CHAPTER 13.

Microinvasive squamous cervical cancer

This chapter deals with microinvasive squamous cervical cancer (Fig. 13.1). It is an introduction to the disease and not a reference text. A gynaecologist caring for women with cervical cancer should, ideally, undertake a subspecialist training course.

13.1 Early preclinical microinvasive disease of the cervix (stages IA1 and IA2)

The management of cancer depends crucially on the stage of the disease. Microinvasive disease, or International Federation of Gynecology and Obstetrics (FIGO) stages IA1 and IA2, constitutes invasive cancer at its earliest stage. It has broken through the basement membrane but does not extend beyond a depth of 3 mm (stage IA1) or 5 mm (stage IA2) or a width of 7 mm.

The risk of lymph node involvement in stage IA1 disease is very low. Ostör (1993), in a study of several thousand cases, estimated the probability of lymph node involvement to be 0.1% if the depth of invasion was less than 1 mm (3 out of 2274 cases) and 0.5% if the depth was between 1 mm and 3 mm (7 out of 1324 cases).

Microinvasive disease is not often symptomatic but may present with abnormal per vaginal bleeding. The referral smear, if there is one, will usually report features of an HSIL but may occasionally describe specific cytological markers for invasion.

13.2 Clinical features of microinvasive disease

"Microinvasive disease" is a widely used term, which refers to very early disease that has breached the basement membrane but has not spread beyond the superficial stroma. Currently, the term is reserved for lesions with a depth of less than 3 mm (stage IA1) or 5 mm (stage IA2) and a width of less than 7 mm. Table 13.1 details the FIGO staging of early invasive squamous cervical cancer.

As noted above, these very early lesions are usually asymptomatic

Fig. 13.1. Low-power view of invasive squamous cervical cancer.

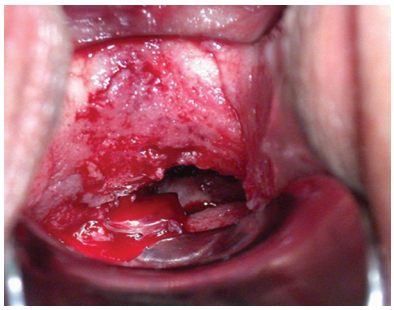


Table 13.1. FIGO staging of early invasive squamous cervical carcinoma

Stage of disease	Description
Stage 0	Precancer or squamous intraepithelial lesion (previously known as CIN)
Stage IA1	Microinvasive lesion Depth < 3 mm, width < 7 mm
Stage IA2	Microinvasive lesion Depth 3–5 mm, width < 7 mm
Stage IB1	Clinical lesion < 4 cm
Stage IB2	Clinical lesion > 4 cm

CIN, cervical intraepithelial neoplasia; FIGO, International Federation of Gynecology and Obstetrics.

and are recognized either colposcopically or, more usually, at histological examination of colposcopically directed biopsies.

A screening test may have been positive. Symptoms, when present, would usually be confined to intermenstrual or postcoital bleeding. There may be a history of previous treatment for cervical precancer or untreated HSIL. Default from follow-up of treated precancer is a common cause of subsequent development of cancer.

Fig. 13.2 shows histological sections of microinvasive disease. In Fig. 13.2a, malignant cells can be seen breaching the basement membrane and spilling into the underlying stroma.

13.3 Colposcopic recognition of microinvasive disease

The colposcopic features of microinvasive disease are not clearly distinguishable from those of HSIL. From a management perspective, it is preferable to know the diagnosis before treatment, because complete excision is so important. When the diagnosis of microinvasion is known, or suspected, it is perhaps worth excising a slightly larger margin of normal tissue around the TZ to allow the pathologist the best possible chance of determining the precise depth of invasion, the lesion margin status, the width and/or volume of the lesion, and, if present, lymphovascular space involvement (LVSI).

The colposcopic features of microinvasion are largely the exaggerated signs associated with HSIL, i.e. a high Swede score (see Annex 4). The lesions are often larger. The acetic acid uptake is faster, and the whiteness is denser and is sometimes described as oyster white. The vascular patterns of punctation and mosaicism are coarser. Also, particular vessel patterns are sometimes present (Fig. 13.3). These include vessel loops, corkscrew patterns, and pollarded vessels (Figs. 13.4–13.7). Completely bizarre and abnormally branching vessels may be present. Also, sometimes the ridge sign or inner border sign may be evident (Figs. 13.8 and 10.5h). Finally, the epithelium may be more friable than normal, and the edges of the lesion may easily peel off or strip away from the underlying stroma during colposcopic application of fluids or contact with cotton swabs

Fig. 13.2. Histological sections of (a, b) a very early stage of invasion: microinvasive disease; (c) stage IA1 disease at low-power magnification; (d) stage IA2 disease at low-power magnification.

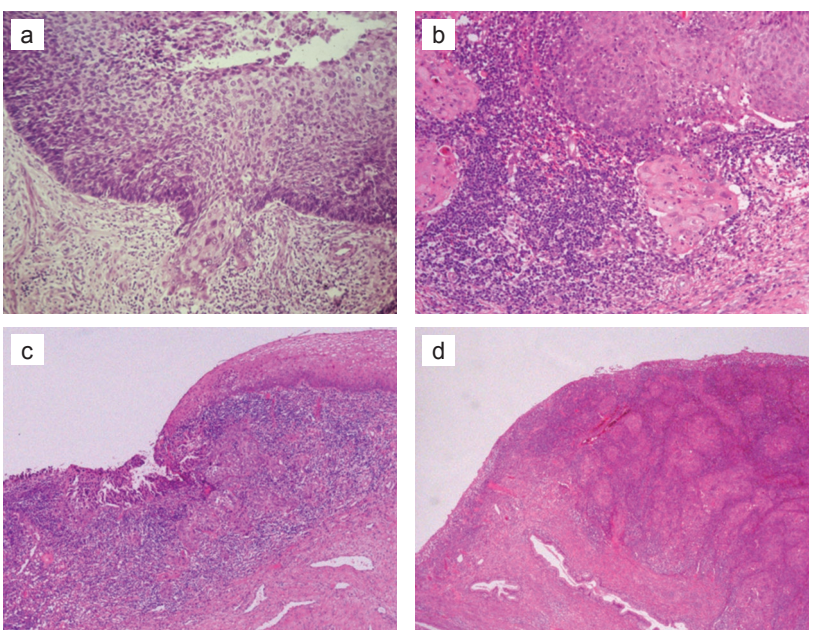


Fig. 13.3. Exaggerated colposcopic signs of HSIL in a case of microinvasion.

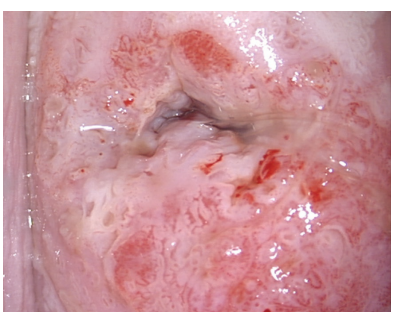


Fig. 13.4. Vascular patterns. (a–f) Abnormal blood vessel patterns (apart from mosaic and punctate patterns) are irregular in a variety of ways. Their common feature is lack of branching and any form of symmetry. (a) Wide hairpin-like vessel. (b) Waste thread vessel. (c) Tendril-like vessel. (d) Bizarre branching waste thread vessel. (e) Pollarded vessel. (f) Comma-shaped or tadpole vessel. Normal blood vessel patterns branch like a tree does. (g) Normal branching vascular patterns, often best seen stretched over a nabothian follicle.

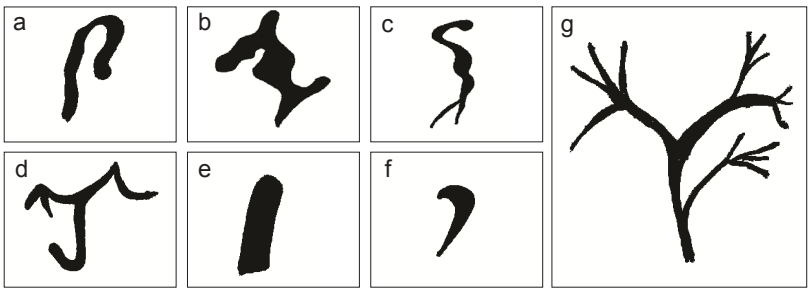


Fig. 13.5. (a) A normally branching tree. (b) A pollarded tree.

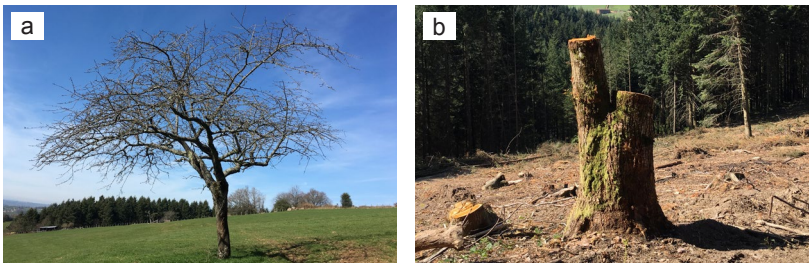


Fig. 13.6. An example of a pollarded vessel, at the centre of the image.

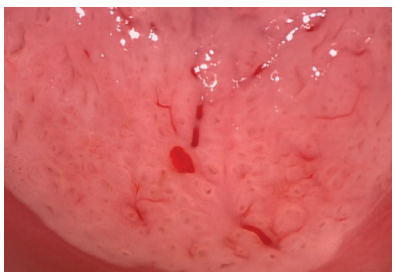


Fig. 13.7. Bizarre branching vessels, seen here using the green filter.

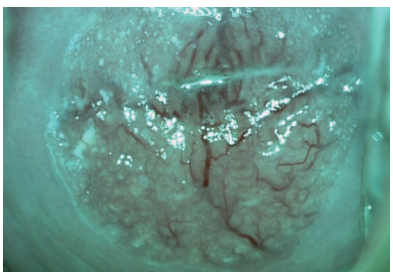


Fig. 13.8. The ridge sign, seen here in an island of acetowhite epithelium.

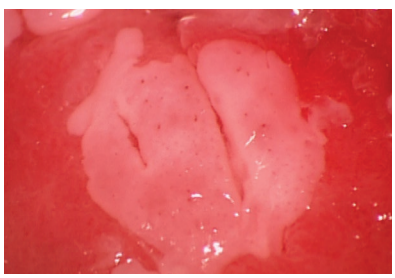
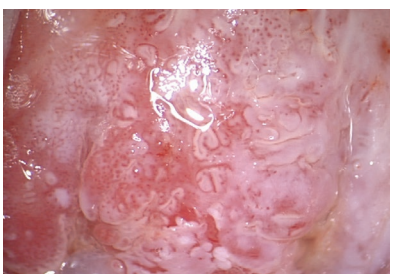


Fig. 13.9. Epithelial stripping, seen here at the 6 o'clock position in this case of microinvasion.



(Fig. 13.9). The colposcopist needs to be especially gentle in performing application of fluid and manipulation of the cervix when the diagnosis of microinvasion is suspected.

13.4 Management of suspected microinvasive disease

The diagnosis of microinvasion can only be made at histology. Furthermore, the stage of invasion can only be accurately assessed if the entire lesion is presented to the pathologist, preferably as one excised specimen.

Unfortunately, punch biopsies are unreliable when assessing possible microinvasion as they are sometimes not deep or wide enough for the pathologist to confidently recognize the disease or its extent. A small loop biopsy or removal of a wedge-shaped piece of tissue using a cold knife (a wedge biopsy) will usually provide an adequate specimen, but once the diagnosis of microinvasion is made or seriously suspected, the entire TZ with a clear margin of normal tissue should be excised as one piece. How this specimen is removed will vary; depending on the experience and expertise of the colposcopist, it is entirely reasonable to use LLETZ, SWETZ, laser excision, or cold-knife excision, providing that the colposcopist can ensure a sufficient margin of normal tissue surrounding the lesion. When there is any extent of endocervical involvement (type 2 or type 3 TZ), the procedure should excise a cylindrical specimen such that the upper extent of the specimen does not cut across or damage lesional tissue with diathermy (Figs. 12.6 and 12.7). For the inexperienced operator, it is probably wiser to perform the excision under general anaesthesia in an operating theatre.

Once the diagnosis has been made, the histology slides should be reviewed by the pathologist to assess as accurately as possible the

lesion's margin status and the depth and width of the invasive disease. LVSI should be actively sought. The case should then be discussed at a multidisciplinary team meeting or, at the very least, at a consultation between the colposcopist and the pathologist.

At the multidisciplinary team meeting, the depth and volume of invasive tissue should be discussed, as well as the degree, if any, of LVSI and the margin status. If there is any question of incomplete excision, which may occur when the diagnosis is first recognized at histology, a repeat excision should be performed. Once the stage of disease is confirmed, treatment may be decided. With microinvasive disease, the excisional treatment already performed may be adequate (Table 13.2).

Table 13.2. Treatment options for cervical cancer

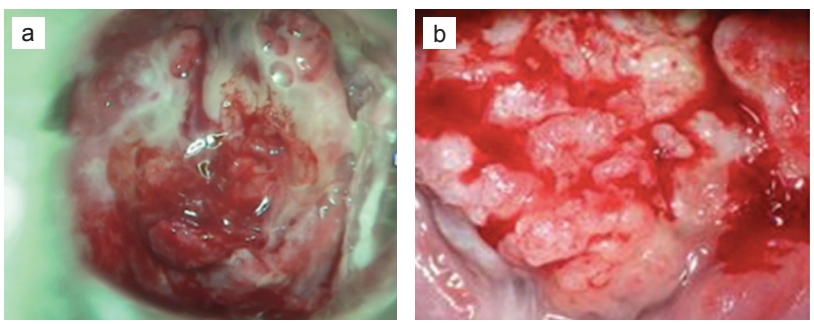
Stage of disease	Minimum treatment	Alternative treatments
Stage IA1	Complete excision of the transformation zone, usually as a type 3 excision	Simple hysterectomy
Stage IA2	Complete excision of the transformation zone, either as a type 3 excision or as a radical trachelectomy and Pelvic lymph node dissection	Radical hysterectomy and pelvic lymph node dissection
Stage IB	Radiotherapy	—
Stages II–IV	Radiotherapy	—

Cervical cancer staging is primarily a clinical assessment (Kurman et al., 2014). The stage is determined according to the size of the tumour and the degree of local and distant spread. The accurate staging of cervical cancer is the most important prognostic indicator for both patient and clinician, and its early and accurate assessment is crucial in determining appropriate therapy. It is detailed precisely in Table 13.1. Initial staging is a clinical assessment using speculum visualization and bimanual digital vaginal and rectal examination. Further assessment after initial suspicion will, of course, include colposcopy and biopsy as well as cystoscopy, endocervical sampling, hysteroscopy, urinary tract imaging, and local and general X-ray and computed tomography (CT) imaging, magnetic resonance imaging (MRI), and even laparoscopic nodal assessment. Unfortunately, imaging techniques will not be available in every unit, and a careful clinical examination will then be even more crucial. The investigations in common use are listed in Table 13.4. The clinical features of invasive cervical cancer are very variable, because the disease in its earliest stage is not visible to the naked eye and in its late stages will have involved several systems.

The early clinical features of cervical cancer are, in many respects, similar to those of cervical infection and include an offensive vaginal discharge and abnormal per vaginal bleeding as well as a friable-looking cervix on naked-eye inspection. Chlamydial infection, protozoal infection (tuberculosis, schistosomiasis, or amoebiasis), and other cervical infections may mimic cervical cancer. Investigation for these infections should include a microbiology and virology screen as well as a colposcopy and biopsy. In later-stage disease, a colposcopy will be of limited value.

The diagnosis of invasive cervical cancer can only be made on the basis of a histological report. Clinical assessment is simply unreliable. Fig. 13.10 shows two cases of cervical disease with exactly similar symptoms (abnormal per vaginal bleeding and an offensive vaginal discharge). Fig. 13.10a shows a case of cervical tuberculosis, and Fig. 13.10b shows a case of invasive cervical cancer. In the case of tuberculosis, the cervix returned to normal after a full course of antituberculous therapy.

Fig. 13.10. (a) A case of tuberculous cervicitis, presenting with postcoital bleeding, intermenstrual bleeding, and offensive vaginal discharge. (b) A case of cervical cancer, presenting with postcoital bleeding, intermenstrual bleeding, and offensive vaginal discharge.



13.5 Stage 1B and greater

Clinical features that may herald cervical cancer include abnormal per vaginal bleeding, particularly contact bleeding. Vaginal discharge and pelvic pain are often present in late-stage disease. Symptoms usually reflect local disease. For example, with lateral spread into the parametrium, ureteric obstruction may occur. Spread to the lateral pelvic sidewall may cause sciatic pain or even

Table 13.3. FIGO classification of malignant tumours of the cervix

Stage	Description
Stage I	Stage I is carcinoma strictly confined to the cervix; extension to the uterine corpus should be disregarded. The diagnosis of both stages IA1 and IA2 should be based on microscopic examination of removed tissue, preferably a cone, which must include the entire lesion.
Stage IA	Invasive cancer identified only microscopically. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm in diameter.
Stage IA1	Measured invasion of the stroma no greater than 3 mm in depth and no wider than 7 mm in diameter.
Stage IA2	Measured invasion of the stroma greater than 3 mm but no greater than 5 mm in depth and no wider than 7 mm in diameter.
Stage IB	Clinical lesions confined to the cervix or preclinical lesions greater than stage IA. All gross lesions even with superficial invasion are stage IB cancers.
Stage IB1	Clinical lesions no greater than 4 cm in size.
Stage IB2	Clinical lesions greater than 4 cm in size.
Stage II	Stage II is carcinoma that extends beyond the cervix but does not extend into the pelvic wall. The carcinoma involves the vagina, but not as far as the lower third.
Stage IIA	No obvious parametrial involvement. Involvement of up to the upper two thirds of the vagina.
Stage IIB	Obvious parametrial involvement, but not into the pelvic sidewall.
Stage III	Stage III is carcinoma that has extended into the pelvic sidewall. On rectal examination, there is no cancer-free space between the tumour and the pelvic sidewall. The tumour involves the lower third of the vagina. All cases with hydronephrosis or a non-functioning kidney are stage III cancers.
Stage IIIA	No extension into the pelvic sidewall but involvement of the lower third of the vagina.
Stage IIIB	Extension into the pelvic sidewall or hydronephrosis or a non-functioning kidney.
Stage IV	Stage IV is carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.
Stage IVA	Spread of the tumour into adjacent pelvic organs.
Stage IVB	Spread to distant organs.

FIGO, International Federation of Gynecology and Obstetrics.

lymphoedema. When the tumour spreads anteriorly, it may cause any urinary symptom, including haematuria, bladder pain, and urinary retention, or even symptoms associated with a vesicovaginal fistula. Posterior involvement will often cause back pain, tenesmus, and symptoms associated with a rectovaginal fistula. With late-stage disease, the symptoms of severe anaemia are common.

On examination of the cervix, early-stage disease (microinvasion) may not be evident to the naked eye, but as the disease progresses, it becomes grossly apparent. Invasive cervical cancer will typically present as an ulcerative or proliferative tumour, which bleeds readily on contact and will often be infected. When tumours are exophytic and grow out into the vaginal space, they tend to become polypoid or papillary and appear as a cauliflower-like growth. When tumours are endophytic, they may infiltrate extensively, with very little epithelial revelation. Endophytic growths may expand the cervix for several centimetres before breaching the epithelial surface. Endophytic cancers often produce a hard, barrel-shaped cervix. Some cancers may be both endophytic and exophytic. Infection is commonly associated with exophytic cancers. With advanced cervical cancer, the cervix usually bleeds on contact. Regional

Table 13.4. Available investigations for staging cervical cancer

Type of investigation	Available investigations
Clinical assessment	• Bimanual vaginal examination • Digital rectal examination • Speculum examination
Endoscopic	• Colposcopy • Cystoscopy • Hysteroscopy
Ultrasonography	
Radiological	• Intravenous urography imaging • Chest and body X-ray examination • Lymphangiography • Computed tomography (CT) scan • Magnetic resonance imaging (MRI) • Positron emission tomography (PET) scan
Histopathological	• Colposcopically directed biopsy • Endocervical curettage • Lymph node sampling

lymph node involvement occurs relatively early.

Later-stage disease will have spread to bladder, rectum, bone (particularly the spine), and the psoas muscle. Ultimately, distant metastases will involve para-aortic lymph nodes, lungs, liver, bone, and other organs.

13.6 Histopathology

In the absence of systematic, high-coverage cervical precancer screening, approximately 90–95% of cases of invasive cervical disease are squamous cell carcinomas (Fig. 13.11a and b), and less than 10% are adenocarcinomas (Fig. 13.11c).

Microscopically, most squamous cell carcinomas appear as infiltrating networks of bands of neoplastic cells with intervening stroma, with a great deal of variation in growth pattern, cell type, and degree of differentiation. The cervical stroma separating the bands of malignant cells is infiltrated by lymphocytes and plasma cells. These malignant cells may be subdivided into keratinizing and non-keratinizing types. The tumours may be well, moderately, or poorly differentiated carcinomas. Approximately 50–60% are moderately differentiated cancers, and the remainder are evenly distributed between the categories of well-differentiated and poorly differentiated cancers.

Keratinizing squamous cell carcinoma is composed of characteristic whorls of epidermoid cells containing central nests of keratin (keratin pearls) (Fig. 13.11a). The nuclei are large and hyperchromatic with coarse chromatin. Intercellular bridges are visible, along with keratohyalin granules and cytoplasmic keratinization. Only few mitotic figures are visible.

Non-keratinizing squamous cell carcinoma (Fig. 13.11b) appears as irregular, jagged nests of plump polygonal cells invading the cervical stroma. There may be dyskeratosis and intercellular bridges. Cellular and nuclear polymorphism is more obvious, and mitotic figures are quite numerous. Keratin pearls are usually absent.

Other, uncommon types of squamous cell carcinoma include condylomatous squamous cell carcinoma (also called verrucous carcinoma), papillary squamous cell carcinoma, lymphoepithelioma-like carcinoma, and squamotransitional cell carcinoma.

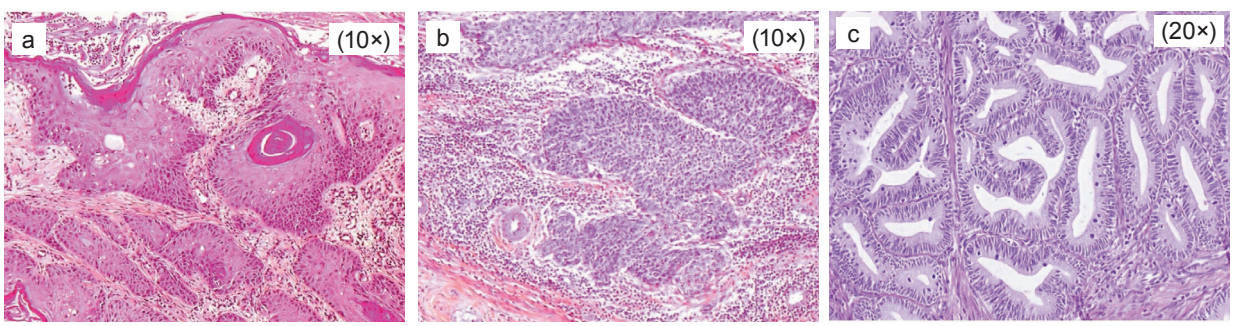
In the absence of screening, adenocarcinoma constitutes approximately 5% of all cervical cancers. Usually, it arises in the endocervical canal from the glandular epithelium.

The most common form of adenocarcinoma is the endocervical cell type, where the abnormal glands are of various shapes and sizes with budding and branching. Most of these tumours are well to moderately differentiated. The glandular elements are arranged in a complex pattern. Papillae may project into the gland lumen and from the surface. Some of the cells may contain a moderate to large amount of mucin.

The other types of adenocarcinoma include intestinal-type, signet ring cell adenocarcinoma, adenoma malignum, villoglandular papillary adenocarcinoma, endometrioid adenocarcinoma, and papillary serous adenocarcinoma. Adenosquamous carcinoma includes tumours with glandular and squamous growth patterns.

The presence of tumour cells within the lumen of a capillary space is evidence of aggressive growth potential in both squamous cell carcinoma and adenocarcinoma of the cervix, and has been correlated with increased risk of regional lymph node metastasis. Invasion of blood vessels occasionally occurs and is a particularly poor prognostic sign, correlating with distant, bloodborne metastasis. Although the cytological features associated with invasive squamous cell carcinoma of the cervix have been well described, cytology is not a reliable method of diagnosing invasive lesions. The definitive diagnosis of an invasive cancer is always based on histopathology. A tissue specimen taken from the periphery of the

Fig. 13.11. (a) Keratinizing well-differentiated squamous cell carcinoma of the cervix. (b) Non-keratinizing well-differentiated squamous cell carcinoma of the cervix. (c) Adenocarcinoma of the cervix.

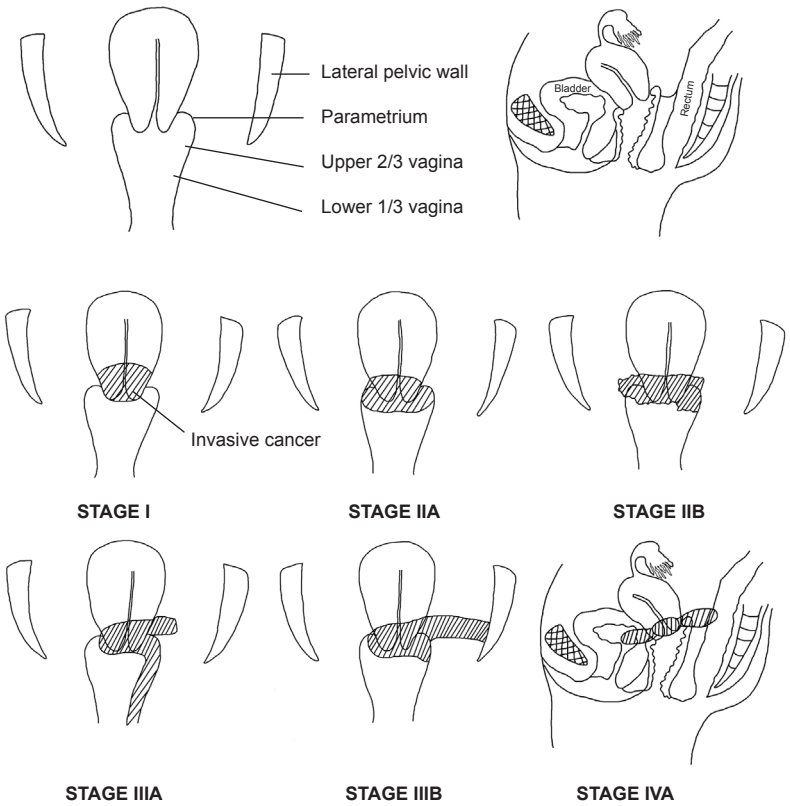


growth is preferred for diagnosis, because this is more likely to contain morphologically intact tumour tissue, whereas a biopsy specimen taken from the centre of a growth may contain necrotic material, which will compromise the accuracy of histological diagnosis. Also, punch biopsies may not procure enough tissue to allow for a confident histological diagnosis. A large punch biopsy, a small loop biopsy, or a wedge biopsy (or a TZ excision biopsy) will allow for a definitive diagnosis.

The best management for a patient with cervical cancer depends crucially on the accurate staging of the disease as well as a comprehensive evaluation of the patient's general physical condition and her individual circumstances. Currently, optimal care cannot be offered to all women in LMICs because of the lack of equipment, lack of trained staff, competing health-care needs, and other factors. Case mortality differences between LMICs and developed countries reflect the lack of resources in LMICs as well as the relative deficiency in health for many low-income women in LMICs.

The global standard staging system is that provided by FIGO. Fig. 13.12 is a diagram of this cervical cancer staging system. It is primarily a clinical staging system, based on the tumour size and the extent of spread from the original epithelium source. As well as clinical assessment of tumour size and spread, an array of methods, if available, will allow more precise staging of disease (Table 13.4). Usually, as well as clinical assessment, X-ray assessment, intravenous pyelogram, skeletal X-ray, and cystoscopy will be available in dedicated cancer centres in LMICs. After as full an assessment as possible has been undertaken, the findings should be documented precisely and the stage determined. Then a management plan may be outlined to the patient and treatment may be begun.

Fig. 13.12. Diagrammatic representation of cervical cancer staging.



13.7 Treatment of squamous microinvasive cervical cancer

The treatment of squamous cervical cancer may be surgical and/or radiotherapeutic. Radiotherapy may be used for all stages of squamous cervical cancer, although in practice few centres would treat stage IA1 disease other than by surgical excision. Surgery is usually reserved for disease confined to the cervix. Radiotherapy regimes vary and may be used exclusively or to shrink the tumour in preparation for surgical excision.

There have been more than 20 different definitions of microinvasion in the literature (Marsden et al., 2006). In summary, the most recent and widely used is the FIGO classification (Kurman et al., 2014), which limits microinvasive disease to a depth of 5 mm and a width of 7 mm (stage IA1 limits the depth to 3 mm and stage IA2 to 5 mm). The likelihood of there being positive lymph nodes in stage IA1 disease is remote. For stage IA1 disease, a simple but complete and intact (i.e. one-piece) excision is the treatment of choice. Chapters 14 and 15 deal, respectively, with the surgical and non-surgical treatment of later-stage disease.

Key points

- The stage of disease is the most crucial factor in managing invasive disease.
- The colposcopic appearances of microinvasion are similar to but often more exaggerated than those associated with high-grade but pre-invasive or intraepithelial change.
- Excisional therapy is the mainstay of treatment for microinvasion.