

Glandular abnormalities, adenocarcinoma in situ, and glandular intraepithelial neoplasia

The implementation of a high-coverage and quality-assured cytology-based screening programme will reduce the incidence of and mortality from cervical cancer, largely because of the effect on squamous disease. This is to be expected, given that cervical cancer preventive screening programmes are designed to detect squamous cell abnormalities and not glandular disease. Even in well-screened populations, adenocarcinoma rates have been largely unaffected. Glandular abnormalities are rare (reported in 0.5–0.8 cases per 1000), but a smear report of glandular abnormality is more predictive of disease than an equivalent squamous abnormality, and not only of purely glandular abnormalities (Krane et al., 2001). The study of Pisal et al. (2003) of 50 smears reporting glandular dyskaryosis found that 13 cases were

cervical glandular disease and only one of those was pure glandular dysplasia. There were 4 cases of microinvasive adenocarcinoma, 2 undifferentiated cancers, 1 squamous cell cancer, and 21 cases of HSIL. Thirteen women had endometrial pathology (8 endometrial cancers), and one woman even had colon cancer. In all, 16 of the 50 women had a malignancy (Pisal et al., 2003).

As many programmes move to HPV-based screening, this may change. Because most glandular disease exists in the endocervical site, glandular precancer will often be missed by visual inspection methods. However, many glandular lesions coexist in the TZ. Furthermore, many glandular lesions are associated with concurrent ectocervical squamous disease. A good illustration of the failure of screening to prevent glandular cancer is the

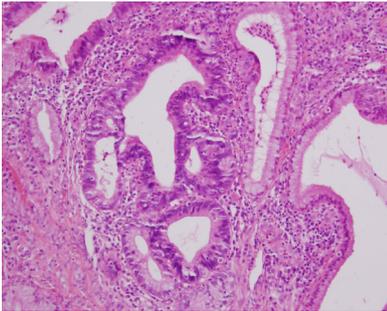
ratio of abnormal glandular smear reports to glandular cancer rates. Although glandular precancer smear reports are 0.02 times as common as squamous lesions, glandular cancer accounts for 20% or all cervical cancer cases.

12.1 Glandular disease

The natural history of glandular precancer (adenocarcinoma in situ) or high-grade glandular abnormality (cervical glandular intraepithelial neoplasia [CGIN]) is not as well mapped out as that of squamous disease. It is highly likely that glandular dysplasia will progress to invasive cancer in a significant proportion of cases, for several reasons.

- Glandular intraepithelial lesions are often found adjacent to invasive lesions.

Fig. 12.1. High-grade glandular dysplasia in a gland crypt.



- The cellularity of CGIN and glandular cancer are very similar morphologically; indeed, differentiating the very earliest stages of invasive adenocarcinoma from intraepithelial disease can be challenging and is often highly subjective (Cullimore et al., 1992).
- The mean age of women who develop adenocarcinoma in situ is about 15 years less than that for invasive glandular cancer.
- Similar HPV types are found in CGIN and glandular cancer cases (Zaino, 2000).

As with squamous disease, low-grade abnormalities are not easily defined or uniformly agreed upon between pathologists, whereas high-grade CGIN (Figs. 12.1 and 12.2) or adenocarcinoma is a relatively robust diagnosis. Also, because high-grade glandular disease is much less common than high-grade squamous cancer (at a ratio of about 1:50), it is

Fig. 12.3. Cross-section of an adenocarcinoma.

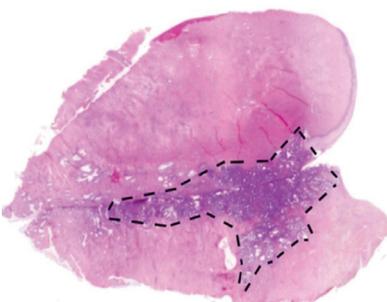
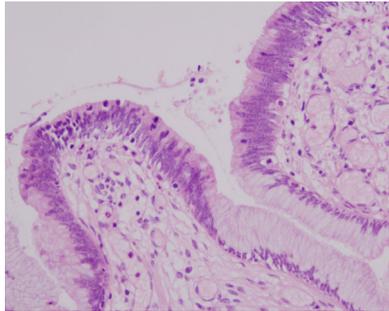


Fig. 12.2. Higher-power magnification view of glandular dysplasia.



not as easily discovered, either cytologically or colposcopically. Finally, the colposcopic signs of high-grade CGIN are less recognizable than those of HSIL.

Several lessons derive from the above-mentioned situation. First, a histological diagnosis is mandatory in making a diagnosis of high-grade CGIN, and the diagnosis needs to be made with a sufficiently large biopsy, whereby it is possible to recognize or rule out disease. There is no place for punch biopsies in the investigation of CGIN. At the very least, a small loop biopsy (or biopsies) is necessary. CGIN and adenocarcinoma (Fig. 12.3) is a challenging diagnosis. Colposcopic examination does not usually discover covert glandular disease, and this is not surprising: the disease is largely endocervical; the concept of an adequate or satisfactory colposcopic examination does not usually apply to glandular

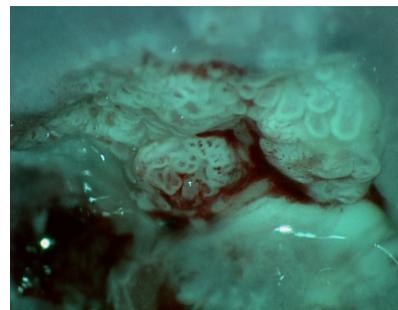
Fig. 12.4. Colposcopic image of a high-grade glandular lesion.



lesions, because of their endocervical site; and the colposcopic signs of glandular disease are more difficult to recognize. Also, because glandular disease is so much less common, it is more difficult to acquire image recognition skills for glandular disease. Colposcopy is important in the investigation and management of suspected glandular disease but on its own has a poor negative or positive predictive value for glandular disease (Ullal et al., 2009), and abnormal cytology is more likely to predict histologically proven glandular disease than is colposcopy. This is one of the reasons why excisional treatment of suspected high-grade glandular disease is fundamentally important. Although colposcopy may recognize signs of glandular disease (Fig. 12.4), it will also often miss the unheralded case (i.e. not suspected cytologically).

The interested reader is referred to an excellent atlas of colposcopic images of glandular disease (Wright, 2010); however, not many colposcopists feel able to reliably recognize glandular disease using colposcopy alone. Typical signs that have been reported include white lesions adjacent to the SCJ, character writing (Fig. 12.5), large gland openings, fused clumped villi, variegated red and white lesions after acetic acid

Fig. 12.5. Colposcopic image of a high-grade glandular lesion using the green filter to highlight blood vessel patterns.



application, and exophytic white lesions.

12.2 Management of suspected glandular dysplasia

The definitive management of glandular dysplasia is excision of the TZ and a proportion of full-thickness endocervical canal epithelium. When a borderline glandular smear has been reported, it may be sufficient to perform colposcopy and biopsy, but where there is any suspicion of genuine CGIN, excisional treatment is mandatory. This is for several reasons.

- Most glandular disease has an endocervical component, and therefore destructive techniques are contraindicated.
- It is often not possible to determine the extent of endocervical involvement of dysplastic epithelium in the canal. Colposcopic assessment of glandular dysplasia is less reliable than with squamous disease.
- Multicentric disease (skip lesions) occurs with glandular disease in about 15% of cases.
- About 50% of cases of glandular disease will have concomitant squamous disease.

12.3 Excisional treatment with CGIN: what type and how big?

A cylindrical type 3 excision should be performed using a straight wire, a cold knife, or a laser to perform the excision. LLETZ may also be used if the operator is experienced and audit reveals clear undamaged margins in excised tissue. It is crucial that the pathologist has sufficient and undamaged tissue with which to make a diagnosis and assess margin involvement. The diagrams in Figs. 12.6 and 12.7 illustrate this point. The traditional cone biopsy has a cone shape and is likely to miss disease at the base of deep cervical clefts, which can extend up

to 5 mm from the margin of the canal (Bertrand et al., 1987). Cylindrical type 3 excisions avoid this potential problem.

12.4 Anatomical distribution of CGIN

The interested reader is referred to John Cullimore's excellent chapter on glandular disease (Cullimore, 2003), and his illustrations of the distribution of CGIN are reproduced in Fig. 12.8. Bertrand et al. (1987), Nicklin et al. (1991), and Teshima et al. (1985) have also examined the subject in detail. The disease is unicentric in more than 85% of cases and arises just above the SCJ. It

Fig. 12.6. A traditional cone biopsy, which risks inadequate excision at the upper margin and excessive removal of stromal tissue.

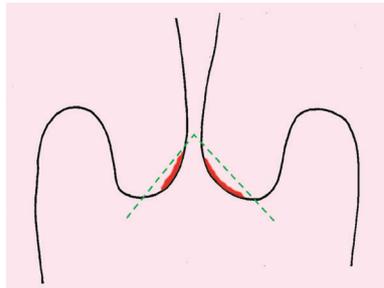


Fig. 12.7. A cylindrical type 3 excision, which is less likely to produce incomplete excision and removes less normal stromal tissue.

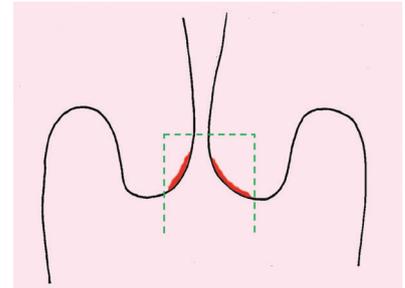
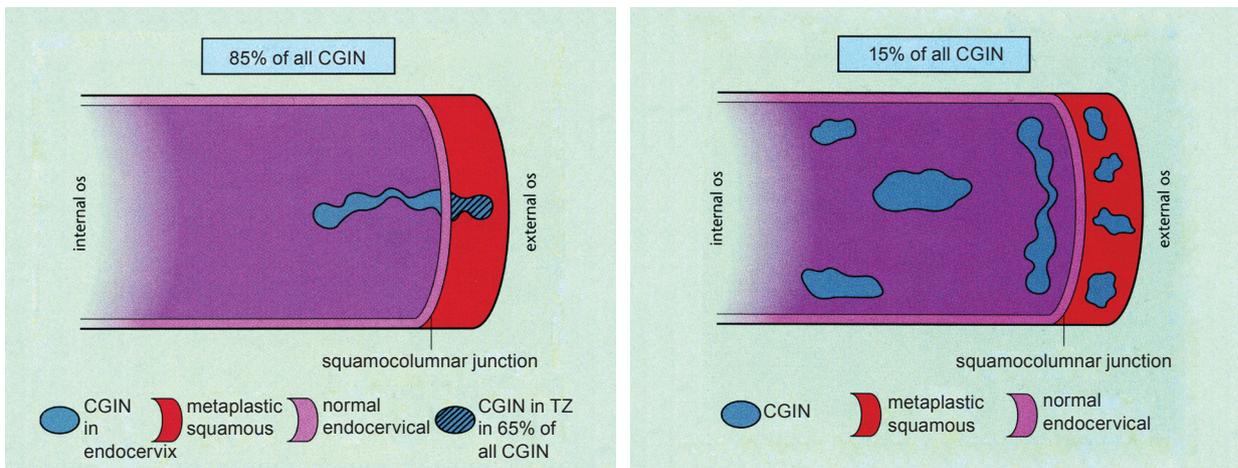


Fig. 12.8. Distribution of cervical glandular intraepithelial neoplasia (CGIN). TZ, transformation zone.

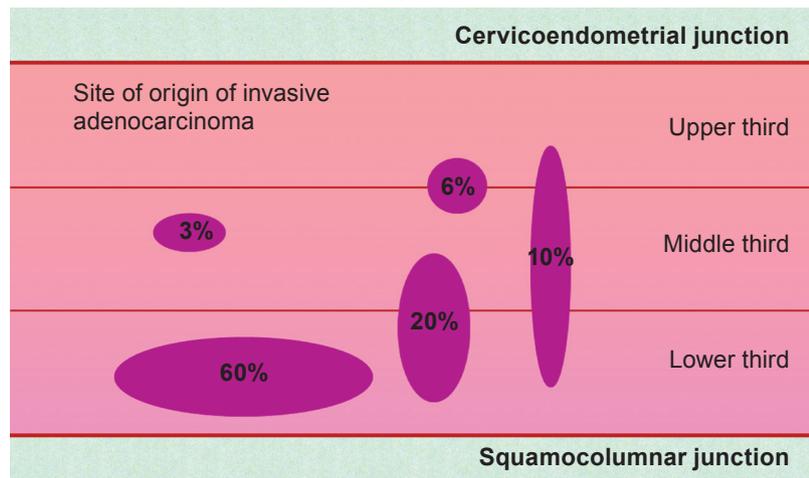


usually extends in a contiguous fashion up the endocervical canal. Skip lesions are uncommon but not rare (Zaino, 2002), but the distribution is multicentric in approximately 15% of cases. Fortunately, in more than 95% of cases in women younger than 36 years, the disease appears to be confined to within 10 mm of the SCJ, whereas in women older than 35 years it can extend to 20 mm or 25 mm above the SCJ.

As for invasive disease, the distribution is equally important (Fig. 12.9). Teshima et al. (1985), reporting the histological findings of 30 cases of early adenocarcinoma of the endocervical glandular epithelium, reported that 27 of 30 originated in the lower third of the canal, and of these 18 were exclusively in the lower third. Lee and Flynn (2000) reported that invasive disease was found originating in or immediately adjacent to the TZ in 78% of their case series. Also, 85% of the cases in their series had associated CGIN or adenocarcinoma in situ. When managing women with abnormal glandular disease, one is as likely to discover covert cancer as covert adenocarcinoma in situ. This is another reason that complete excision and histopathologically clear margins are crucial when treating glandular dysplasia.

These findings have important clinical implications. How much of the endocervical canal should be excised is influenced by the position of the SCJ (the upper limit of the TZ) as well as the woman's age, her fertility aspirations, and the likelihood of default from follow-up. Glandular disease typically presents in women of reproductive age, and many women will not have completed their family, so that taking the minimum amount of tissue necessary would seem sensible. However, there is good evidence that histologically involved margins are a risk factor for residual disease,

Fig. 12.9. Distribution of the site of origin of adenocarcinoma in the endocervical canal.



and clear margins are powerful as negative predictors of residual/recurrent disease. Salani et al. (2009) undertook a meta-analysis of observational studies including a total of 1278 patients and found positive margins to be associated with a clinically important increase in the risk of both residual precancerous glandular disease and the development of invasive disease (Table 12.1).

12.5 Individualizing treatment with CGIN

Taking the above-mentioned data into account, a reasonable approach to the management of CGIN is to individualize it. For young women who still wish to have children, it is reasonable to limit the excision to 12–15 mm above the TZ and, also, to include the entire TZ in the specimen. Coincident squamous disease is common (NHS, 2010). If the woman

has completed her family, then the initial excision should include a further 5 mm of endocervical canal. For women older than 35 years in whom future fertility is not desired, the initial excision should be 20–25 mm of endocervical canal epithelium and, of course, should also include the TZ. For whichever excisional length is chosen, the excision should be cylindrical and should excise a one-piece specimen. Invasive disease (squamous or glandular) should not be excised in pieces. After the precise diagnosis has been made and invasive cancer has been ruled out, the patient may be followed up until she has completed her family. It is important to recognize that clear margins do not give the same degree of negative prediction against recurrence as with squamous disease. The risk of recurrence after treatment for glandular disease is 3 times that for squamous disease. Once the patient has

Table 12.1. Risk associated with incomplete excision

Risk	Positive margins	Negative margins
Risk of residual CGIN	19.4%	2.6%
Risk of subsequent invasive cancer	6%	0.35%

CGIN, cervical glandular intraepithelial neoplasia.

completed her family, a hysterectomy is probably wise. Until then, follow-up with endocervical brush cytology, HPV testing, and colposcopic examination at least annually is prudent; recent NHS Cervical Screening Programme guidelines imply that this can be further rationalized since the

addition of HPV testing (NHS, 2016), although the evidence base for this recommendation is unclear. Women who decide not to have a hysterectomy in the presence of true glandular disease need to know that there is a risk of residual disease and of the development of invasive cancer,

which is more difficult to monitor than ectocervical squamous precancer. Finally, when HPV vaccination programmes become universal, CGIN rates will begin to fall. CGIN is universally associated with high-risk HPV (types 16 and 18).

Key points

- The diagnosis of cervical glandular intraepithelial neoplasia (CGIN) can only be made at histology.
- Cytology and colposcopy are unreliable methods of detecting CGIN.
- Punch biopsies are an unreliable means of detecting CGIN.
- Excision of the transformation zone and part of the endocervical canal is the diagnostic and treatment method of choice for CGIN.
- Negative margins are good but not absolutely reliable markers of complete treatment.
- With precancerous glandular disease, the definitive treatment is hysterectomy, which may usually be deferred until the patient has completed her family.
- Conservative management of CGIN is justified in young women, assured of adequate follow-up, until the patient has completed her family, when hysterectomy should be considered.
- Follow-up should continue for 10 years or more, or until hysterectomy and for 1 year after hysterectomy.