly with the implementation of Pap screening, cervical glandular adenocarcinoma is globally on the rise, especially among young women. In particular, while cases of glandular cervical cancer were making up only 5% to the summation of cervical cancers in the 50's, they have now risen up to 25% during the last decades.[2-3]

The "new", revised Bethesda cytological classification system (TBS 2001), defines four different entities of glandular lesions of the cervix

Table 1: The Bethesda 2001 system for reporting cervical cytology results (TBC 2001)

Atypical Glandular cells (AGC) • endocervical • endometrial • not otherwise specified (NOS)
Atypical glandular cells, favor neoplastia (AGC Favor Neoplasia) • endometrial • endocervical • not otherwise specified (NOS)
Endocervical adenocarcinoma in situ (AIS)
Endocervical adenocarcinoma

uteri (Table 1)[4]. In this way the older "AGUS" (atypical glandular cells of undetermined significance) terminology is abolished and is replaced with the term "AGC", to avoid confusion with the squamous counterpart (ASCUS). Furthermore, two distinct categories of atypical glandular cells are determined with the use of special morphological criteria, correlated with the risk of underlying malignancy (FN-favor neoplasia, and AIS-adenocarcinoma in situ), while cytologists and pathologists are encouraged to comment on the possible source of the atypical cells, as their origin differentiates their management (endocervical, endometrial, unspecified).

Epidemiological Data

A. Atypical Glandular Cells (AGC)

The rate of detection of atypical glandular cells (AGC) in the cervicovaginal smear (Pap Test) is very low varying from 0.4% to 0.8% depending on the study[5]. The presence of AGC significantly increases the possibility of high grade squamous or glandular dysplasia (HSIL or AIS) in 9-38% of the cases, and the risk of invasive cervical or endometrial cancer in 3-17% of the cases.[6-9]

The origin of the atypical glandular cells and the related risk of malignancy, as defined with the implementation of special cytologic diagnostic criteria, represent major prognostic factors. Studies with large series of patients confirm that AGC-FN is linked to higher risk of malignancy than that of AGC-NOS (atypical glandular cells-not otherwise specified). The prevalence of precancer (dysplasia) or cancer in women with AGC-NOS is 9-41%, while in AGC-FN it might reach 96%[9].

Accordingly, a significant percentage of AGC (70%) corresponds to benign lesions [10]. Atypical glandular cells might be related with endometrial polyps, intrauterine contraceptive devices (IUD), or chronic endometritis – especially if the cells are described as of endometrial origin. Additionally, detection of atypical glandular cells in Pap smears has been described in some rare

cases of cervical endometriosis as well as in cases of "tuboendometrial metaplasia" – TEM in women who have previously undergone conization.

The latter (TEM) was initially described in 1988 as a benign glandular cytological change that could potentially be misinterpreted as cGIN (cervical Glandular Intraepithelial Neoplasia). It was identified as a distinct entity in 1991[11], as a reactive cellular change of the glandular cells of the regenerating endocervix post conization. "TEM" should be considered as a likely diagnosis in cases of smears with atypical or metaplastic glandular cells in women post conization, so that a contemplated unnecessary re-operation on the cervix is avoided.

Other benign situations that present as glandular changes and should be distinguished from true glandular dysplasia are: HPV infection, endocervicitis, active glandular atypia related to irradiation or thermal effect, congenital squamocolumnar junction (CTZ – in this case the "atypical" cells exhibit acanthotic characteristics) as well as hormonal effects (tamoxifen, diethylstilbestrol). These changes could additionally be attributed to "Arias-Stella reaction", appearing as atypical glandular cells in the course of pregnancy (decidual reaction).

Widespread use of combined oral contraceptive pills, genital herpes, (HSV), poor hygiene, multiparity, early sexual debut in combination with increased number of sexual partners and obesity are additional documented risk factors predisposing towards the development of glandular cervical changes. On the contrary, some studies suggest a possible protective role for endometrial devices (IUD).[12]

B. Adenocarcinoma in situ (AIS)

AIS originates from the glandular endothelium of the endocervix and is recognized as precursor lesion of infiltrating adenocarcinoma. The median age at presentation ranges between 35-39 y.o., and the time span needed for its development is between 5-13 years.[13] Factors impeding the diagnosis of AIS are the multifocal localization of the lesions, cytology's poor performance in terms of sensitivity and specificity (50% to 72-80% in co-existent lesions) as well as colposcopy's limitations in terms of diagnostic sensitivity and specificity[14]. AIS's relative frequency, while compared with high-grade squamous counterparts (CIN2/3) is quite low, while it frequently co-exists with them (47.3%)[15]. However, during the last decades a significant rise of cases with AIS has been documented, especially among young women, predominantly in the Western World[12]. This trend is attributed mainly to modern pathologists' and cytologists' improved competence in the recognition of glandular lesions, to the abilities of liquid-based cytology (LBC), and to the increased exposure of young women to HR- HPV's (High-Risk-HPV's) (HPV16, 18 & 45), in 96% of cases.[12,16]

C. Microinvasive cervical adenocarcinoma

Microinvasive cervical adenocarcinoma still remains a controversial clinical entity. It is defined as invasion of the cervical stroma to a depth < 3 mm. with overall length < 7mm. (FIGO stage IA1)[17]. Simple hysterectomy rather than radical hysterectomy remains the practiced treatment of choice for women with micro-invasive cervical adenocarcinoma. Radical hysterectomy with simultaneous pelvic and para-aortic lymphadenectomy remains the practiced treatment of choice for women with microinvasive cervical adenocarcinoma. However, recent studies illustrate excellent survival rates equivalent to those of the squamous microinvasive counterpart with more conservative surgical approach (conization), mainly among women who desire to preserve their fertility [18-20].

D. Cervical Adecocarcinoma

As stated, cervical adecocarcinoma's prevalence is lower compared to it's squamous infiltrative counterpart, 24.9% and 69.3% respectively[21]. However, increasing trends are documented globally among young women (<40 y.o.), with significant geographical fluctuations[3]. This rise is

attributed predominantly to two factors: a) the increased exposure to HR-HPV's, and b) the poor - in general - performance of cytology in correctly characterizing glandular lesions, in a manner that precursor lesions are not identified until the tumor develops to reach an infiltrative stage[22].
An increased prevalence (as high as 85-90%[16]) of HR-HPV's (HPV16, 18, 45) has been documented in cervical adecocarcinoma's. Consequently, preventive anti-HPV vaccination is anticipated to induce a significant reduction in the prevalence of the disease in the future. Modified radical hysterectomy remains the treatment of choice for cervical adenocarcinoma. However, prognosis and survival of patients is poorer compared to the infiltrative squamous counterpart because of the increased probability of pelvic lymphatic metastases[23].

HPV- related glandular cervical lesions

According to recent studies, HR-HPV's (18, 16, 31 and 45) have been identified approximately in 38% of the entirety cervical columnar lesions[9,10]. However, HPV positiveness in synchronous high-grade squamous and glandular lesions (adenocarcinoma) reaches 93%, while in AIS and in AGC it is 71% and 29% respectively[9,10,24].
In cervical adenocarcinoma the rate of HPV detection varies around 60.5%, with HR genotypes isolated in 92% of positive cases[25]. In particular, HPV16 is documented in 30-55% of cases, while HPV18 is detected in 40-60% of women with glandular lesions, conferring an elevated risk for development of cervical adenocarcinoma[9,10,12,13]. HPV45 and HPV31 account for the remainder 7% up to 9% of cases[13].
In a global perspective, the detection of HR-HPV is associated with a 81-fold increased risk for cervical adenocarcinoma development. HPV genotypes' prevalence illustrates significant geographic fluctuation among regions; in Eastern Asia for example, HPV18 is more frequent than HPV16[12].

The role of cytology

The sensitivity of conventional cytology in the detection of glandular lesions varies, overall it is rather low (45% - 76%)[22]. Liquid-based cytology (LBC) provides smears of superior quality, yielding improved sensitivity, specificity, reproducibility and stronger correlation with the final histological diagnosis. In LBC, detection rate for glandular lesions ranges from 72% to 87.1%.[22,26] LBC however is not without limitations and drawbacks, being unable to detect inaccessible cellular abnormalities that lie deep in the endocervical canal. Furthermore, even if some lesions are indeed detected, difficulties might arise in their identification and classification, given that the morphologic criteria of atypical glandular cells are poorly defined.
In a recent study it was illustrated that the detection rate of "pure" glandular high-grade lesions (HcGIN, AIS) was higher compared to mixed type lesions with squamous counterpart (AIS & coexistent HSIL); 75.2% and 47.3% respectively[15].
Finally, a recent meta-analysis of 12 studies which included 1374 women with endocervical adenocarcinoma corroborates that cervical mass screening predominantly decreased the risk of development of subsequent severe squamous SIL's rather than those of the columnar epithelium[27].

Combination of cytology and HPV-DNA test (co-testing)

According to recent studies, the addition of HPV-DNA test in the cytological work-up (co-testing) for women aged >30, contributes to earlier and safer detection of cervical precancer[16,28,29].
A substantial 63% of women with cervical adenocarcinomas diagnosed over a 5-year span though initially presented with negative (normal) cytology had a positive HPV-DNA test at enrollment[30]. Furthermore, among 72 glandular lesions (cGIN) that had been tested with HPV-DNA test, 70 (97.2%) proved HPV positive[31].
The above points emphasize the importance of incorporating HPV-DNA test in the initial workup

of atypical glandular cells. Especially in the management of women with AGC and negative colposcopy (without findings), an initial positive HPV-DNA test is an important tool in the discrimination of women in high risk of harboring insidious glandular lesions.

The role of colposcopy

Disappointingly, glandular cervical lesions do not posses straightforward, accurate, specific nor exclusive colposcopic criteria. Glandular lesions are often left unrecognized during meticulous colposcopy, since they can be hidden deep in the endocervical canal, or be located in the deeper part of a glandular 'crypt' under the metaplastic epithelium, while in 60% of cases colposcopy is not diagnostic (unsatisfactory - inadequate because of type 2 or 3 TZ). Therefore colposcopy's sensitivity in the recognition of glandular lesions or invasive disease is extremely low; while in several cases insidious lesions resemble and mimic normal findings. Inexperience among colposcopists in the recognition of atypical glandular patterns is expected and justified, but accentuates further the issues.

However colposcopy's negative predictive value still remains relatively high (80%), rendering the procedure essential in the management of women with atypical glandular cells. The following colposcopic criteria are considered as the most 'characteristic' or 'suggestive' of glandular changes: (1) Distinct acetowhite areas boasting large crypt openings following application of acetic acid in 85% of cases, (2) Whitish or reddish macula's in smooth, flat areas of columnar epithelium with swelling, bulging and fusion of the cylindric villi, coexisting amidst squamous lesions, (3) Raised papillary projections, within off-white areas, following application of acetic acid, and (4) Atypical blood vessels, without mosaicism or punctuation patterns.

Unsurprisingly, given the absence of exclusive colposcopic criteria for the recognition of glandular endocervical lesions, the differential diagnosis is difficult (Table 2)[32]. Additionally, the common co-existence of squamous lesions (LSIL/HSIL) in more than 50% of women with glandular lesions is usually more pronounced and therefore drives the diagnostic work-up[6-9,15]. However, according to the standard procedures, each women with a smear exhibiting ACG should undergo colposcopy, in order to unearth a possible lesion, visualize the ectocervix and the squamous epithelium (possible co-existant squamous CIN in 50% of cases) and finally assess the current anatomic situation (vagina-cervix-corpus uterii) aiming to select the most purposeful excisional treatment modality.

Table 2: Differential diagnosis of cervical glandular lesions

Cervical Polyps
Papillary cervicitis
Salpingo -endometrial metaplasia (TEM)
Microadenomatous hyperplasia
Tubular Conjunctions
Regenerating atypia (inflamation)
Mesonephric remnants
Arias -Stella reactions
HPV-infection
Micro -papillary hyperplasia
Endometrial hyperplasia - endometrioid epithelial type
Atypia following radiation therapy (RT)
Cervical endometriosis/ Cervical metaplasia

Topographical development of glandular lesions

Knowledge of the architectural pattern followed during the course of glandular lesions (cGIN/AIS) extension is an essential prerequisite for their optimal diagnosis and treatment. Thus, about

82% of all lesions are located within 1 cm from the SCJ (squamous columnar junction), while 65% are located within the TZ (Transformation Zone). In contrast, only 18% of the changes are interspersed amidst the length of the endocervical canal (skip lesions). Therefore, glandular lesions exhibit a multifocal growth pattern along the canal (islets of abnormal glandular tissue) ranging from 5 to 25mm (median 12mm)[33-35].

Management of Women with AGC

Cytology, punch cervical biopsies and endocervical sampling, solely or in combination may just raise the suspicion of a possible glandular cervical lesion, but are unable to give a definitive diagnosis. Keys to the concept of the necessary diagnostic work-up are the multifocal growth patterns of glandular disease and the age of patient, both reflecting on the frequency, type, and localization of the in-question lesions.

The Updated Consensus Guidelines for the management of women with abnormal cervical smears issued by the of American Society Colposcopy and Cervical Pathology (ASCCP, 2013)[36,37] are indeed very informative and essentially differentiate the initial diagnostic approach of women with cytological AGC depending on the documentation or not of atypical endometrial cells. For smears harboring atypical endometrial cells, initial evaluation commences with endocervical and endometrial sampling, with colposcopy following only if no endometrial pathology is identified. Endometrial sampling is warranted in the initial management of women 35 years of age and older, as there exists a substantial risk (5%) for severe endometrial pathology (hyperplasia or adenocarcinoma)[38].

In all the other subcategories, colposcopy with endocervical sampling (Pipelle/curettage) is the mainstay of the initial evaluation. This is supplemented by endometrial sampling, for women younger than 35 but with clinical indications suggesting increased risk for endometrial neoplasia (unexplained vaginal bleeding, conditions suggesting chronic anovulation)[36-37].

Due to the high prognostic value the cytological documentation of atypical glandular cervical cells confers for occult high grade glandular lesions (HG-cGIN/AIS) or cervical adenocarcinoma, further diagnostic evaluation is warranted. It should be emphasized that repeating the Pap smear has low sensitivity in detecting or verifying a possible high grade glandular lesion (cGIN/adenoCa), and is thus not encouraged.

Subsequent management of women with AGC-NOS cytology (Atypical Glandular Cells Not Otherwise Specified) among whom CIN 2+, AIS or CxCa is not identified, is the repetition of two consecutive co-testing's at 12 and 24 months. If both tests are negative, then a return for a repeat co-testing in 3 years time is recommended [36,37]. Otherwise, if any test is abnormal, colposcopy is warranted.

For women with AGC-NOS and documented squamous CIN2+ but without glandular neoplasia identified histologically during the initial diagnostic evaluation of AGC, further management is advised as per the 2012 Consensus Guidelines depending on the type of the lesion found[36,37].

Correspondingly, subsequent work-up for women with initial cytological high grade glandular abnormalities (Atypical Glandular Cells Favor Neoplasia/Adenocarcinoma in situ - AGC-FN/AIS), among whom invasive disease was not identified during the initial colposcopic evaluation, a diagnostic excisional procedure is warranted. This should be in the form of a wide and deep cone biopsy which encompasses the totality of the transformation zone and the most part of the endocervical canal, aiming at one intact specimen with interpretable margins. Endocervical curettage is also performed at that time [36,37,39].

Management of AGC or Cytologic AIS in Special Conditions

Atypical Glandular Cells in Pregnancy and the Puerperium

Reporting of atypical glandular cells represents an uncommon cytological diagnosis in pregnancy and early puerperium (until 6 weeks post partum). Difficulties in the accurate cytological diagnosis are caused by decidual cells, trophoblastic cells, Arias-Stella reaction and other pregnancy-related changes. However, the diagnosis of AGCs has significant clinical impact because of the high frequency of co-existent severe cervical pathology (HG-CIN, AIS-adenocarcinoma in situ, invasive squamous CaCx, HPV infection, molar pregnancy). Colposcopy is therefore warranted in this patient group but biopsies are justified only to exclude invasive disease[40]. Obviously endocervical curettage and endometrial biopsy are omitted.

Young women aged 21-24

Indeed this represents a very rare clinical scenario. Same management is suggested for the general population as per updated ASCCP (American Society for Colposcopy and Cervical Pathology) guidelines.

Benign Glandular Changes

For asymptomatic, premenopausal women with benign endometrial cells, endometrial stromal cells, or histiocytes, no further diagnostic evaluation is recommended. The literature illustrates an increased representation of atypical endometrial cells in liquid-based cytology samples, attributed perhaps to easier harvesting from deeper zones of the endocervical canal[19]. In those cases, the day of the menstrual cycle at sampling must be taken into account, as well as the use of hormones or oral contraceptive pills (COC), intrauterine devices (IUD) and clinical signs suggesting risk for endometrial pathology. However, in some instances, normal endometrial cells might be misinterpreted as atypical glandular cells by the cytologist.

For postmenopausal women with smears harboring benign endometrial cells, endometrial assessment is recommended. Adversely [Conversely], in hysterectomised women with smears harboring benign glandular cells, no further diagnostic evaluation is recommended[36,37].

Therapeutic Approach for Women with AGC

In the past, the only alternative therapeutic choice for high-grade glandular lesions (HGIN/AIS) was the performance of total hysterectomy[27-28]. Total hysterectomy still represents the treatment of choice for (a) women who have completed childbearing, (b) cases with involved conization margins, or positive for disease endocervical sampling obtained at the time of excision (in such cases, re-cone to exclude invasive disease is mandated), (c) cases with recurrence of disease after conservative management, (d) women who desire for definitive treatment, and (e) women with practical difficulties in regular post-operative follow-up.

Conservative surgical management (conization) represents an acceptable treatment option for young women with adenocarcinoma in situ (AIS) or microinvasive adenocarcinoma (FIGO stage IA1) who wish to preserve their fertility. According to the 2013 ASCCP guidelines,[36,37] when the cone excision margins are involved, or the endometrial sampling tissue obtained at the time of the excisional procedure is positive for disease (positive ECC-endocervical curettage), two alternative managements are acceptable: a)re-excision to obtain clear margins (preferred) and b) follow-up vigilance, which is an acceptable option, with reevaluation following in 6 months, using a combination of co-testing, colposcopy and endocervical sampling.

Otherwise, in clear excision margins, obtaining informed consent from the patients is essential, stressing on the necessity of long-term follow-up (>20 years) for timely detection of residual/recurrent disease[36,37]. Recent studies illustrate excellent survival rates for women with

AIS and microinvasive adenocarcinoma, similar of those of microinvasive squamous[18,19,20,41,-42,43,44,45,46]. However, compared to the microinvasive squamous counterpart, further randomized prospective studies are needed to reinforce the safety of conservative management[46].

Factors that determine the choice of therapeutic approach:

1. Age of women; as glandular lesions appear one decade later from their squamous counterparts. Among young women (36-40 years of age) an ectocervical localization of the disease is the usual growth pattern, with shallow depth of invasion and usually limited size of the affected area.
2. Desire for childbearing and concerns on fertility preservation.
3. Colposcopy findings
4. The status of conization margins.

Surgical techniques of cone excision/biopsy

The main purpose of cervical conization is the excision of the whole transformation zone (TZ) and the lower part of endocervical canal ideally in one intact surgical specimen avoiding fragmentation. For nulliparous young women (30-35 years of age) with desire for fertility and satisfactory colposcopy, the surgeon aims for a cylindrical-shaped cone with a 10-15 mm length, including the entirety of the TZ with an additional 10 mm above the squamocolumnar junction (SCJ).

For women >35 years of age who have completed childbearing with non-satisfactory colposcopy, a cylindrical cone is also recommended with a 20-25mm length and a 5mm depth of excision from the border of the endocervical canal in order to exclude invasive or residual disease lurking deep in a "crypt", even if the cone surgical margins are reassuring (negative for disease).

Cold knife (scalpel) conization (CKC) remains the treatment method of choice (Table 3)[47]. Stumdorf sutures should be positioned with caution; in a manner they do not hamper easy identification of emerging VaIN (Vaginal Intraepithelial Neoplasia) during postoperative follow-up. Alternative, laser conization is preferred over large loop excision of transformation zone (LLETZ) since margin status and interpretability are crucial for future treatment planning.

Complications of conservative treatment

Documentation of incomplete excision - residual disease in the first follow-up visit, or recurrence in subsequent follow-up visits after conization, represents possibly the ultimate negative prognostic factor, indicating failure of the conservative surgical management[48].

Table 3: Excisional methods of treatment

CKC *(Cold - Knife Con ization)* - scaplel
LLETZ / LEEP *(Large Loop Excis ion of the Transformation Zone /Loop Electrosurgical Excision al Procedure)*
LCB *(Laser Cone Biopsy)*
NETZ *(Needle Loop Excision of the Transformation Zone)*

The main short term surgical complication is primary cervical hemorrhage (quite frequently observed due to increased depth of conization), while in the following 8-10 days the combination

of sloughing of the eschar and post-operative infection of cervix might cause secondary cervical hemorrhage.

Among long-term post-operative complications: difficulties arise in colposcopic evaluation of TZ because of cervical stenosis (mainly after cold knife conization with >50% removal of endocervical cone) or due to intense use of electrocoagulation.

Adverse long-term obstetrical implications should be probably anticipated in all the aforementioned excisional treatment modalities which aim for a depth of excision over 10-15mm, namely: increased rates of neonatal prematurity and morbidity, birth of low birth-weight (LBW) babies, preterm premature rupture of membranes (PPROM), preterm birth and possible increased rates of cesarean sections (CS)[48,49,50].

The main factors responsible for post-operative residual or persistence disease are analyzed in Table 4.

Table 4: Risk factors for recurrent/residual disease

Positive specimen surgical margins for disease
Type of cone excision
Length of cone surgical specimen
Endocervical curettage - positive for disease
Detection of high -risk (HR - HPV) HPV types postoperative
Satellite glandular lesions in end ocervical canal
Women aged (>35 years)

1. Conization Margins (Table 5)

When the margins of the cone biopsy specimen are positive, residual disease is documented at rates varying from 13% to 75% (average 52.7%)[47,48,51,52]. In these cases, a further excisional procedure is required in order to obtain clear margins and thus exclude occult invasive disease.

When the margins are free of disease, occult residual disease ranges from 0% to 44% (average 19.3%)[47,48,51,52,53,54]. However, even in cases of negative margins, women remain at risk for residual or recurrent disease for a prolonged period. In a recent meta-analysis investigating the prognostic value of the surgical margins in conizations for AIS, 47.5% of women underwent a repeated excisional procedure in order to detect residual disease. [48]. Hence, when a conservative method is contemplated, vigilant long term follow up using cytology, HPV DNA testing and colposcopy is mandatory.

2. Endocervical curettage during conization

According to a recent study, the performance of endocervical curettage at the time of conization has better positive predictive value (100% vs. 47%, p<0,01), when compared to margin status, and improved negative predictive value (94% vs. 57%, p=0,01) over margin status in detecting residual disease among women who opt for conservative treatment in AIS[54,55]. However, previous studies have raised concerns regarding the predictive value and the safety of practicing endocervical curettage, as residual disease has been detected in 67%[56].

In the USA, both historically and also according to the updated ASCCP algorithms endocervical

sampling in the form of curettage is mandatory, as it is considered helpful in the work-up of glandular lesions, and it is thus never omitted; possibly for additional medico-legal issues. In contrast, some European authorities, for example

Detection of high-risk HPV genotypes (HR-HPV DNA test) contributes significantly in the detection of residual/recurrent disease during post-op follow-up[59,60]. A negative HR-HPV DNA test post-operatively designates patients with

Table 5: Correlation between selection of excisional treatment and positive surgical margins of the cone specimen

Method	Positive surgical margins
LLETZ	75%
Lase Cone	57%
CKC	24%

BSCCP do not recommend endocervical curettage "in any case"[57] given that the samples are often unsatisfactory and the lesion depth cannot be assessed precisely, relying for the diagnosis in the histological evaluation of a large, deep 'cylindrical' cone.

3. Combination of prognostic factors in detecting invasive endocervical disease

A helpful prognostic index for residual disease is the consideration of "suspicion of invasion" in conization pathology specimens (PSI - Pathologic Suspicion of Invasion), as well as a positive ECC (EndoCervical Curettage).

In patients with invasive disease in hysterectomy specimens, positive PSI in combination with positive ECC was illustrated in 75% and 100% of cases respectively. In patients with positive PSI and positive ECC, positive predictive value (PPV) for invasive disease is 33%. Moreover, the negative prognostic value (NPV) of a negative PSI for invasive disease is 94%. Furthermore, negative predictive value (NPV) for invasive disease if both prognostic markers (PSI/ECC) are negative reaches 100%[58].

4. HPV-DNA test

low risk for residual or recurrent disease. In contrast, a positive HR-HPV DNA test possibly represents the most robust independent recurrence prognostic factor.

Debate is ongoing regarding the optimal "Test of Cure" (TOC), whether it should be HR-HPV genotyping as a stand-alone test or a combination of HR-HPV genotyping plus cytology ("co-testing") in the pursuit of residual or recurrent disease. However, it is accepted that a small percentage of patients who had 'conservative' surgical treatment (conization) will finally turn up with persistent, recurrent, or progressive disease (HG-cGIN or microinvasive adenocarcinoma) rather late in the course of post-operative follow up; prolonged vigilance is therefore warranted[59].

Excisional treatment modalities

In the typical "cold knife" scalpel conization (CKC), surgical margins do not exhibit thermal injuries in contrast with other excisional modalities (predominantly LLETZ) which can possibly impair the diagnostic accuracy of the histological interpretation. Rates for recurrent or residual disease are statistically significantly

lower, compared with other excisional treatments[47,56], possibly because of the usually large volumes of the excised specimens. On the other hand, the latter might represent the reason that CKC exhibits the highest rates of complications when compared with other techniques, mainly primary and secondary post-operative bleeding, constriction of the ectocervical os (producing future inadequate smears), neonatal prematurity, and obstetric morbidity[49,50].

Laser conization illustrates a favorable profile in the treatment of AIS, and is almost as effective as CKC[53].

Loop conization (LLETZ/LEEP) should preferably by executed under constant colposcopic view. Unfortunately, without prior planning, sufficient accessibility and surgical field, and without selection of the appropriate electrode (loop), it produces shallow cones (±10-15mm), frequently with extensive thermal damage in the excision borders, rendering the evaluation of the surgical margins uncertain. The "top-hat" technique may well achieve tissue removal in sufficient depths; however there might again be uncertainty on the surgical margins. However, newer studies encourage the use of LLETZ with excellent effectiveness and prolonged follow up [56,62,63,64].

Postoperative follow-up

It has been repeatedly mentioned that regular and prolonged (at least 20-25 years) post operative follow up is mandatory for the timely detection of therapeutic failures (residual, recurrent or invasive disease)[65]. A judicious approach could be i) 6-months: cytology or co-testing, ii) 12 months: cytology or co-testing, iii) 18 months: cytology and iv) 24 months: cytology or co-testing; co-testing to be repeated in a yearly-basis thereafter. Colposcopy is not mandatory but can be very helpful as indicated. Detection of HPV postoperatively has possibly higher sensitivity, specificity and prognostic value in the detection of recurrent disease, compared to cytology or conzation margin status[66,67,68]. Following completion of the individual's family, a definite solution is advised (hysterectomy), not only due to incomplete understanding of the biological course of the disease, but predominantly because of the incessant pending danger of developing AIS/endocervical adenocarcinoma[65].

Recent literature has conclusively illustrated that preventive anti-HPV vaccination is effective in the long-term protection of women from high-grade cervical intraepithelial lesions attributed to HR-HPV genotypes (mainly 16, 18). Accordingly, in countries with organised vaccination systems which achieved high population coverage, a substantial reduction in the incidence of cervical adenocarcinoma is anticipated.[16,68]

Conclusions

Although atypical glandular cells represent a relatively rare finding in cytology smears, their management remains difficult and problematic, not only because of their occult origin, but also because of the stronger correlation with dysplastic or pre-invasive lesions compared to the squamous counterparts. There is a genuine increase in their incidence, attributed to increased rates of HPV infection, their facilitated recognition with the aids of LBC, and the increased vigilance of cytologists both towards unmasking the entity and also signing a relevant report. Their clinical significance varies, given the wide range of underlying pathology which exists.

For younger patients, the appropriate management of glandular lesions is difficult to be standardised and it is often individualized, tailored to their fertility concerns. However, management of menopausal women with severe glandular cervical lesions should follow the relevant guidelines of the scientific societies and health authorities.

When conservative surgical approach is contemplated for young women, detailed advising is mandatory on the possible postoperative complications and the increased

rates of recurrent or residual disease, while regular follow-up is mandatory. Given that the natural history and the evolution of glandular dysplasias to adenocarcinoma have been not yet fully elucidated, upon completion of the family, a definite treatment (hysterectomy) is advised.

References

1. Sankaranarayanan R, Ferlay J. Worldwide burden of gynaecological cancer: the size of the problem. Best Pract Res Clin Obstet Gynaecol. 2006; 20:207-25.

2. Vizcaino AP, Moreno V, Bosch FX, Muñoz N, Barros-Dios XM, Parkin DM. International trends in the incidence of cervical cancer: I. Adenocarcinoma and adenosquamous cell carcinomas. Int J Cancer. 1998; 75:536-45.

3. Bray F, Carstensen B, Møller H, Zappa M, Zakelj MP, Lawrence G et al. Incidence trends of adenocarcinoma of the cervix in 13 European countries. Cancer Epidemiol Biomarkers Prev. 2005; 14:2191-9.

4. Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M et al; Forum Group Members; Bethesda 2001 Workshop. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA 2002; 287:2114-9.

5. Davey DD, Neal MH, Wilbur DC, Colgan TJ, Styer PE, Mody DR. Bethesda 2001 implementation and reporting rates: 2003 practices of participants in the College of American Pathologists Interlaboratory Comparison Program in Cervicovaginal Cytology. Arch Pathol Lab Med. 2004; 128:1224-9.

6. Sharpless KE, Schnatz PF, Mandavilli S, Greene JF, Sorosky JI. Dysplasia associated with atypical glandular cells on cervical cytology. Obstet Gynecol. 2005; 105:494-500.

7. DeSimone CP, Day ME, Tovar MM, Dietrich CS 3rd, Eastham ML, Modesitt SC. Rate of pathology from atypical glandular cell Pap tests classified by the Bethesda 2001 nomenclature. Obstet Gynecol. 2006; 107:1285-91.

8. Tam KF, Cheung AN, Liu KL, Ng TY, Pun TC, Chan YM et al. A retrospective review on atypical glandular cells of undetermined significance (AGUS) using the Bethesda 2001 classification. Gynecol Oncol. 2003; 91:603-7.

9. Derchain SF, Rabelo-Santos SH, Sarian LO, Zeferino LC, de Oliveira Zambeli ER, do Amaral Westin MC et al. HPV DNA detection and histological findings in women referred for atypical glandular cells or adenocarcinoma in situ in their Pap smears. Gynecol Oncol. 2004; 95:618-23.

10. Schnatz PF, Guile M, O'Sullivan DM, Sorosky JI. Clinical significance of atypical glandular cells on cervical cytology. Obstet Gynecol. 2006; 107:701-8.

11. Ismail SM. Cone biopsy causes cervical endometriosis and tuboendometrioid metaplasia. Histopathol 1991; 18:107–114.

12. Castellsagué X, Díaz M, de Sanjosé S, Muñoz N, Herrero R, Franceschi S et al. International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. J Natl Cancer Inst. 2006; 98:303-15.

13. Herzog TJ, Monk BJ. Reducing the burden of glandular carcinomas of the uterine cervix. Am J Obstet Gynecol. 2007; 197:566-71.

14. Lee KR, Minter LJ, Granter SR. Papanicolaou smear sensitivity for adenocarcinoma in situ of the cervix. A study of 34 cases. Am J Clin Pathol. 1997; 107:30-5.

15. van Aspert-van Erp AJ, Smedts FM, Vooijs GP. Severe cervical glandular cell lesions and severe cervical combined lesions: predictive value of the Papanicolaou smear. Cancer 2004; 102:210-7.

16. Ault KA, Joura EA, Kjaer SK, Iversen OE, Wheeler CM, Perez G et al. Adenocarcinoma in situ and associated human papillomavirus type distribution observed in two clinical trials of a quadrivalent human papillomavirus vaccine. Int J Cancer. 2011; 128:1344-53.

17 Bean SM, Kurtycz DF, Colgan TJ. Recent developments in defining microinvasive and early invasive carcinoma of the uterine cervix. J Low Genit Tract Dis 2011; 15:146-57.

18. Ostör A, Rome R, Quinn M. Microinvasive adenocarcinoma of the cervix: a clinicopathologic study of 77 women. Obstet Gynecol. 1997; 89:88-93.

19. Webb JC, Key CR, Qualls CR, Smith HO. Population-based study of microinvasive adenocarcinoma of the uterine cervix. Obstet Gynecol. 2001; 97:701-6.

20. Sopracordevole F, Canzonieri V, Giorda G, De Piero G, Lucia E, Campagnutta E. Conservative treatment of microinvasive adenocarcinoma of uterine cervix: long-term follow-up. J Low Genit Tract Dis. 2012; 16:381-6.

21. Smith HO, Tiffany MF, Qualls CR, Key CR. The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States-a 24-year population-based study. Gynecol Oncol. 2000; 78: 97-105.

22. Krane JF, Granter SR, Trask CE, Hogan CL, Lee KR. Papanicolaou smear sensitivity for the detection of adenocarcinoma of the cervix: a study of 49 cases. Cancer. 2001; 93:8-15.

23. Eifel PJ, , Morris M, Smith TL. Adenocarcinoma as an independent risk factor for disease recurrence in patients with stage IB cervical carcinoma. Gynecol Oncol.; 59:38-44.

24. Sharpless KE, O'Sullivan DM, Schnatz PF. The utility of human papillomavirus testing in the management of atypical glandular cells on cytology. J Low Genit Tract Dis. 2009; 13:72-8.

25. Skyldberg BM, Murray E, Lambkin H, Kelehan P, Auer GU. Adenocarcinoma of the uterine cervix in Ireland and Sweden: human papillomavirus infection and biologic alterations. Mod Pathol.; 12:675-82.

26. Schorge JO, Hossein Saboorian M, Hynan L, Ashfaq R. ThinPrep detection of cervical and endometrial adenocarcinoma: a retrospective cohort study. Cancer 2002; 96:338-43.

27. International Collaboration of Epidemiological Studies of Cervical Cancer. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. Int J Cancer. 2007; 120:885-91.

28. Cuzick J, Arbyn M, Sankaranarayanan R, Tsu V, Ronco G, Mayrand MH et al. Overview of human papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries. Vaccine. 2008; 26 Suppl 10:K29-41.

29. Sankaranarayanan R, Nene BM, , Jayant K, Muwonge R, Budukh AM et al. HPV screening for cervical cancer in rural India. NEJM 2009; 360:1385-94.

30. Katki HA, Kinney WK, Fetterman B, Lorey T, Poitras NE, Cheung L et al. Cervical cancer risk

for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. Lancet Oncol. 2011; 12:663-72.

31. Zhao C, Li Z, Austin RM. Cervical screening test results associated with 265 histopathologic diagnoses of cervical glandular neoplasia. Am J Clin Pathol. 2013; 140:47-54.

32. El-Ghobashy AA, Shaaban AM, Herod J, Herrington CS. The pathology and management of endocervical glandular neoplasia. Int J Gynecol Cancer. 2005; 15:583-92.

33. Jaworski RC, Pacey NF, Greenberg ML, Osborn RA. The histologic diagnosis of adenocarcinoma in situ and related lesions of the cervix uteri. Adenocarcinoma in situ. Cancer 1988; 61:1171-81.

34. Zaino RJ. Symposium part I: adenocarcinoma in situ, glandular dysplasia, and early invasive adenocarcinoma of the uterine cervix. Int J Gynecol Pathol. 2002; 21:314-26.

35. Ruba S, Schoolland M, Allpress S, Sterrett G. Adenocarcinoma in situ of the uterine cervix: screening and diagnostic errors in Papanicolaou smears. Cancer 2004; 102:280-7.

36. Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M et al. 2012 ASCCP Consensus Guidelines Conference. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis. 2013; 17:S1-S27.

37.http://www.asccp.org/Portals/9/docs/Algorithms7.30.13.pdf.

38. Simsir A, Carter W, Elgert P, Cangiarella J. Reporting endometrial cells in women 40 years and older: assessing the clinical usefulness of Bethesda 2001. Am J Clin Pathol. 2005; 123:571-5.

39. Jordan J, Arbyn M, Martin-Hirsch P, Schenck U, Baldauf JJ, Da Silva D et al. European guidelines for quality assurance in cervical cancer screening: recommendations for clinical management of abnormal cervical cytology, part 1. Cytopathology. 2008; 19:342-54.

40. Tam KF, Cheung AN, Szeto A, Ngan HY. Atypical glandular cells diagnosed during pregnancy and the postpartum period: a retrospective analysis. Eur J Obstet Gynecol Reprod Biol 2011; 155:213–216.

41. Andersen ES, Nielsen K. Adenocarcinoma in situ of the cervix: a prospective study of conization as definitive treatment. Gynecol Oncol. 2002; 86:365-9.

42. Kennedy AW, Biscotti CV. Further study of the management of cervical adenocarcinoma in situ. Gynecol Oncol. 2002; 86:361-4.

43. Krivak TC, Rose GS, McBroom JW, Carlson JW, Winter WE 3rd, Kost ER. Cervical adenocarcinoma in situ: a systematic review of therapeutic options and predictors of persistent or recurrent disease. Obstet Gynecol Surv. 2001; 56:567-75.

44. Soutter WP, Haidopoulos D, Gornall RJ, McIndoe GA, Fox J, Mason WP et al. Is conservative treatment for adenocarcinoma in situ of the cervix safe? BJOG.2001; 108:1184-9.

45. Azodi M, Chambers SK, Rutherford TJ, Kohorn EI, Schwartz PE, Chambers JT. Adenocarcinoma in situ of the cervix: management and outcome. Gynecol Oncol. 1999; 73:348-53.

46. Reynolds EA, Tierney K, Keeney GL, Felix JC,

Weaver AL, Roman LD et al. Analysis of outcomes of microinvasive adenocarcinoma of the uterine cervix by treatment type. Obstet Gynecol. 2010; 116:1150-7.

47. Ostör AG, Duncan A, Quinn M, Rome R. Adenocarcinoma in situ of the uterine cervix: an experience with 100 cases. Gynecol Oncol. 2000; 79:207-10.

48. Salani R, Puri I, Bristow RE. Adenocarcinoma in situ of the uterine cervix: a metaanalysis of 1278 patients evaluating the predictive value of conization margin status. Am J Obstet Gynecol. 2009; 200:182.e1-5.

49. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. Lancet.2006; 367: 489-98.

50. Bevis KS, Biggio JR. Cervical conization and the risk of preterm delivery. Am J Obstet Gynecol. 2011; 205:19-27.

51. Shin CH, Schorge JO, Lee KR, Sheets EE. Conservative management of adenocarcinoma in situ of the cervix. Gynecol Oncol. 2000; 79:6-10.

52. Dedecker F, Graesslin O, Bonneau S, Quéreux C. Persistence and recurrence of in situ cervical adenocarcinoma after primary treatment. About 121 cases. Gynecol Obstet Fertil. 2008; 36:616-22.

53. Dalrymple C, Valmadre S, Cook A, Atkinson K, Carter J, Houghton CR et al. Cold knife versus laser cone biopsy for adenocarcinoma in situ of the cervix-a comparison of management and outcome. Int J Gynecol Cancer. 2008; 18:116-20.

54. Denehy TR, Gregori CA, Breen JL. Endocervical curettage, cone margins, and residual adenocarcinoma in situ of the cervix. Obstet Gynecol. 1997; 90:1-6.

55. Lea JS, Shin CH, Sheets EE, Coleman RL, Gehrig PA, Duska LR et al. Endocervical curettage at conization to predict residual cervical adenocarcinoma in situ. Gynecol Oncol. 2002 Oct; 87:129-32.

56. Kim JH, Park JY, Kim DY, Kim YM, Kim YT, Nam JH. The role of loop electrosurgical excisional procedure in the management of adenocarcinoma in situ of the uterine cervix. Eur J Obstet Gynecol Reprod Biol. 2009; 145:100-3.

57. Luesley D, Leeson S. NHSCSP 20, 2nd Edition - May 2010, ISBN 978 1 84463 069 1.

58. ElMasri WM, Walts AE, Chiang A, Walsh CS. Predictors of invasive adenocarcinoma after conization for cervical adenocarcinoma in situ. Gynecol Oncol. 2012; 125:589-93.

59. Costa S, Venturoli S, Negri G, Sideri M, Preti M, Pesaresi M et al. Factors predicting the outcome of conservatively treated adenocarcinoma in situ of the uterine cervix: an analysis of 166 cases. Gynecol Oncol. 2012; 124: 490-5.

60. Katki HA, Schiffman M, Castle PE, Fetterman B, Poitras NE, Lorey T et al. Five-year risk of recurrence after treatment of CIN 2, CIN 3, or AIS: performance of HPV and Pap cotesting in posttreatment management. J Low Genit Tract Dis. 2013; 17:S78-84.

61. Bryson P, Stulberg R, Shepherd L, McLelland K, Jeffrey J. Is electrosurgical loop excision with negative margins sufficient treatment for cervical ACIS. Gynecol Oncol. 2004;93:465-8.

62. Girardi F, Heydarfadai M, Koroschetz F, Pickel H, Winter R. Cold-knife conization versus

loop excision: histopathologic and clinical results of a randomized trial. Gynecol Oncol. 1994; 55:368-70.

63. van Hanegem N, Barroilhet LM, Nucci MR, Bernstein M, Feldman S. Fertility-sparing treatment in younger women with adenocarcinoma in situ of the cervix. Gynecol Oncol. 2012; 124: 72-7.

64. Hwang DM, Lickrish GM, Chapman W, Colgan TJ. Long-term surveillance is required for all women treated for cervical adenocarcinoma in situ. J Low Genit Tract Dis. 2004; 8:125-31.

65. Paraskevaidis E, Arbyn M, Sotiriadis A, Diakomanolis E, Martin-Hirsch P, Koliopoulos G et al. The role of HPV DNA testing in the follow-up period after treatment for CIN: a systematic review of the literature. Cancer Treat Rev. 2004; 30: 205-11.

66. Zielinski GD, Bais AG, Helmerhorst TJ, Verheijen RH, de Schipper FA, Snijders PJ et al. HPV testing and monitoring of women after treatment of CIN 3: review of the literature and meta-analysis. Obstet Gynecol Surv. 2004; 59:543-53.

67. Arbyn M, Paraskevaidis E, Martin-Hirsch P, Prendiville W, Dillner J. Clinical utility of HPV-DNA detection: triage of minor cervical lesions, follow-up of women treated for high-grade CIN: an update of pooled evidence. Gynecol Oncol. 2005; 99:S7-11.

68. Seoud M, Tjalma WA, Ronsse V. Cervical adenocarcinoma: moving towards better prevention. Vaccine 2011; 29:9148-58.

HJOG
An Obstetrics and Gynecology International Journal

Abstract in Greek

Αντιμετώπιση γυναικών με κυτταρολογική βλάβη αδενικού επιθηλίου του τραχήλου της μήτρας. Νέα βιβλιογραφικά δεδομένα

Νικολάου Μαρίνος[1], Παπαδημητρίου Ιφιγένεια[2], Μιχαήλ Γεώργιος[2], Ανδρουτσόπουλος Γεώργιος[2], Αντωνάκης Γεώργιος[2], Ρελάκης Κωνσταντίνος[3], Δεκαβάλας Γεώργιος[2]

[1]Μαιευτική - Γυναικολογική κλινική, Γενικό Νοσοκομείου Αγίου Νικολάου, Κρήτη, Ελλάδα

[2]Μαιευτική - Γυναικολογική κλινική, Πανεπιστήμιου Πατρών, Ιατρική Σχολή, Πάτρα, Ελλάδα

[3]Μαιευτική - Γυναικολογική κλινική, Πανεπιστήμιο Κρήτης, Ιατρική Σχολή, Ηράκλειο Κρήτης, Ελλάδα

Υπεύθυνος Επικοινωνίας: Νικολάου Μαρίνος MD, Τμήμα Μαιευτικής και Γυναικολογίας, Γενικό Νοσοκομείου Αγίου Νικολάου, Κρήτη, Ελλάδα, **Τηλ:** +302841343578/ +306972897699 - **Fax:** +302841100839 - **Email:** nikolaoumarinos@yahoo.gr

Παραλήφθηκε: 20/3/2014, Εγκρίθηκε: 27/3/2014

Περίληψη

Η συχνότητα εμφάνισης των αδενικών τραχηλικών αλλοιώσεων έχει αυξηθεί σημαντικά κατά τη διάρκεια των τελευταίων δύο δεκαετιών, ιδίως μεταξύ των νέων γυναικών. Αυτή η αύξηση οφείλεται κατά κύριο λόγο στην αυξανόμενη επικράτηση αυτής της οντότητας, καθώς και τις πρόσφατες εξελίξεις στην κυτταρολογία. Άτυπα αδενικά κύτταρα (AGC) που ανευρίσκονται μετά από κυτταρολογική εξέταση Παπανικολάου μπορεί να υποκρύπτουν μια σημαντική υποκείμενη παθολογία. Η φυσική ιστορία και εξέλιξη των αδενικών αλλοιώσεων του τραχήλου μήτρας της σε σύγκριση με αυτό των πλακωδών είναι λιγότερο κατανοητή. Οι ιοί HPV υψηλού κινδύνου (HPV16, 18 και 45) έχουν εντοπιστεί με υψηλή συχνότητα σε αδενικές βλάβες. Κυτταρολογία και κολποσκόπηση παρουσιάζουν φτωχή ευαισθησία στη διάγνωση του αδενικού αλλοιώσεων. Οι διαδικασίες διαγνωστικής εκτομής είναι υψίστης σημασίας για την διαχείριση των υψηλού βαθμού βλαβών. Οι θεραπευτικές επιλογές είναι η συντηρητική χειρουργική επέμβαση, κυρίως με κωνοειδή εκτομή ή οριστική θεραπεία (κυρίως υστερεκτομή). Η κωνοειδής εκτομή του τραχήλου της μήτρας φαίνεται να δίνει ικανοποιητικά αποτελέσματα, ιδίως σε νεαρές γυναίκες με υψηλού βαθμού αλλοιώσεις του αδενικού επιθηλίου, που επιθυμούν να διατηρήσουν τη γονιμότητά τους. Ωστόσο, η επαρκής παροχή συμβουλών θα πρέπει να παρέχονται στους ασθενείς πριν τις θεραπευτικές αποφάσεις. Η μακροχρόνια παρακολούθηση είναι υποχρεωτική για τις γυναίκες που έλαβαν θεραπεία για αδενικές βλάβες για τον εντοπισμό τυχόν υπολειμματικής νόσου και τα πρώτα σημάδια της υποτροπής.

Λέξεις κλειδιά: βλάβη αδενικού επιθηλίου του τραχήλου της μήτρας, διαγνωστικές εξετάσεις, επιλογές θεραπείας.