GUIDELINES ON ADENOCARCINOMA IN SITU OF THE CERVIX: CLINICAL FEATURES AND REVIEW OF MANAGEMENT

These guidelines have been prepared by the SOGC/GOC/SCC Policy and Practice Guideline Committee and were approved by the Council of the SOGC.

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Cervical intra-epithelial glandular lesions have a morphological spectrum (akin to squamous) that ranges from mild changes to severe abnormalities. The entire spectrum is referred to as “cervical intra-epithelial glandular neoplasia” and is abbreviated as CIGN, CGIN or GIN.  

The diagnosis of adenocarcinoma in situ (ACIS) is made by some method of excision. The specimen, preferably cylindrical in shape, must have negative (disease free) lateral and upper margins. The ratio of adenocarcinoma in situ to severe squamous dysplasia/carcinoma in situ averages 1:50 meaning that glandular comprises roughly 2% of in situ cases whereas the malignant glandular lesions make up six to 18 percent of all invasive cervical cancers. In both stages, 46 to 72 percent of lesions contain a counterpart squamous component (being, therefore, of mixed type).

Screening and invasive detection methods used to identify lesions and determine the presence of persistent or recurrent disease (cytology, colposcopy, biopsy and endocervical curettage) are inaccurate and unreliable. This is because of inadequate cytologic sampling in some cases, the existence of various colposcopic mimics (the most commonly encountered being metaplasia, condylomata, invasive adenocarcinoma, invasive squamous cancer and microglandular hyperplasia), most colposcopists’ lack of experience with these lesions (due to their rarity) and the inadequacy of endocervical curettage in some cases.

A denocarcinoma in situ has a length (the distance over the tissue surface between caudal and cephalad edges) not usually exceeding 15 mm. The underlying cervical crypt (“gland”) involvement does not usually exceed four millimetres. Although ACIS has many architectural and histological patterns, management is not influenced by these patterns.

The management of ACIS continues to be controversial. Cervical excision (like the traditional “conization” but with the specimen cylindrical in shape) is proposed as conservative management for patients desirous of future fertility. The excised specimen must have negative margins, meaning that the outer and upper margins of the specimen are free of disease and that the disease is completely contained within the excised tissue. Follow-up cytology, colposcopy and endocervical curettage may not be accurate in identifying persistent disease and/or detecting recurrent disease. If fertility is not an issue, simple routine hysterectomy is advocated, even though the specimen contains negative margins. Although disease can still be present in the hysterectomy specimen, it is usually ACIS and rarely an invasive adenocarcinoma. In the case of positive margins, meaning disease is noted at the upper and/or outer surface of the excised specimen, the probability of finding an invasive lesion in the excised tissue is enhanced.

Patients who choose conservative management must be counselled about the importance of compliance and the potential risks of early undetected persistent or recurrent glandular disease, despite negative screening and invasive detection methods. This is because some cases of persistent or recurrent glandular disease have been reported after excision, despite negative specimen margins.

KEY WORDS
Glandular lesions of the cervix, adenocarcinoma in situ of the cervix, colposcopy of glandular cervical lesions.

INTRODUCTION

A denocarcinoma in situ of the uterine cervix (ACIS) was first described in 1953 by Friedell and McKay. It is now apparent that cervical intra-epithelial glandular lesions have a morphological spectrum (akin to squamous) that ranges from mild changes to severe abnormalities. The entire spectrum is referred to as “cervical intra-epithelial glandular neoplasia” and is abbreviated as CIGN, CGIN or GIN. This spectrum has been divided into two grades: low- and high-grade CIGN . The low grade includes such entities as glandular atypia and glandular dysplasia. The high grade consists solely of adenocarcinoma in situ . The International Society of Gynaecologic Pathologists’ terminology includes the terms:

(i) glandular atypia (non-neoplastic changes associated with inflammation and radiotherapy);
(ii) atypical hyperplasia (glandular dysplasia) of less severe changes than adenocarcinoma in situ;
(iii) adenocarcinoma in situ.
collect a sizeable series and gain experience with
colposcopic identification.

PROBLEMS IN THE DETECTION OF
ADENOCARCINOMA IN SITU

The problems in identifying ACIS arise because of
imperfect cytology (not indicating a glandular lesion),
colposcopic inexperience causing one to fail to recog-
nize the sometimes subtle patterns, and the size and location of the lesion.

CYTOLOGY

Cytology smears, particularly cervical scrapes, may not contain diagnostic cells. Nguyen found that only about 60 percent of ACIS cases had been detected by previous exfoliative cervical-vaginal cytology examinations. Endocervical sampling may improve the ability to detect ACIS. A problem is that cells demonstrating ACIS, even if present on the smear, may not be noticed.

In the Bethesda System for reporting cervical-vaginal cytological smears, atypical endocervical cells which are thought to be of borderline or very early abnormality are classified as “atypical glandular cells of undetermined significance” (AGUS). This category is further qualified in the cytology report as to whether a reactive (e.g. relating to tissue repair) or a premalignant (ACIS) process is favoured. Some lesions eventually determined to be ACIS are originally given the AGUS cytological classification.

In a cytological specimen, ACIS must be differentiated from the following: reactive and regenerative changes in the columnar and squamous epithelium; Arias-Stella changes in the cervix; cervical polyp; mesonephric duct remnants; tubal or serous metaplasia; cervical endometriosis; microglandular hyperplasia; endocervical changes associated with an intra-uterine contraceptive device; squamous dysplasia involving glandular epithelium, invasive cervical adenocarcinoma and invasive endometrial adenocarcinoma. The determination is made by the cytopathologist or cytologist.

COLPOSCOPY

Most gynaecologists have found colposcopy to be of little value in recognizing ACIS. This is because ACIS produces little alteration in the surface contour, and because the neoplastic “glands” are buried beneath the surface. The lack of firm criteria upon which to base a suspicion of glandular disease is due in part to the rarity of these cases and, hence, the inexperience of even the most “experienced” colposcopists. Colposcopists are trained to recognize patterns in the transformation zone associated with normal squamous epithelium, squamous metaplasia and squamous cervical intra-epithelial neoplasia, but not the sometimes subtle clues pointing to glandular disease. Most cases of ACIS are within the transformation zone or its immediate vicinity, and it is beginning to be recognized that they often have specific features that will lead the enlightened colposcopist to suspect that a glandular lesion is present. The most common colposcopic finding is that ACIS is mimicking the immature transformation zone.

After acetic acid application, fused villi demonstrating ACIS are often seen as discreet patches varying in size. They look similar to fused villous processes or early metaplasia. Approximately one-half of the ACIS cases have an accompanying villous process which is usually high grade. The squamous component is usually colposcopically visible, whereas the ACIS component can lie proximally, involving the cervical canal, or lie beneath metaplastic epithelium or an abnormal transformation zone and, thus, out of colposcopic view. As a result of the location of the ACIS, the exfoliative cytology may represent only the abnormal squamous component, thus influencing the colposcopist to look for only the squamous lesion. Furthermore, the colposcopic biopsy may identify the squamous lesion with the ACIS disease being detected only on a subsequent cone or within a hysterectomy specimen.

WHEN THE FOLLOWING TYPES OF
LESIONS ARE NOTED COLPOSCOPICALLY,
ACIS SHOULD BE SUSPECTED

1. Elevated lesions. If elevated lesions, especially those exhibiting an irregular surface, are overlying columnar epithelium, the differential diagnosis includes: metaplasia; condylomata; ACIS; invasive adenocarcinoma and microglandular hyperplasia.

2. Lesions with large “gland”/crypt openings in

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association with other abnormal colposcopic features.
Many ACIS lesions can occupy the endocervical canal in whole or in part. Such lesions demonstrate a patchy red and white surface (not the uniformly dense white seen in high-grade squamous intraepithelial neoplasia). Frequently, large “gland”/crypt openings are seen with excessive mucus production.

3. Papillary-like lesions.
Papillary excrescences must be differentiated from the normal papillary glandular mucosa (the villous structures of columnar epithelium constituting the “ectopy”), metaplasia, condylomata, A CIS, invasive adenocarcinoma, invasive squamous cell carcinoma and microglandular hyperplasia.

4. Epithelial budding.
A denocarcinoma in situ can proliferate in a “budding-like” formation. When observed colposcopically, a differentiation should be made between immature metaplastic epithelium, immature condylomata and A CIS.

5. Lesions with a patchy red and white surface.
When such a surface coloration is seen, the colposcopist should differentiate between a developing normal transformation zone, A CIS and invasive adenocarcinoma.

6. A typical blood vessel formations.
A denocarcinoma in situ can demonstrate a variety of blood vessel patterns. The common ones are “waste-thread-like” and “tendril-like” in association with some very bizarre formations including “root-like” and “character-writing-like”. A though atypical blood vessel formations can be seen in both A CIS and invasive adenocarcinoma, they are more common in the latter. Punctuation, mosaicism and “corkscrew-like” vessel formations, although common in squamous disease, do not appear in glandular disease.

7. High-grade squamous lesions.
A denocarcinoma in situ can lie distinctly lateral
to, but more commonly lies above, the squamous component (within the endocervical canal). The cytology frequently reflects only the squamous component (usually high grade). The colposcopist is programmed mentally for squamous disease and most likely gives no thought to the possibility of a co-existing glandular component. When the cytology is high-grade squamous, colposcopists should automatically be aware that an ACIS component might be present and should look for it.

8. Two or more squamous lesions separated by glandular-appearing epithelium. Primary (i.e. not post-treatment) squamous lesions do not “skip”; they are always contiguous.

There is no single colposcopic appearance which characterizes glandular dysplasia, adenocarcinoma in situ or adenocarcinoma. To complicate matters, in many cases colposcopic appearances of these entities often mimic other conditions. The five standard colposcopic criteria (vascular patterns, intercapillary distance, surface contour, colour tone and clarity of demarcation) apply to squamous and not glandular lesions. Other colposcopic features are helpful in differentiating metaplasia, condylomata, squamous intra-epithelial neoplasia, invasive squamous cell carcinoma, metaplasia and glandular disease. They are: lesion location over columnar epithelium, not contiguous with the squamo-columnar junction; large “gland”/crypt openings; papillary structure; budding; patchy red and white colouration; waste-thread, tendril, root and character-writing blood vessels and blood vessel looped dots. Some features can be used to eliminate a lesion from consideration; such features as punctuation and true mosaicism are seen only in squamous intra-epithelial lesions. A thoughmany colposcopically recognized features are common to a variety of diseases, paying attention to surface patterns and blood vessels can greatly help the colposcopist to discover glandular disease (Table 1) when it is present, and to differentiate it from other conditions.

THE DISTRIBUTION OF ADENOCARCINOMA IN SITU

A. The Length of A denocarcinoma in situ

The length of A CIS cases have an associated squamous component (CIN or invasive squamous cell carcinoma). It is interesting that squamous and adenocarcinomas are not usually seen within the same “gland”/crypt. A denocarcinoma in situ can be identified histologically in underlying cervical “glands”/crypts involving them entirely or in part but not skipping one locus of disease within a “gland”/crypt. Disease does skip “glands”/crypts, however, so a normal “gland”/crypt might lie between two diseased ones. The depth of involvement is generally superficial (averaging 2.5 mm) not usually exceeding four mm below the surface. Extensions to six mm are described rarely. Invariably, normal “glands”/crypts are seen beneath. The involved “glands”/crypts may be focal or, more rarely, may intermingle with normal “glands”/crypts. The transition between the normal and neoplastic epithelium, whether on the surface or in the lining of the “glands”/crypts, is abrupt.

A denocarcinoma in situ has many architectural and histological patterns. The architectural patterns include cribiform, epithelial budding and papillary formations. The histological patterns include the most common type (Type I) resembling endocervical adenocarcinoma, which is subdivided into an endocervical type (those lesions with intracytoplasmic mucin) and an endometrial type (those lesions with mucin limited to the brush border). The less common type (Type II) is identified by the presence of abundant intracytoplasmic mucin vacuoles (goblet cells) with variable size, clear nuclei and enlarged nuclei, resembling colonic or intestinal epithelium. Neither architectural nor histological type plays a role in the management of the patient. They are, however, responsible for the varying colposcopic expressions. Type I lesions create the transformation zone-like colposcopic findings and Type II is associated with large “gland”/crypt openings and excessive mucus.

DIFFERENTIATING ADENOCARCINOMA IN SITU OF THE CERVIX FROM OTHER HISTOLOGICAL FINDINGS

The differential diagnosis of A CIS in a histological specimen includes: microglandular hyperplasia;
mesonephric duct hyperplasia; tubal or serous metaplasia (ciliated cell metaplasia); cervical endometriosis; cervical invasive adenocarcinoma; adenomatoid proliferation ("tunnel clusters"); glandular dysplasia and glandular atypia (inflammatory related). Making this differentiation is the pathologist's responsibility.

MANAGEMENT OF ADENOCARCINOMA IN SITU OF THE CERVIX

When ACIS is found in a specimen or is suspected cytologically or colposcopically, an excisional procedure, producing a specimen with negative margins (one in which the surgical lines of excision are histologically free of disease), is necessary to be sure that no invasive adenocarcinoma is present. Some thought should be given to the size (length and width) of the specimen. It should be cylindrical in shape and should account for the depth of crypt involvement and the linear extent of the disease. The excision should be carried out under colposcopic guidance. If the colposcopic biopsy or biopsies contains A CIS and the lesion was not predicted by colposcopy, the practitioner should examine the cervix with the colposcope again, noting the lower lesion border and, if possible, the upper margin (the entire linear extent). These measurements serve as a guide for determining the dimensions of the specimen to be produced by the excisional procedure.

The cylindrical excision is performed best with an Ultrapulsed\textsuperscript{TM} carbon dioxide laser plus scalpel excision of the apex. A scalpel alone can be used, but it is more difficult to obtain a cylindrical specimen with scalpel alone. Monopolar electrosurgical (loop excision) current follows the path of least resistance (into the glandular mucus) and, thus, can potentially distort the glandular epithelium, making histological interpretation difficult if not impossible.

The safe conservative management of the patient who does not want to compromise her fertility, in most centres, depends on the pathological reporting of negative surgical margins in the excised specimen. The adequacy and accuracy of screening and invasive detection methods are inadequate for reliable detection of persistent and recurrent disease. Many colposcopists are now following carefully, with colposcopy and cytology and where indicated, biopsy, women who do not want a simple hysterectomy until they complete their families.

Patients who choose to be followed this way must be counselled about the importance of compliance and the potential risks of undetected persistent and recurrent glandular disease, despite negative follow-up findings.

A. SIGNIFICANCE OF NEGATIVE MARGINS IN THE EXCISED SPECIMEN

Most studies indicate that if the excised specimen's margins are negative, then conservative management is permissible in those women who desire future childbearing. Negative margins are associated with persistent A CIS in the extirpated uterus in 12.5 percent of cases (accumulated analysis). Studies have identified, on occasion, invasive adenocarcinoma, even when specimens had negative margins.

The follow-up management should consist of cytology, colposcopy and endocervical curettage every four months for one year and every six months thereafter. O nce reproduction is complete, hysterectomy has been advocated. The question remains whether this is necessary in the compliant patient with no evidence of persistent disease. More long-term studies are necessary to address this issue.

B. SIGNIFICANCE OF POSITIVE MARGINS IN THE EXCISED SPECIMEN

Cumulative studies indicate that positive margins in the excised specimen are of great significance because of the high risk of residual A CIS (46 % of cases) and invasive adenocarcinoma (16.7 % of cases). Repeat excision is necessary to obtain negative margins for the conservatively managed patient who desires further childbearing. Repeat excision, producing negative margins, is also necessary before a simple hysterectomy is performed on the patient who desires no future childbearing. Failure to do so in the latter circumstance may result in inappropriate surgery (simple hysterectomy instead of radical hysterectomy), should invasive adenocarcinoma be found in the extirpated uterine cervix.

REFERENCES

3. Gloor E, Hurlimann J. Cervical intraepithelial neoplasia