CHAPTER 16.

Follow-up after treatment of cervical intraepithelial neoplasia (CIN)

International practice varies for almost every clinical circumstance, and follow-up after treatment of CIN is no exception. The availability of clinical, laboratory, and nursing staff as well as the cost to the patient of attendance for follow-up will influence the follow-up arrangements. The advice that follows is based on the available evidence and does not take into account which tests or facilities are available locally.

Traditionally, women have been invited to attend for a follow-up colposcopic examination and cervical smear at relatively frequent intervals for 1–2 years before being returned to routine screening in the community. Table 16.1 details advice in the United Kingdom in 2016 (NHS, 2016). Practice in most European countries is similar, although in office practice, more frequent attendance for colposcopy is often advised.

16.1 Risk of development of invasive disease in treated women

Treatment confers a profoundly reduced risk of developing cancer for women who have had SIL (Kalliala et al., 2005; McCredie et al., 2008). However, treated women remain at risk. Indeed, treated women have a 2–5-fold increased risk of developing cervical cancer compared with the general population (Soutter et al., 1997). Much of this increased risk may be attributed to poor compliance with long-term follow-up (Khalid et al., 2011; Soutter et al., 2006; Strander et al., 2007). It does not appear that the grade of abnormality or the type of treatment affects the long-term risk (Kalliala et al., 2005, 2007). The nightmare scenario for every colposcopist is to see a patient with cancer some years after treatment for cervical precancer. Such a case is shown in Fig. 16.1.

Some women are more at risk than others. Women who have positive margins at histology, i.e. incomplete excision, have a 6-fold increased risk of residual disease (Ghaem-Maghami et al., 2007). Women who are older than 50 years at the time of treatment (Flannelly et al., 2001) or who have a persistently positive oncogenic HPV test are also more likely to have residual disease. Women who have a large type 2 or type 3 TZ have a 3-fold increased risk of having incomplete excision reported at histology. For women with a large, endocervical TZ, particular attention should be paid to the SCJ during initial treatment, to avoid a second excision. In most women who have a positive margin, there is no need to do an automatic second excision, because the great majority

Table 16.1. Clinical guidelines of the NHS Cervical Screening Programme

Duration and frequency of follow-up after treatment for CIN under the HPV "test of cure" protocol
• Women who have been treated for CIN1, CIN2, or CIN3 should be invited 6 months after treatment for "test of cure" repeat cytology in the community. Patient compliance with follow-up protocols should be encouraged.
• Women with a sample that has been reported as negative, or as showing borderline changes or low-grade dyskaryosis, and whose HR-HPV test is negative should be recalled in 3 years, whatever their age. Where the 3-year test is negative, women older than 50 years can return to 5-yearly routine recall.
• Women with a sample that has been reported as negative, or as showing borderline changes or low-grade dyskaryosis, and whose HR-HPV report is positive should be referred for colposcopy.
• Women with a sample that has been reported as showing high-grade dyskaryosis should be referred for colposcopy. No HR-HPV test is required.
• Women with a sample that has been reported as negative, or as showing borderline changes or low-grade dyskaryosis, and whose HR-HPV test result is unavailable should undergo repeat cytology at 3 months.
• Women who reach 65 years must still complete the protocol and otherwise comply with national guidance.
• Women in annual follow-up after treatment for CIN are eligible for the HPV test of cure at their next screening test unless that test is carried out at colposcopy.

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HR-HPV, high-risk HPV; NHS, United Kingdom National Health Service.

of these women (86%) will have normal epithelium (Ghaem-Maghami et al., 2011). However, they do require more considered and perhaps longer follow-up in the clinic than those who have complete excision reported at histology. Finally, women who are older than 50 years *and also* have involved margins should have elective retreatment by way of excision (Flannelly et al., 2001).

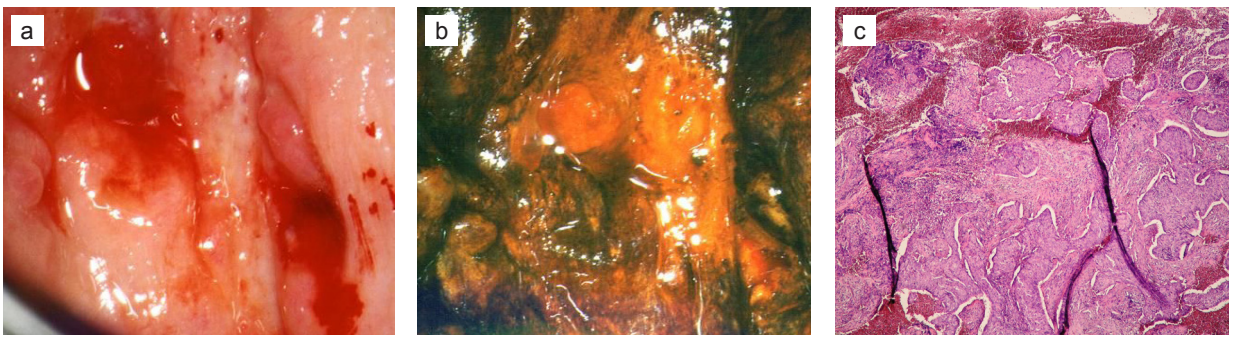
16.2 Current guidelines

Because most residual disease will be recognized in the first 1–2 years (Chew et al., 1999), follow-up testing should be comprehensive in these first 2 years. Until recently, the standard follow-up regime in most colposcopy centres has involved two or more cytology smears and two or more colposcopic examinations during the first 1–2 years, followed by regular cytology for 10 years or more. There is conflicting evidence about the effectiveness of colposcopy over cytology in detecting treatment failures, with some reporting that colposcopy enhances detection (Baldauf et al., 1998) and others reporting no advantage (Gardeil et al., 1997).

A visit to a colposcopy clinic offers other advantages, for example the opportunity to review the case history and counsel the patient about the need for longer-term follow-up, as well as the colposcopic recognition of cervical stenosis or possible functional incompetence. However, colposcopy is relatively expensive. In developing countries it is sometimes simply too difficult and too expensive for women to attend for colposcopic examination, and self-testing for high-risk HPV is a very reasonable alternative.

Self-testing for HPV has been shown to be superior to cytology collection by a physician in terms of sensitivity for CIN2 or greater (Lazcano-Ponce et al., 2011). A physician-taken HPV sample is even more

Fig. 16.1. This case reveals invasive cancer at the vaginal vault some 10 years after treatment for cervical precancer as HSIL-CIN3. (a, b) Low-power colposcopy images of the vaginal vault (a) before and (b) after the application of iodine. (c) Histopathology image; invasive disease is evident.



sensitive and is the gold standard test for post-treatment monitoring. There is very good evidence that HPV testing is more sensitive than cytology for detecting HSIL (Ronco et al., 2014). In the screening context, this means more sensitive detection of HSIL, less frequent testing, and lower surveillance costs (Uijterwaal et al., 2014).

16.3 Oncogenic HPV testing after treatment

The advantages of HPV testing make it the test of choice after treatment, when its high sensitivity and negative predictive value are so important (Arbyn et al., 2005).

Figs. 16.2 and 16.3 show meta-analyses of studies that compared high-risk HPV testing with cytology and with positive margin status for the detection of residual disease after treatment of CIN; HPV testing was superior in both comparisons. Several subsequent comparisons have confirmed the superiority of HPV testing as the best test of cure (Uijterwaal et al., 2014). Where cost is not a factor and facilities are available, there is also evidence that the recognition of HPV type 16 confers a particular risk of residual disease (Gök et al., 2007), but this test is still relatively expensive and is not yet universally available.

Perhaps not surprisingly, co-testing with cytology and oncogenic HPV is the most reassuring of all, and a negative co-test at both 6 months and 24 months carries a risk of finding HSIL during the subsequent 5 years of less than 1%, which is as low as that associated with a normal smear in a screened population (Kocken et al., 2011). The positivity rate for HPV testing after treatment falls steeply from 3 months to 12 months, and therefore it is prudent to perform the HPV test 12–18 months after treatment (Coupé et al., 2007).

16.4 Specific circumstances

16.4.1 Microinvasive disease and incomplete excision

Incomplete excision of microinvasive cancer should be managed, a priori, by a repeat excision without waiting for follow-up tests.

16.4.2 Adenocarcinoma in situ

The natural history of glandular precancer is less well documented than with squamous disease, and follow-up protocols should be even more rigorous. Because skip lesions occur in about 15% of cases

Fig. 16.2. Meta-analysis of studies comparing high-risk HPV testing with cytology for the detection of residual disease after treatment of CIN.

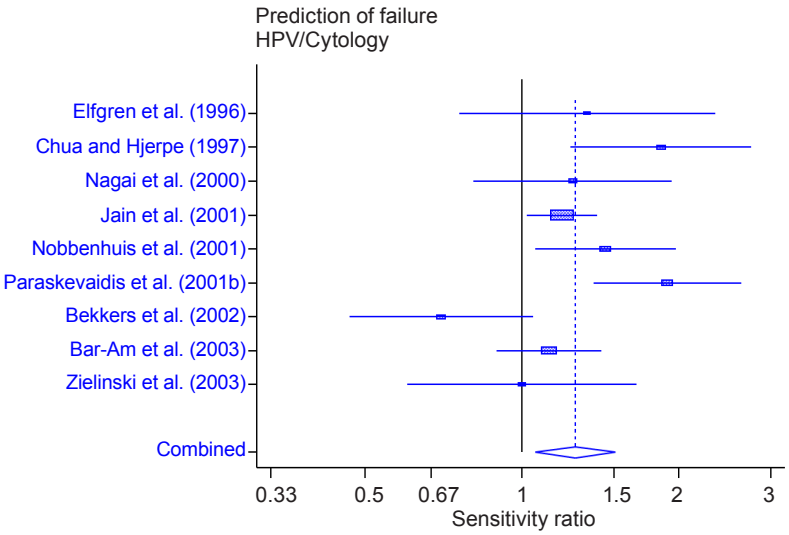
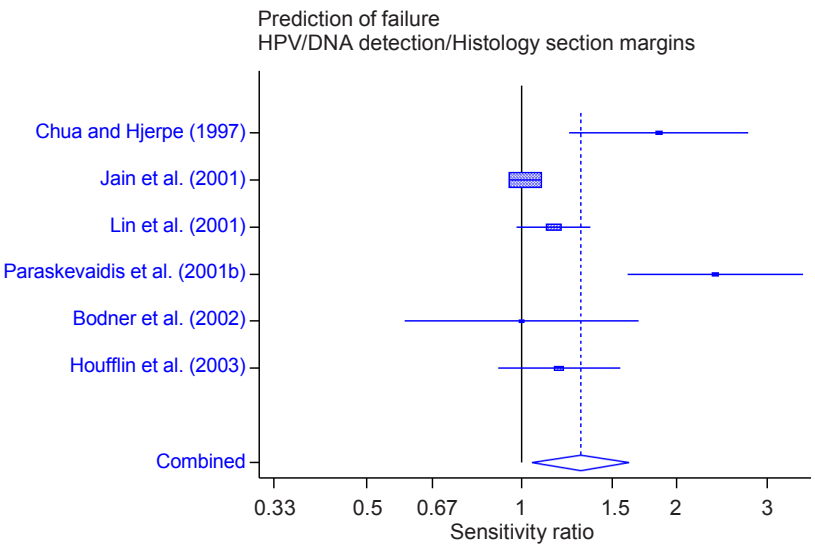


Fig. 16.3. Meta-analysis of studies comparing high-risk HPV testing with positive margin status for the detection of residual disease after treatment of CIN.



of glandular disease, margin status is less reassuring. Where there is any doubt about margin status, a repeat excision of endocervical epithelium should be performed. Also, residual/recurrent glandular disease occurs more frequently (15%) than with squamous disease. Follow-up of women treated for adenocarcinoma in situ should include cytology specimens taken from the endocervical canal separately to the ectocervical smear, and HPV testing should be performed on all follow-up cervical samples. When the patient has completed her family, a simple hysterectomy should be performed (NHS, 2010).

16.4.3 Duration of follow-up

Long-term studies have found a 5-fold increased risk of developing cervical cancer in women who have been treated for CIN, and this increased risk lasts for at least 20 years (Soutter et al., 2006). Therefore, most authorities advise follow-up for at least this long, although not necessarily in a clinic setting. Also, the profound protection afforded by a negative co-test (negative cytology and HPV testing) means that women may usually be followed up in the community.

16.4.4 Follow-up after hysterectomy

For women in whom previous frequent screening tests have been normal, there is no need for continued screening. Where a hysterectomy was done in part because of CIN and where the margins of excision were complete, it would seem prudent to perform co-testing at least annually for the first 2 years, and if these are both negative, then no further follow-up is necessary.

For women with incomplete or uncertain excision of CIN, follow-up should be conducted as if the cervix were still in situ (vault smear and HPV test at 6 months and 18 months, and annual combined tests for 20 years, regardless of the grade of the original disease).

16.5 Summary

Women being offered treatment for SIL or microinvasive disease should be advised that follow-up treatment is essential to reduce the risk of cancer to almost zero. Default from follow-up is probably the single most important reason for cancer development in women who have been treated for SIL. HPV testing is the most sensitive test of cure currently available. Self-testing is a reasonable alternative to attendance at a colposcopy clinic or doctor's office.

Key points

- Follow-up monitoring is crucial.
- Women who have been treated for suspected cervical precancer have a 5-fold increased risk of developing cervical cancer compared with women who have not had an abnormal smear.
- No method of treatment of CIN is 100% successful.
- The increased risk of residual or recurrent disease lasts for at least 20 years.
- Risk factors for residual disease include:
  - positive margins at histology;
  - older than 50 years at the time of treatment; and
  - positive oncogenic HPV test at follow-up after treatment.
- The main reason for the development of cancer after treatment is default from follow-up.
- Default rates may be improved by considering self-testing for oncogenic HPV.
- Co-testing with cytology and oncogenic HPV is superior to all other methods of monitoring women after treatment.