

A histological section of the uterine cervix, stained with hematoxylin and eosin (H&E). The image shows numerous glandular structures, likely endocervical glands, which are lined by a single layer of columnar epithelial cells. The glands are filled with a pinkish, eosinophilic material, possibly mucus. The surrounding stroma is composed of connective tissue and contains scattered inflammatory cells. The overall architecture is organized into a regular pattern of glands separated by thin layers of stroma.

## CHAPTER 5

### **Tumours of the Uterine Cervix**

Cervical carcinoma is the second most common cancer in women worldwide. Chronic infection with human papillomavirus (HPV) is a necessary event in the evolution of cervical carcinomas. The incidence of cervical cancer, which is predominantly of the squamous cell type, has markedly declined in many developed countries, mainly due to cytological screening programmes. Today, more than 80% of women dying from cervical cancer live in developing countries. It is anticipated that preventive HPV vaccination will become available in the near future.

## WHO histological classification of tumours of the uterine cervix

<b>Epithelial tumours</b>		<b>Neuroendocrine tumours</b>	
<b>Squamous tumours and precursors</b>		Carcinoid	8240/3
Squamous cell carcinoma, not otherwise specified	8070/3	Atypical carcinoid	8249/3
Keratinizing	8071/3	Small cell carcinoma	8041/3
Non-keratinizing	8072/3	Large cell neuroendocrine carcinoma	8013/3
Basaloid	8083/3	Undifferentiated carcinoma	8020/3
Verrucous	8051/3		
Warty	8051/3	<b>Mesenchymal tumours and tumour-like conditions</b>	
Papillary	8052/3	Leiomyosarcoma	8890/3
Lymphoepithelioma-like	8082/3	Endometrioid stromal sarcoma, low grade	8931/3
Squamotransitional	8120/3	Undifferentiated endocervical sarcoma	8805/3
Early invasive (microinvasive) squamous cell carcinoma	8076/3	Sarcoma botryoides	8910/3
Squamous intraepithelial neoplasia		Alveolar soft part sarcoma	9581/3
Cervical intraepithelial neoplasia (CIN) 3 /	8077/2	Angiosarcoma	9120/3
squamous cell carcinoma in situ	8070/2	Malignant peripheral nerve sheath tumour	9540/3
Benign squamous cell lesions		Leiomyoma	8890/0
Condyloma acuminatum		Genital rhabdomyoma	8905/0
Squamous papilloma	8052/0	Postoperative spindle cell nodule	
Fibroepithelial polyp			
<b>Glandular tumours and precursors</b>		<b>Mixed epithelial and mesenchymal tumours</b>	
Adenocarcinoma	8140/3	Carcinosarcoma (malignant müllerian mixed tumour; metaplastic carcinoma)	8980/3
Mucinous adenocarcinoma	8480/3	Adenosarcoma	8933/3
Endocervical	8482/3	Wilms tumour	8960/3
Intestinal	8144/3	Adenofibroma	9013/0
Signet-ring cell	8490/3	Adenomyoma	8932/0
Minimal deviation	8480/3		
Villoglandular	8262/3	<b>Melanocytic tumours</b>	
Endometrioid adenocarcinoma	8380/3	Malignant melanoma	8720/3
Clear cell adenocarcinoma	8310/3	Blue naevus	8780/0
Serous adenocarcinoma	8441/3		
Mesonephric adenocarcinoma	9110/3	<b>Miscellaneous tumours</b>	
Early invasive adenocarcinoma	8140/3	Tumours of germ cell type	
Adenocarcinoma in situ	8140/2	Yolk sac tumour	9071/3
Glandular dysplasia		Dermoid cyst	9084/0
Benign glandular lesions		Mature cystic teratoma	9080/0
Müllerian papilloma			
Endocervical polyp		<b>Lymphoid and haematopoietic tumours</b>	
<b>Other epithelial tumours</b>		Malignant lymphoma (specify type)	
Adenosquamous carcinoma	8560/3	Leukaemia (specify type)	
Glassy cell carcinoma variant	8015/3		
Adenoid cystic carcinoma	8200/3	<b>Secondary tumours</b>	
Adenoid basal carcinoma	8098/3		

<sup>1</sup> Morphology code of the International Classification of Diseases for Oncology (ICD-O) {921} and the Systematized Nomenclature of Medicine (<http://snomed.org>). Behaviour is coded /0 for benign tumours, /2 for in situ carcinomas and grade 3 intraepithelial neoplasia, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

<sup>2</sup> Intraepithelial neoplasia does not have a generic code in ICD-O. ICD-O codes are only available for lesions categorized as squamous intraepithelial neoplasia grade 3 (e.g. cervical intraepithelial neoplasia 3) = 8077/2, squamous cell carcinoma in situ = 8070/2, glandular intraepithelial neoplasia grade 3 = 8148/2 and adenocarcinoma in situ = 8140/2.



## TNM and FIGO classification of carcinomas of the uterine cervix

TNM classification <sup>1,2</sup>			T3a	IIIA	Tumour involves lower third of vagina, no extension to pelvic wall	
T – Primary Tumour			T3b	IIIB	Tumour extends to pelvic wall or causes hydronephrosis or non-functioning kidney	
TNM Categories	FIGO Stages		T4	IVA	Tumour invades mucosa of bladder or rectum or extends beyond true pelvis	
TX		Primary tumour cannot be assessed	Note: The presence of bullous oedema is not sufficient to classify a tumour as T4.			
T0		No evidence of primary tumour	M1	IVB	Distant metastasis	
Tis	0	Carcinoma in situ (preinvasive carcinoma)	N – Regional Lymph Nodes <sup>3</sup>			
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)	NX		Regional lymph nodes cannot be assessed	
T1a	IA	Invasive carcinoma diagnosed only by microscopy. All macroscopically visible lesions - even with superficial invasion - are T1b/Stage IB	N0		No regional lymph node metastasis	
T1a1	IA1	Stromal invasion no greater than 3.0 mm in depth and 7.0 mm or less in horizontal spread	N1		Regional lymph node metastasis	
T1a2	IA2	Stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less	M – Distant Metastasis			
Note: The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumour from the epithelial-stromal junction of the adjacent most superficial epithelial papilla to the deepest point of invasion.			MX		Distant metastasis cannot be assessed	
Vascular space involvement, venous or lymphatic, does not affect classification.			M0		No distant metastasis	
			M1		Distant metastasis	
Stage Grouping						
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a2/IA2	Stage 0	Tis	N0	M0
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension	Stage IA	T1a	N0	M0
T1b2	IB2	Clinically visible lesion more than 4 cm in greatest dimension	Stage IA1	T1a1	N0	M0
T2	II	Tumour invades beyond uterus but not to pelvic wall or to lower third of the vagina	Stage IA2	T1a2	N0	M0
T2a	IIA	Without parametrial invasion	Stage IB	T1b	N0	M0
T2b	IIB	With parametrial invasion	Stage IB1	T1b1	N0	M0
T3	III	Tumour extends to pelvic wall, involves lower third of vagina, or causes hydronephrosis or non-functioning kidney	Stage IB2	T1b2	N0	M0
			Stage IIA	T2a	N0	M0
			Stage IIB	T2b	N0	M0
			Stage IIIA	T3a	N0	M0
			Stage IIIB	T1, T2, T3a	N1	M0
				T3b	Any N	M0
			Stage IVA	T4	Any N	M0
			Stage IVB	Any T	Any N	M1

<sup>1</sup> {51,2976}.

<sup>2</sup> A help desk for specific questions about the TNM classification is available at <http://tnm.uicc.org>.

<sup>3</sup> The regional lymph nodes are the paracervical, parametrial, hypogastric (internal iliac, obturator), common and external iliac, presacral, and lateral sacral nodes.

<sup>1</sup> {51,2976}.

<sup>2</sup> A help desk for specific questions about the TNM classification is available at <http://tnm.uicc.org>.

<sup>3</sup> The regional lymph nodes are the paracervical, parametrial, hypogastric (internal iliac, obturator), common and external iliac, presacral, and lateral sacral nodes.

# Epithelial tumours

M. Wells  
A.G. Östör  
C.P. Crum  
S. Franceschi  
M. Tommasino

J.M. Nesland  
A.K. Goodman  
R. Sankaranarayanan  
A.G. Hanselaar  
J. Albores-Saavedra

This section covers the entire spectrum of invasive squamous and glandular carcinomas and their intraepithelial precursor lesions that originate for the most part from the transformation zone of the cervix. In addition, benign epithelial tumours are described which are not considered precursors of invasive cancer.

## Epidemiology

In 1990 cervical cancer comprised 10% of cancers in women for a total of approximately 470,000 cancer cases world-wide [846], representing the third most common cancer in females and the most common cancer in Sub-Saharan Africa, Central America, South Central Asia and Melanesia. Approximately 230,000 women die annually from cervical cancer, and over 190,000 of those are from developing countries. Zimbabwe and India stand out not only for their high incidence but also for an unfavourable incidence to mortality ratio. Some relatively high-incidence countries can also be found in Eastern and Central Europe [1638].

The incidence of cervical cancer has been declining in the last three or four decades in most developed countries predominantly due to the introduction of cervical screening programmes. Other reasons include a decrease in parity [1943] and improved living conditions [226]. In women under 45 years of age, however, mortality rates are levelling off or increasing in several countries [226]. Stable or, in some instances, upward mortality trends in high-risk populations in Latin America [2395] and Eastern Europe [1638] are especially disturbing. Finally, adenocarcinoma of the cervix, which accounts for 10-15% of all cervical cancers, has shown an increased incidence in the last three decades [3028].

## Aetiology

Sexually transmitted virus, human papillomavirus (HPV), is the major aetiological factor, as shown by:

(1) the identification of HPV DNA in most cervical cancer biopsy specimens worldwide [3044];

(2) relative risks (RRs) for cervical squamous cell and adenocarcinoma of greater than 70 for several high-risk HPV types in case-control studies [1199, 1293];

(3) RRs of approximately 10 for women with HPV infection in cohort studies [3143].

Several host and environmental factors contribute, however, to enhance the probability of HPV persistence and progression to cervical neoplasia. Immune impairment, whether due to immunosuppressive treatments [274] or human immunodeficiency (HIV) infection [913, 920], increases the risk of cervical intraepithelial neoplasia (CIN) and invasive cancer of the cervix 5 to 10-fold. Among HPV-DNA positive women long-term use of oral contraceptives [1911], high parity [1943], tobacco smoking [3164] and certain sexually transmitted infections, such as Chlamydia trachomatis [2733], are associated with a RR between 2 and 4.

## HPV-induced carcinogenesis

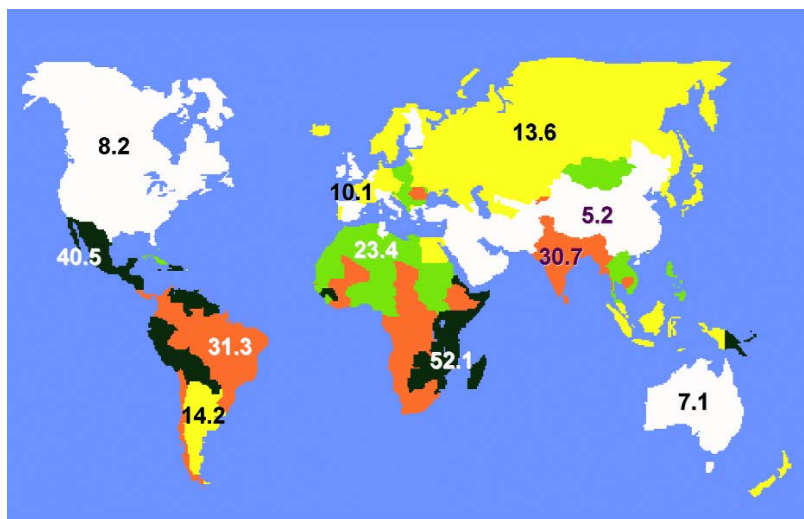
The products of two early genes, *E6* and *E7*, have been shown to play a major role

in HPV-mediated cervical carcinogenesis. This has been established by three different lines of evidence:

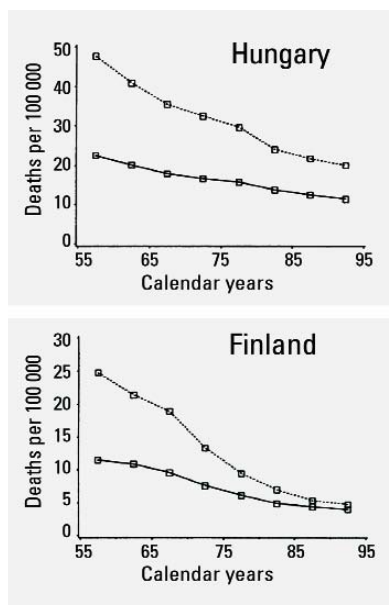
(1) The first indication came from the analysis of HPV-infected cells, which showed that viral DNA is randomly integrated in the genome of the majority of cervical carcinomas. Integration leads to disruption of several viral genes with preservation of only the *E6* and *E7* genes, which are actively transcribed.

(2) The discovery that *E6* and *E7* proteins are able to induce cellular transformation in vitro confirmed their oncogenic role. Immortalized rodent fibroblasts can be fully transformed by expression of HPV 16 *E6* or *E7* protein. These rodent cells acquire the ability to grow in an anchorage-independent manner and are tumorigenic when injected in nude mice. In addition, HPV 16 *E6* and *E7* are able to immortalize primary human keratinocytes, the natural host cell of the virus. In agreement with the in vitro assays, transgenic mice co-expressing both viral genes exhibit epidermal hyperplasia and various tumours.

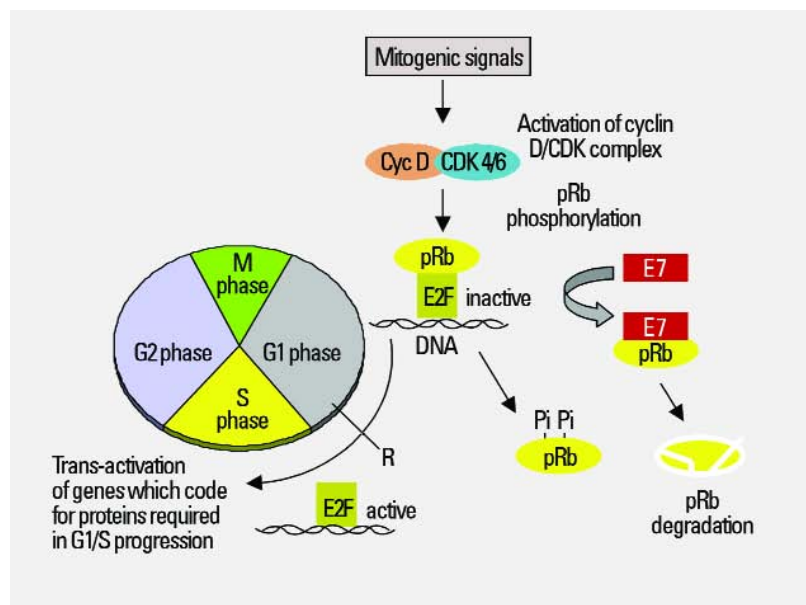
(3) Finally, biochemical studies have clarified the mechanism of action of *E6*



**Fig. 5.01** Global burden of cervical cancer. Age-standardized incidence rates (ASR) per 100,000 population and year. From Globocan 2000 [846].



**Fig. 5.02** A marked decrease in the mortality of uterine cancer (cervix and corpus) has been achieved in many countries. Upper curves: age group 35-64 years. Lower curves: all age groups combined. From F. Levi et al. {1637}.



**Fig. 5.03** Deregulation of the restriction point (R) by HPV16 E7. In quiescent cells, pRb is present in a hypophosphorylated form and is associated with transcription factors, e.g. members of the E2F family, inhibiting their transcriptional activity. When quiescent cells are exposed to mitogenic signals, G1 specific cyclin D/CDK complexes are activated and phosphorylate pRb in mid-G1 phase, causing release of active E2F and progression through the restriction point (R). E7 binding to pRb mimics its phosphorylation. Thus, E7 expressing cells can enter S phase in the absence of a mitogenic signal. From M. Tommasino {2938a}.

and E7. The viral oncoproteins are able to form stable complexes with cellular proteins and alter, or completely neutralize, their normal functions.

The best understood interactions of E6 and E7 with cellular proteins are those involving the tumor suppressor proteins TP53 and pRb, respectively. Both interactions lead to a rapid degradation of the cellular proteins via the ubiquitin pathway. The major role of TP53 is to safeguard the integrity of the genome by inducing cell cycle arrest or apoptosis, while pRb plays a key role in controlling the correct G1/S transition acting at the restriction point (R) of the cell cycle. Therefore, loss of TP53 and pRb functions results in abrogation of apoptosis and in unscheduled proliferation. Both events greatly increase the probability of HPV-infected cells evolving towards malignancy.

### Clinical features

#### Signs and symptoms

Early invasive cancers can be asymptomatic. As the tumour grows and becomes exophytic, vaginal bleeding and discharge are the two most common

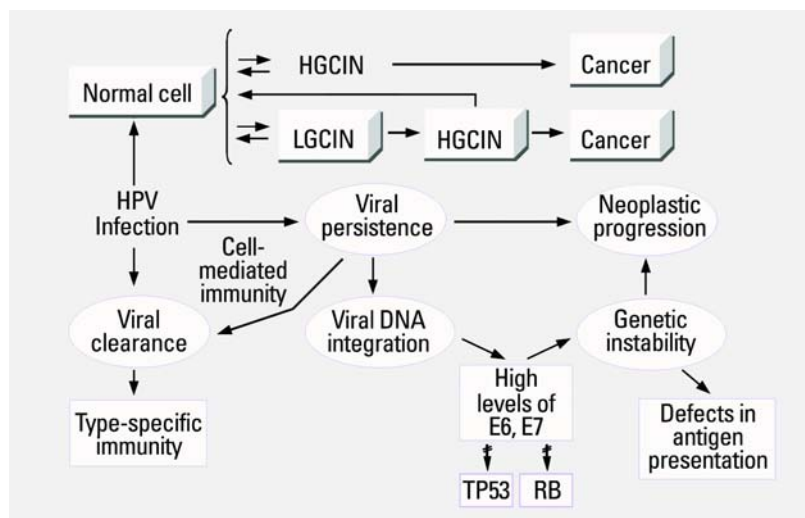
symptoms. With lateral growth into the parametrium, the ureters become obstructed. If both ureters are obstructed, the patient presents with anuria and

uraemia. Pelvic sidewall involvement can cause sciatic pain and, less commonly, lymphoedema of the lower extremities. Anterior tumour growth in advanced

**Table 5.01**

Risk factors for cervical cancer: HPV infection vs. persistence and malignant transformation.

Risk factor	HPV infection	HPV persistence and transformation	Reference
Multiple sex partners	+	n.e.	{320}
Partner's multiple partners	+	n.e.	{320}
Poor hygiene	+	n.e.	{193}
Absence of male circumcision	+	+	{423}
Immunodeficiency, HIV	+	+	{920}
High parity	n.e.	+	{1944}
Oral contraceptives	n.e.	+	{1911}
Smoking	n.e.	+	{2826}
STDs other than HPV	n.e.	+	{108,2734}
Poor nutritional status	n.e.	+	{2324}
STDs = Sexually transmitted diseases (especially <i>C. trachomatis</i> ). n.e. = No evidence for being a risk factor at this time.			



**Fig. 5.04** Mechanisms of human papillomavirus (HPV) carcinogenesis. LG = Low grade, HG = High grade, CIN = Cervical intraepithelial neoplasia, RB = Retinoblastoma gene.

stage disease causes urinary frequency, bladder pain and haematuria. Direct extension into the bladder may cause urinary retention from bladder outlet obstruction and eventually a vesicovaginal fistula. Posterior extension leads to low back pain, tenesmus and rectovaginal fistula. On examination cervical cancer may appear as a red, friable, exophytic or ulcerated lesion. Rectovaginal palpation can detect induration or nodularity of the parametria in advanced lesions.

#### Colposcopy

The colposcope is a noninvasive binocular instrument with a magnification of 6 to 40-fold designed to examine the cervix. The area of the cervix where the transformation of columnar to metaplastic squamous epithelium occurs is known as the transformation zone. Since most cervical neoplasia arises in the transformation zone, the relevant colposcopic signs are observed within its limits. Whenever the transformation zone is not seen in its entirety, the colposcopy is termed "unsatisfactory".

Colposcopy involves the application of 4-5% acetic acid on the cervix and is based on the colour and margin of the aceto-white epithelium, the surface contour, the arrangement of the blood vessels and iodine staining. Abnormal colposcopic findings include leukoplakia, aceto-white epithelium, punctation and mosaic and atypical vessels [372,417,2705]. White keratotic lesions apparent before the application of acetic acid are termed "leukoplakia".

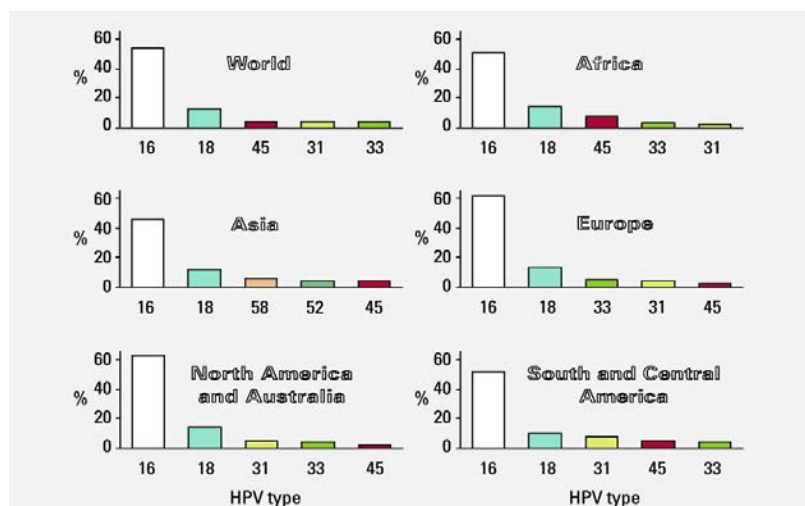
Aceto-white epithelium, which appears only after contact with acetic acid, is most marked with cervical intraepithelial neoplasia (CIN) and early invasive cancer. Significant lesions are sharply delineated, densely opaque and persist for several minutes. Glandular lesions produce more subtle changes [3159].

Fine or coarse stippling within aceto-white epithelium produced by the end-on view of finger-like intraepithelial capillaries is called punctation. A mosaic pattern arises when the stromal ridges containing the blood vessels subdivide the aceto-white epithelium into blocks of varying size and shape. Atypical tortuous vessels with bizarre irregular branches showing gross variation in calibre are suggestive of early invasive disease. Cervical neoplasia fails to stain deeply with iodine due to the lack of glycogen. Variations in quality and quantity of the above atypical appearances help in differentiating cervical neoplasia from physiological, benign, infective, inflammatory and reactive changes in the cervix. Colposcopy and histopathology are complementary to the diagnosis and management of CIN.

#### Tumour spread and staging

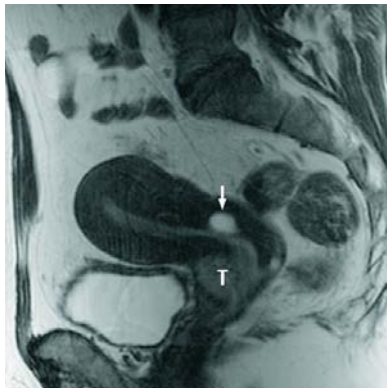
Cervical cancer is the only gynaecological cancer that is clinically staged by physical examination, chest X-ray, intravenous pyelogram, cystoscopy and proctoscopy. The staging of cervical tumours is by the TNM/FIGO classification [51,2976].

One-half of early invasive foci originate from the surface epithelium [2349]. The uterine corpus is commonly involved as the tumour expands. Ovarian metastasis is rare, occurring more frequently in bulky cancers and in adenocarcinomas as compared to squamous cell cancers [1914,1966]. Clinically undetected parametrial spread is identified by histological examination in 31-63% of stage IB



**Fig. 5.05** Worldwide distribution of HPV types in invasive carcinoma of the cervix. From G.M. Clifford et al. [528].





**Fig. 5.06** Sagittal T2-weighted MRI of a cervical carcinoma (T). This projection facilitates preoperative staging. The arrow indicates the presence of ovula Nabothi.

and 58% of stage IIA patients [221]. Cervical cancers spread along fascial planes. As the parametria are invaded, the incidence of pelvic node involvement increases to 36% [221]. All para-aortic nodal metastases are associated with pelvic node metastasis; 11.5% of stage IB, 26.7% of stage IIA and 40% of stage IIB cancers had pelvic node involvement and 2.1%, 0% and 7.2% of these had para-aortic node involvement respectively [2514]. In contrast to the orderly lymphatic spread of cervical cancers, lung and brain metastases reflect haematogenous spread and are an aberrant behaviour that cannot be predicted by stage of disease [1737].

### Precursor lesions

Precursor lesions of squamous cell carcinoma and adenocarcinoma are well defined with the exception of low grade cervical glandular intraepithelial neoplasia, i.e. glandular dysplasia or glandular atypia.

### Somatic genetics

#### TP53

Inactivation of *TP53* appears to play a key role in the development of cervical carcinoma [1178,2911] either because binding with the E6 protein of oncogenic HPV types inactivates it or because it undergoes mutation. Patterns of *TP53* immunoreactivity suggest also that *TP53* inactivation is important in the progression from intraepithelial to invasive neoplasia [1659,2004,2954]. *TP53* reactivity has been demonstrated in both in situ

and invasive adenocarcinoma [495, 1807]. *TP53* gene alterations are rare in minimal deviation adenocarcinoma [2937] and are not found in villoglandular adenocarcinomas [1363].

#### Loss of heterozygosity

Loss of heterozygosity (LOH) has been detected in multiple chromosomal regions in CIN (3p, 5p, 5q, 6p, 6q, 11q, 13q, 17q), invasive carcinoma (3p, 6p, 6q, 11q, 17p, 18q) and lymph node metastases from cervical carcinomas (3p, 6p, 11q, 17p, 18q, X) [263,666, 1119,1444,1445,1584,1706,1712]. These changes accumulate in a fashion that parallels the progression of cervical carcinoma and indicate the stepwise nature of cervical carcinogenesis. Chromosomal instability is probably an early event. At least two tumour suppressor genes on 6p related to invasive cervical carcinoma have been demonstrated in 50% of cases of low grade CIN and in 90% of cases of high grade CIN [447].

#### FHIT gene

Recent studies have found that abnormalities of the *FHIT* (fragile histidine triad) gene, including loss of heterozygosity, homozygous deletions and aberrant transcripts, are common in cervical carcinomas, implicating this gene in cervical carcinogenesis [1938,2807,3187]. *FHIT* abnormalities have been observed

in various histological types of cervical carcinomas [2616].

*FHIT* gene abnormalities have been found in both CIN and invasive carcinoma, but the incidence did not increase with progression to invasion or with advancing clinical stage [1964]. By contrast, another group [3188] found aberrations of *FHIT* to be more common in invasive carcinomas than in CIN suggesting that *FHIT* gene inactivation occurred as a late event in cervical carcinogenesis, after the tumour had acquired an invasive character

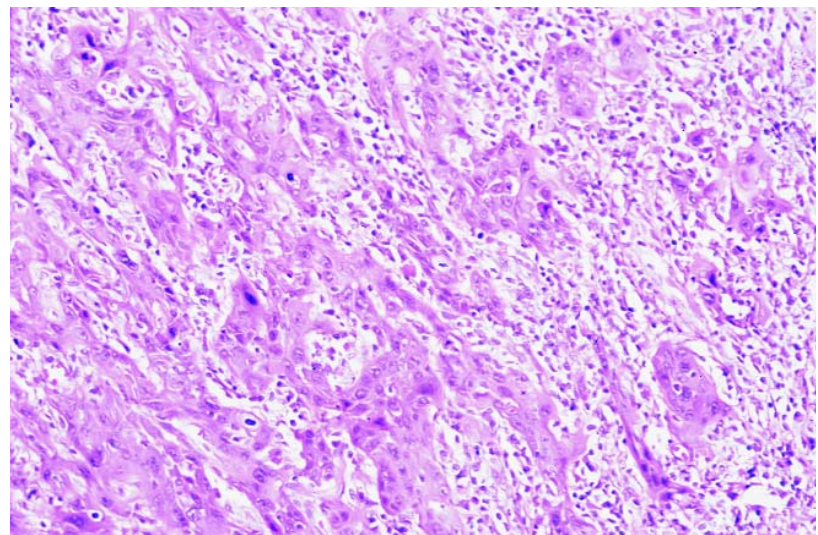
#### Monoclonality

The finding that early invasive carcinoma is monoclonal supports the view that monoclonality is not a late event due to clonal competition or selection [1086]. Nearly all cases of high grade CIN have been found to be monoclonal, whilst only a small proportion of low grade CIN are monoclonal [489,789,2184].

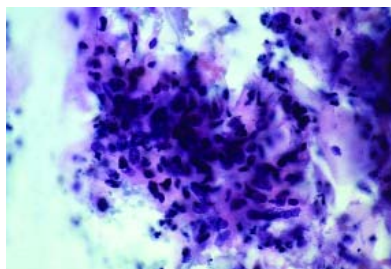
Recurrent chromosome aberrations have been demonstrated in both invasive cervical squamous carcinoma and high grade CIN, there being a consistent chromosome gain at 3q and deletions at 3p [1208,1469].

#### Genetic susceptibility

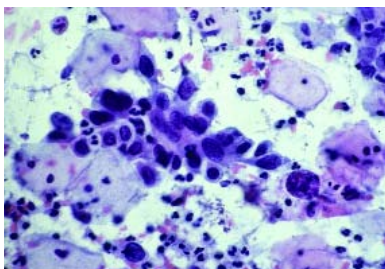
Few studies have addressed familial clustering in cervical carcinoma [743, 2230], the largest report being based on



**Fig. 5.07** Squamous cell carcinoma, non-keratinizing type. The tumour has a tentacular, or "finger-like" infiltrative pattern.



**Fig. 5.08** Keratinizing squamous cell carcinoma. Note the partly spindle-shaped cells with eosinophilic cytoplasm and hyperchromatic nuclei.



**Fig. 5.09** Non-keratinizing squamous cell carcinoma. There is a syncytium with anisokaryosis, irregular distributed coarsely chromatin and nucleoli.

the Swedish Family-Cancer Database {1184}. The relative risk when the mother or a daughter was affected by cervical cancer was 2. An aggregation of tobacco-related cancers and cancers linked with HPV and immunosuppression was found in such families. Thus, familial predisposition for cervical cancer is likely to imply genes which modulate immune response, e.g. human leukocyte antigen (HLA) haplotypes {2524} and/or shared sexual or lifestyle factors in family members.

### Prognosis and predictive factors

#### Clinical criteria

The clinical factors that influence prognosis in invasive cervical cancer are age, stage of disease, volume, lymphatic spread and vascular invasion {370,663, 673,818,970,1506,2525,2672,2782}. In a large series of cervical cancer patients treated by radiation therapy, the frequency of distant metastases (most frequently to the lung, abdominal cavity, liver and gastrointestinal tract) was shown to increase with increasing stage of disease from 3% in stage IA to 75% in stage IVA {818}.

Radiotherapy and surgery produce similar results for early invasive cancer (stages IB and IIA). More advanced lesions (IIB to IV) are treated with a combination of external radiotherapy and intracavitary radiation. Randomized phase III trials have shown a significant overall and disease free survival advantage for cisplatin-based therapy given concurrently with radiotherapy {1063, 2908}. A significant benefit of chemoradiation on both local (odds ratio 0.61) and distant recurrence (odds ratio 0.57) has been observed. The absolute benefit with combined therapy on overall survival was 16%. Based on this evidence, concurrent chemotherapy with radiothera-

py is emerging as the new standard of care for advanced cervical cancer.

#### Histopathological criteria

Among histopathological variables based on histological findings and not included in the staging system for cervical cancer {1532}, the grading of tumours does not seem to be a strong predictive factor {3233}. In non-squamous cell carcinomas the only histological type of cervical cancer of prognostic significance is small cell carcinoma {68}. There is some evidence that women with adenocarcinoma and adenosquamous carcinoma have a poorer prognosis than those with squamous cell carcinoma after adjustment for stage {2314}.

#### Genetic predictive factors

**TP53.** The prognostic value of TP53 immunoreactivity in cervical carcinoma is controversial. Some have found no association between p53 overexpression or the presence of mutant p53 protein and clinical outcome {1267,2251}, whilst others have reported that TP53 expression identifies a subset of cervical carcinomas with a poor prognosis {2969}.

**c-erbB.** Frequent amplification of c-erbB-2 has been documented in cervical carcinoma {2634}, and c-erbB-2 immunostaining has been found to be significantly associated with poor survival and was considered to be a marker of high risk disease {1998}. Additionally, c-erbB-2 immunostaining was found to be an important prognostic factor for predicting tumour recurrence in cervical carcinomas treated by radiotherapy {1967, 2026}. On the other hand, overexpression of c-erbB-3 oncoprotein in squamous, adenosquamous and adenocarcinomas of the cervix showed no association with clinical outcome {1267}

**c-myc.** c-myc amplification has been demonstrated in CIN and invasive cervical carcinoma {110,666,2004} suggesting that it is important in early cervical carcinogenesis. Moreover, c-myc overexpression correlates with high risk HPV-positive neoplasia and with cellular proliferation {666}. It has been claimed that an increased level of c-myc transcripts is strongly indicative of a poor prognosis in early stage cervical carcinoma {1314} but not in late stage disease {2823}.

## Squamous tumours and precursors

### Definition

Primary squamous epithelial tumours of the uterine cervix, either benign or malignant.

### ICD-O codes

Squamous cell carcinoma	8070/3
Keratinizing	8071/3
Non-keratinizing	8072/3
Basaloid	8083/3
Verrucous	8051/3
Warty	8051/3
Papillary	8052/3
Lymphoepithelioma-like	8082/3
Squamotransitional cell	8120/3
Microinvasive squamous cell carcinoma	8076/3
Cervical intraepithelial neoplasia 3	8077/2
squamous cell carcinoma in situ	8070/2
Squamous papilloma	8052/0

## Squamous cell carcinoma

### Definition

An invasive carcinoma composed of squamous cells of varying degrees of differentiation.

### Macroscopy

Macroscopically, squamous cell carcinoma may be either predominantly exophytic, in which case it grows out from the surface, often as a papillary or polypoid excrescence, or else it may be mainly endophytic, such that it infiltrates into the surrounding structures without much surface growth.



### Histopathology

There have been few recent developments in the histological diagnosis of frankly invasive squamous cell carcinoma of the cervix {362,1201}. They vary in their pattern of growth, cell type and degree of differentiation. Most carcinomas infiltrate as networks of anastomosing bands with intervening stroma and appear as irregular islands, sometimes rounded, but more usually angular and spiked. Often, particularly in small tumours, CIN may be found on the surface and at the edge of the invasive tumour, and, occasionally, difficulty may be encountered in distinguishing between invasive islands and CIN involving crypts. Similarly, invasion cannot be excluded when neoplastic squamous epithelium shows features of CIN 2 or 3 but underlying stroma is not present.

A number of histological grading systems have been proposed that depend upon the type and degree of differentiation of the predominant cell {2794}. A simpler classification is a modification of the four grades of Broders {350} and subdivides the tumours into well differentiated (keratinizing), moderately differentiated and poorly differentiated types. Approximately 60% are moderately differentiated, and the remaining tumours are evenly distributed between the well and poorly differentiated groups.

A simple two-tiered classification is recommended, keratinizing and non-keratinizing, to avoid nosological confusion with small cell carcinoma, a term that should be reserved for tumours of neuroendocrine type.

The cervical stroma separating the islands of invasive carcinoma is usually infiltrated by a variety of cell types, mainly lymphocytes and plasma cells. A markedly eosinophilic stromal response {262} or a foreign body type giant cell reaction is occasionally seen.

A variety of histological types of squamous cell carcinoma have been described.

#### Keratinizing

These tumours contain keratin pearls composed of circular whorls of squamous cells with central nests of keratin. Intercellular bridges, keratohyaline granules and cytoplasmic keratinization are usually observed. The nuclei are usually large and hyperchromatic with coarse chromatin. Mitotic figures are not fre-

quent and are usually seen in the less-well differentiated cells at the periphery of the invasive masses.

In cytological preparations the cells usually have bizarre shapes with mostly eosinophilic cytoplasm and large, irregular, hyperchromatic nuclei. Necrotic debris is present.

#### Non-keratinizing

These tumours are composed of generally recognizable polygonal squamous cells that may have individual cell keratinization and intercellular bridges, but keratin pearls are absent. Cellular and nuclear pleomorphism is more obvious than in the well differentiated tumours, and mitotic figures are usually numerous. In cytological preparations the cells are solitary or arranged in syncytia and show anisokaryosis. The nuclei are relatively large with unevenly distributed, coarsely granular chromatin and may have irregular nucleoli

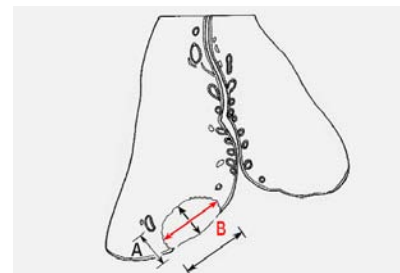
#### Basaloid

Basaloid squamous cell carcinoma is composed of nests of immature, basal type squamous cells with scanty cytoplasm that resemble closely the cells of squamous carcinoma in situ of the cervix. Some keratinization may be evident in the centres of the nests, but keratin pearls are rarely present. In the vulva this tumour has been associated with HPV infections, predominantly type 16 {1541,2936}.

This underrecognized variant of squamous cell carcinoma is an aggressive tumour with basaloid features {1057}. This tumour along with adenoid cystic carcinoma is at one end of the spectrum of basaloid tumours of the cervix. At the opposite end are low grade lesions such as adenoid basal carcinoma. To avoid confusion in the diagnosis of a cervical tumour with basaloid features, the term "basaloid carcinoma" should be avoided {1057}.

#### Verrucous

Verrucous carcinoma is a highly differentiated squamous cell carcinoma that has a hyperkeratotic, undulating, warty surface and invades the underlying stroma in the form of bulbous pegs with a pushing border. The tumour cells have abundant cytoplasm, and their nuclei show minimal atypia. Features of HPV infection are not evident. Verrucous carcinomas



**Fig. 5.10** Schematic representation of the FIGO definition of stage 1A carcinoma of the cervix. A: Depth of invasion no greater than 5 mm; B: Horizontal spread 7 mm or less.

have a tendency to recur locally after excision but do not metastasize. They are distinguished from condyloma by their broad papillae that lack fibrovascular cores and the absence of koilocytosis. Verrucous carcinoma is distinguished from the more common types of squamous cell carcinoma in that it shows no more than minimal nuclear atypia.

#### Warty

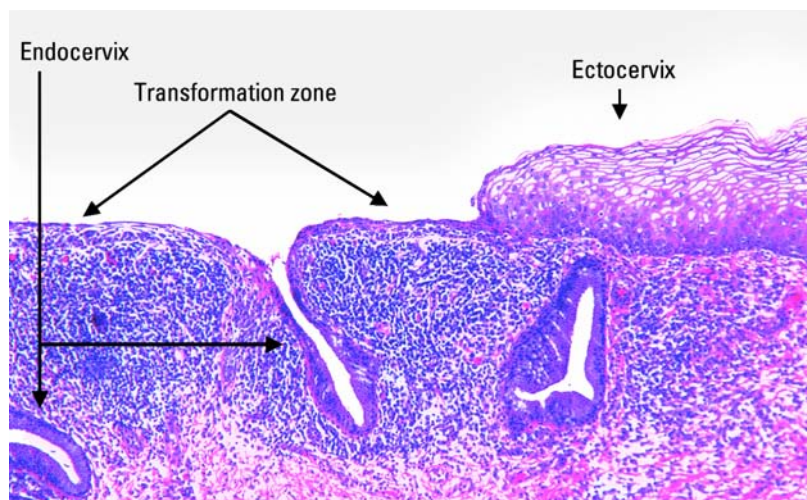
This lesion is defined as a squamous cell carcinoma with a warty surface and cellular features of HPV infection {720, 1541,2936}. High risk HPV-DNA is typically detected {2936}. It is also referred to as condylomatous squamous cell carcinoma.

#### Papillary

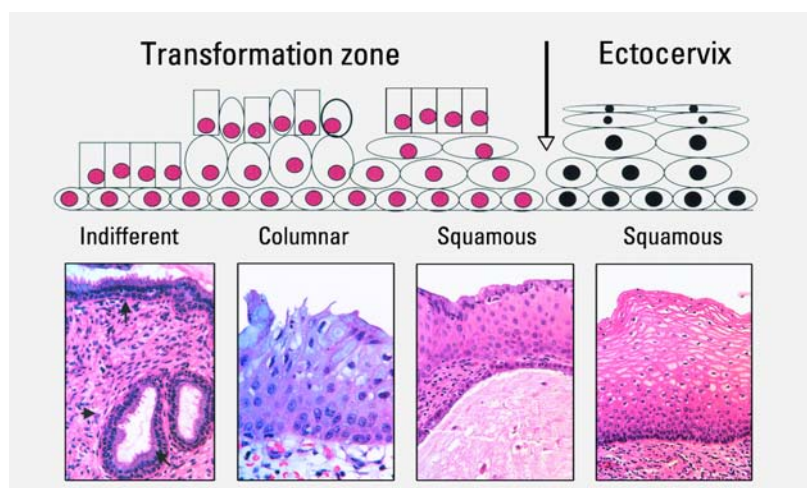
This is a tumour in which thin or broad papillae with connective tissue stroma are covered by epithelium showing the features of CIN. Whilst a superficial biopsy may not reveal evidence of invasion, the underlying tumour is usually a typical squamous cell carcinoma {345,2333}. Such tumours are positive for HPV type 16. Papillary squamous cell carcinoma differs from warty squamous carcinoma by the inconspicuous keratinization and lack of cellular features of HPV infection and from transitional cell carcinoma by its squamous cell differentiation {345}.

#### Lymphoepithelioma-like

Histologically, lymphoepithelioma-like carcinoma is strikingly similar to the nasopharyngeal tumour of the same name. It is composed of poorly defined islands of undifferentiated cells in a background intensely infiltrated by lym-



**Fig. 5.11** Transformation zone of the cervix. Photomicrograph of the early (immature) cervical transformation zone consisting of a thin layer of basal cells between the ectocervical and endocervical mucosa.



**Fig. 5.12** Transformation zone of the cervix. Schematic of the transformation zone (upper) illustrating the range of differentiation beyond the original squamocolumnar junction (vertical arrow). This area supports (from left to right) reserve cells that are indifferent (yet uncommitted, arrows) or committed to squamous and columnar differentiation as depicted in the photomicrographs below.

phocytes. The tumour cells have uniform, vesicular nuclei with prominent nucleoli and moderate amounts of slightly eosinophilic cytoplasm. The cell borders are indistinct, often imparting a syncytial-like appearance to the groups. Immunohistochemistry identifies cytokeratins within the tumour cells and T-cell markers in the majority of the lymphocytes. The presence of an intense chronic inflammatory reaction in a tumour indicates a cell-mediated immune reaction, and some evidence suggests that lymphoep-

ithelioma-like carcinoma of the cervix may have a favourable prognosis. Using the polymerase chain reaction to examine frozen tissue from a lymphoepithelioma-like carcinoma of the cervix, Epstein-Barr virus (EBV) genomic material was not identified in a case from the United States [3084]. On the other hand EBV DNA was identified in 11 of 15 lymphoepithelioma-like carcinomas from Taiwan, whereas HPV DNA was uncommon (3 of 15) suggesting that EBV may play a role in the aetiology of this tumour

in their Asian population [2957]. It is of note that EBV was not identified in a case analysed from Spain [1696]. Thus, if EBV plays a role in the genesis of this tumour, it exhibits geographical variation.

#### ***Squamotransitional carcinoma***

Rare transitional cell carcinomas of the cervix have been described that are apparently indistinguishable from their counterpart in the urinary bladder. They may occur in a pure form or may contain malignant squamous elements [56,66,1488]. Such tumours demonstrate papillary architecture with fibrovascular cores lined by a multilayered, atypical epithelium resembling CIN 3. The detection of HPV type 16 and the presence of allelic losses at chromosome 3p with the infrequent involvement of chromosome 9 suggest that these tumours are more closely related to cervical squamous cell carcinomas than to primary urothelial tumours [1672,1742]. Furthermore, these tumours are more likely to express cytokeratin 7 than 20, which suggests only a histological, rather than an immunophenotypic, resemblance to transitional epithelium [1488]. There is no evidence that this tumour is related to transitional cell metaplasia [1140,3085], an infrequently occurring somewhat controversial entity in the cervix.

#### ***Early invasive squamous cell carcinoma***

##### **Definition**

A squamous cell carcinoma with early stromal invasion, the extent of which has not been precisely defined, and a low risk of local lymph node metastasis.

##### **Synonym**

Microinvasive squamous cell carcinoma.

##### **Histopathology**

Certain features of high grade CIN increase the likelihood of identifying early invasion. These include:

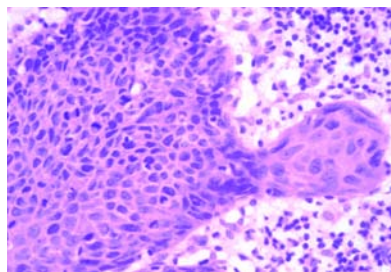
- (1) Extensive CIN 3,
- (2) Widespread, expansile and deep extension into endocervical crypts.
- (3) Luminal necrosis and intraepithelial squamous maturation [57].

The first sign of invasion is referred to as early stromal invasion; this is an unmeasurable lesion less than 1 mm in depth that can be managed in the same way as high grade CIN. The focus of early

stromal invasion often appears to be better differentiated than the overlying CIN. Early stromal invasion is encompassed in the term microinvasive carcinoma.

The criteria for the diagnosis of microinvasive carcinoma were historically based on the depth of invasion, and the ascribed upper limit has varied in the literature from 3 to 5 mm. Microinvasive carcinoma now equates most closely to FIGO stage IA, the definition of which includes both the depth and horizontal dimension of the tumour. The current FIGO staging is controversial because it does not recognize early stromal invasion as a separate entity [371]. Whether microinvasive carcinoma should include FIGO Stage IA2 because there is a significantly increased risk of local lymph node metastasis between 3 and 5 mm depth of invasion has also been questioned. Pooled data indicate that a maximum depth of invasion of 3 mm or less is associated with a risk of lymph node metastasis of <1% and a risk of an invasive recurrence of 0.9%. On the other hand, invasion of 3.1-5.0 mm is associated with an overall risk of lymph node metastases of 2% and a recurrence rate of 4% [2138]. Microinvasive squamous cell carcinoma is usually associated with stromal oedema and a stromal desmoplastic and lymphocytic response, features that aid in its distinction from crypt involvement by CIN. Immunohistochemical stains for CD31 and CD34 may aid in the recognition of lymphatic vascular space involvement.

Preclinical invasive carcinomas of the cervix with dimensions greater than those acceptable as stage IA carcinoma should be designated by the histopathologist simply as stage IB carcinomas.



**Fig. 5.13** Early squamous cell carcinoma of the cervix. Early stromal invasion is indicated by a bud of more mature squamous cells extending from a focus of in situ carcinoma.

**Table 5.02**

Classification of HPV-associated intraepithelial lesions of the cervix.

Term	HPV risk category	Comparison of classification systems		
		Two-tiered CIN	Dysplasia/CIS	SIL
Exophytic condyloma	Low risk	—	—	LGSIL
Squamous papilloma	Low risk	—	—	LGSIL
Flat condyloma	Low and high risk	—	—	LGSIL
CIN 1	Low and high risk	Low grade CIN	Mild dysplasia	LGSIL
CIN 2	High risk	High grade CIN	Moderate dysplasia	HGSIL
CIN 3	High risk	High grade CIN	Severe dysplasia/CIS	HGSIL
CIN = Cervical intraepithelial neoplasia SIL = Squamous intraepithelial lesion CIS = Carcinoma in situ		LG = Low grade HG = High grade		

"Finger-like" or "confluent" patterns of stromal invasion are of questionable clinical significance and probably are a reflection of a greater depth of stromal invasion.

### Cervical intraepithelial neoplasia

#### Definition

The spectrum of CIN representing the precursor lesions of cervical squamous cell carcinoma [2368].

#### Synonyms

Dysplasia/carcinoma-in-situ, squamous intraepithelial lesion.

#### Epidemiology

The risk of CIN is closely linked to the number of sexual partners and to HPV exposure. It is highest in early reproductive life [1160]. HPV is detected in as many as 39% of adolescents in a single screening visit [2451], and 20% of women under age 19 in a sexually transmitted disease clinic developed CIN 2 or 3 [1513]. The strong association between HPV 16 and high grade CIN coupled with follow-up studies suggests that infections by this virus induce a high grade lesion over a relatively short period of time [586,1513,1699]. The risk of CIN drops substantially in the fourth and fifth decades, coinciding with a sharp reduction in frequency of HPV attributed to the development of immunity to HPV and

elimination of the virus from the genital tract in most women. Other factors influencing risk include immunological, such as HIV infection, and other host factors, including coincident cervical infections and HLA status.

#### Aetiology

At puberty there is a change in the anatomical relationships of the lower part of the cervix composed of squamous epithelium, an original squamocolumnar junction and endocervical columnar epithelium. There is eversion of the columnar epithelium, which undergoes squamous metaplasia through a sequence of reserve cell hyperplasia, immature squamous metaplasia and mature squamous metaplasia with the formation of a new squamocolumnar junction. These histological changes are entirely physiological. However, it is this epithelium of the cervical transformation zone that is particularly susceptible to oncogenic stimuli.

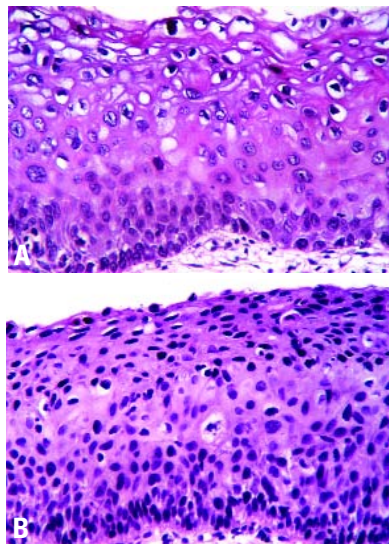
In the last 25 years "flat" and exophytic condylomata of the cervix and CIN have been linked by an association with HPVs, many of them weakly or strongly associated with cancer (intermediate and high risk HPVs) [586,737,1014,1841,2305]. Although some HPVs are not associated with cervical cancer (low risk HPVs), the majority are associated with high risk HPVs [1699]. High risk HPV infection may present histologically as CIN 1, although certain infections, such as HPV type 16,



have a strong association with high grade CIN lesions [587,1088,1699, 1878,3127]. CIN represents the preinvasive counterpart of invasive cervical squamous cell carcinoma, and there is now abundant evidence for its malignant potential. However, there is no inevitability about neoplastic progression; such lesions may regress, remain phenotypically stable or progress [2137].

### Histopathology

Conventionally, these are subjectively divided into three grades: CIN 1, 2 and 3, though the histological features represent a diagnostic continuum. Increasingly, there is a tendency to use a two-tiered classification of low and high grade CIN that equates to CIN 1 and CIN 2 and 3 respectively. These precursors may also be referred to as low and high grade squamous intraepithelial lesion (SIL) [2177]. Because of the inherent difficulty in distinguishing pure HPV infection from unequivocal CIN 1 in flat, non-condylomatous epithelium (sometimes confusingly referred to as flat condyloma), HPV infection alone is included in the low grade SIL category, a terminology that has been more widely accepted by cytopathologists [1612]. The relationship of the varying terminology is shown in Table 5.1.



**Fig. 5.14** **A** Cervical intraepithelial neoplasia (CIN 1). The upper two-thirds of the epithelium show maturation and focal koilocytosis. There is mild atypia throughout. **B** CIN 2. Nuclear abnormalities are more striking than in CIN 1, and mitoses are seen (centre). The upper third of the epithelium shows maturation.

### Cervical intraepithelial neoplasia 1

Maturation is present in the upper two-thirds of the epithelium, and the superficial cells contain variable but usually mild atypia, which may include viral cytopathic effect (koilocytosis). Nuclear abnormalities are present throughout but are slight. Mitotic figures are present in the basal third and are not numerous. Abnormal forms are rare.

### Cervical intraepithelial neoplasia 2

Maturation is present in the upper half of the epithelium, and nuclear atypia is conspicuous in both the upper and lower epithelial layers. Mitotic figures are generally confined to the basal two-thirds of the epithelium. Abnormal forms may be seen.

### Cervical intraepithelial neoplasia 3

Maturation (including surface keratinization) may be absent or confined to the superficial third of the epithelium. Nuclear abnormalities are marked throughout most or all of the thickness of the epithelium. Mitotic figures may be numerous and are found at all levels of the epithelium. Abnormal mitoses are frequent.

### Growth fraction

HPVs, particularly high risk HPVs, are associated with alterations in the cell

cycle. Therefore, cell cycle biomarkers may be useful in distinguishing non-diagnostic atypia from CIN. Expression of a generic cell cycle proliferation marker (Ki-67) is typically confined to the suprabasal cells of the lower third of the normal epithelium. The presence of Ki-67 positive cells in the upper epithelial layers occurs in HPV infection, which induces cell cycle activity in these cells [1881,2356]. P16<sup>ink4</sup>, a cyclin-dependent kinase inhibitor, is a promising marker of CIN [1422,2527].

### Differential diagnosis

Transitional cell metaplasia is a benign condition that may be mistaken for high grade CIN. After the menopause immature squamous mucosa may exhibit histological features resembling transitional epithelium [1140,3085].

### Related lesions

CIN is usually associated with the cytopathic effects of HPV infection, which include koilocytosis, dyskeratosis and multinucleation. Koilocytosis is characterized by karyomegaly, nuclear enlargement with binucleation, irregularities in the nuclear membrane and hyperchromasia [1508]. Atypical reserve cell hyperplasia and atypical immature squamous metaplasia may be regarded as variants of CIN, though grading of such lesions may be difficult [979,2179].

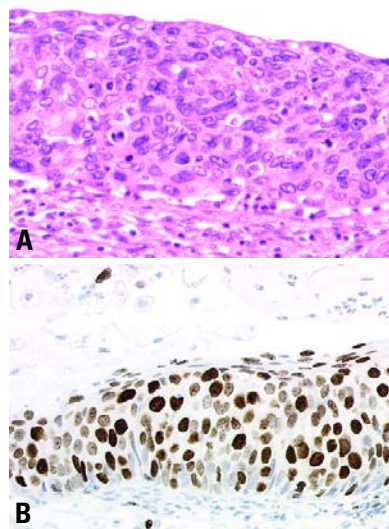
### Cytopathology

In cytology the grading of CIN is largely based on nuclear characteristics. The number of abnormal cells and the relative nuclear area increase with the severity of the lesion.

In CIN 1 the cells show a slightly enlarged nucleus (less than one-third of the total area of the cell), some anisokaryosis, finely granular and evenly distributed chromatin and mild hyperchromasia. The cytoplasmic borders are well defined.

In CIN 2 the cells and nuclei vary in size and shape. The nuclear to cytoplasmic ratio is increased (nucleus less than half of cell area). Nuclear chromatin is moderately hyperchromatic and shows some irregular distribution.

In CIN 3 the nuclear to cytoplasmic ratio is high (nucleus at least two-thirds of cell area). Nuclei are hyperchromatic with coarsely granular and irregularly distributed chromatin.



**Fig. 5.15** **A** Cervical intraepithelial neoplasia 3. Squamous epithelium consists entirely of atypical basaloid cells. Note the moderate nuclear polymorphism, coarse chromatin and mitotic figures in the upper half of the epithelium. **B** Ki-67 staining shows proliferation in all cell layers.

Cells typical of carcinoma in situ are arranged singly or in syncytial aggregates (indistinct cell borders and overlapping nuclei). Cytoplasm is scarce or absent; nuclei are round to oval.

### Prognosis and predictive factors

Systematic reviews of randomized controlled trials in subjects who underwent cryotherapy, laser ablation, loop electro-surgical excision procedure (LEEP) or surgical conization for the treatment of CIN of any grade reveal no substantial differences in outcome [1777,2068, 2299].

## Benign squamous cell lesions

### Condyloma acuminatum

#### Definition

A benign tumour characterized by papillary fronds containing fibrovascular cores and lined by stratified squamous epithelium with evidence of HPV infection, usually in the form of koilocytosis.

#### Aetiology

The exophytic condyloma is strongly associated with HPV types 6 and 11 [3057].

#### Histopathology

These lesions exhibit acanthosis, papillomatosis and koilocytosis. The latter is characterized by karyomegaly, nuclear enlargement with binucleation, irregularities in the nuclear membrane and hyperchromasia. These lesions closely resemble vulvar condylomas [585].

### Squamous papilloma

#### Definition

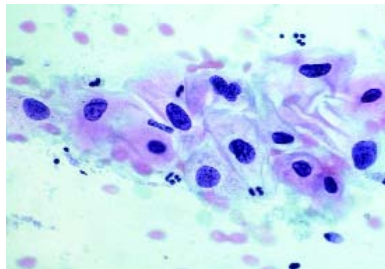
A benign tumour composed of a single papillary frond in which mature squamous epithelium without atypia or koilocytosis lines a fibrovascular stalk.

#### Epidemiology

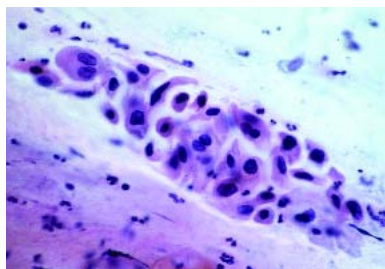
Lesions with a histological appearance similar to squamous papillomas of the vagina and vulva are rare in the cervix.

#### Aetiology

There is no evidence that squamous papilloma as defined above is or is not related to human papillomavirus.



**Fig. 5.16** Cervical intraepithelial neoplasia 1. Cells have well defined cell borders, slightly enlarged nuclei and some anisokaryosis.



**Fig. 5.18** Cervical intraepithelial neoplasia 2. Cells and nuclei vary in size and shape; nuclear chromatin is hyperchromatic and irregularly distributed.

#### Macroscopy

The squamous papilloma is usually solitary, arising on the ectocervix or at the squamocolumnar junction.

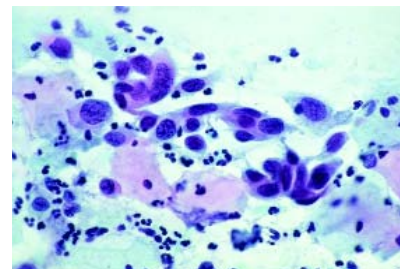
#### Histopathology

Histological examination shows a single papillary frond composed of mature squamous epithelium without atypia or koilocytosis lining a fibrovascular stalk.

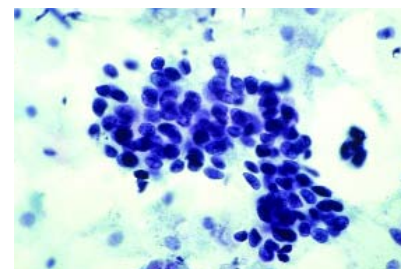
#### Differential diagnosis

Squamous papilloma is distinguished from condyloma by the absence of complex branching papillae and koilocytes. However, it is important to note that there may be a time during the evolution of condylomas when koilocytes are not easily identifiable.

Squamous papilloma also should be distinguished from papillary immature metaplasia of the cervix, which is characterized by slender filiform papillae and also does not have koilocytosis [3057]. In the latter condition the squamous epithelium is less mature with higher nuclear to cytoplasmic ratios but lacks nuclear atypia. Papillary immature metaplasia has been associated with HPV types 6 or 11 [3057].



**Fig. 5.17** Cervical intraepithelial neoplasia 3. Cells have increased nuclear to cytoplasmic ratios, anisokaryosis and coarsely granular chromatin.



**Fig. 5.19** Cervical intraepithelial neoplasia 3 (carcinoma in situ). The syncytial aggregate of round to oval nuclei which have coarsely granular chromatin.

### Fibroepithelial polyp

#### Definition

A polyp lined by squamous epithelium that contains a central core of fibrous tissue in which stellate cells with tapering cytoplasmic processes and irregularly shaped thin-walled vessels are prominent features.

#### Synonym

Stromal polyp.

#### Aetiology

Unlike condyloma, fibroepithelial polyps rarely contain HPV nucleic acids [1837], and, thus, are not related to HPV infection.

#### Clinical features

This lesion can occur at any age but has a predilection for pregnant women.

#### Macroscopy

These are polypoid lesions and are usually solitary.

#### Histopathology

These polypoid lesions are characterized by a prominent fibrovascular stroma cov-

ered by squamous epithelium [380]. Unlike squamous papilloma, they do not show acanthosis or a papillary architecture. Bizarre stromal cells, marked hypercellularity and elevated mitotic counts including atypical forms have been described that can lead to an erroneous diagnosis of sarcoma [2067].

## Glandular tumours and precursors

### ICD-O codes

Adenocarcinoma, NOS	8140/3
Mucinous adenocarcinoma	8480/3
Endocervical	8482/3
Intestinal	8144/3
Signet-ring cell	8490/3
Minimal deviation	8480/3
Villoglandular	8262/3
Endometrioid adenocarcinoma	8380/3
Clear cell adenocarcinoma	8310/3
Serous adenocarcinoma	8441/3
Mesonephric adenocarcinoma	9110/3
Early invasive adenocarcinoma	8140/3
Adenocarcinoma in situ	8140/2

## Adenocarcinoma

### Definition

A carcinoma that shows glandular differentiation.

### Clinical features

About one-half of all adenocarcinomas are exophytic, polypoid or papillary masses. Others are nodular with diffuse enlargement or ulceration of the cervix. Deep infiltration of the wall produces a barrel-shaped cervix. Approximately 15% of patients have no visible lesion.

## Histopathology

Immunohistochemistry may be useful to distinguish between benign and malignant conditions of the cervix, to discriminate between the various subtypes and to separate primary endocervical from primary endometrial tumours. The tumour that is estrogen receptor positive, vimentin positive and carcinoembryonic antigen negative is almost certainly of endometrial origin, whilst an endocervical source is very likely for the tumour that is estrogen receptor negative, vimentin negative and carcinoembryonic antigen positive [424,1822]. A moderate to high Ki-67 proliferation index also points towards endocervical neoplasia [495]. It is equally important to recognize that none of these stains are needed in the majority of cases, where the clinical evidence and history are entirely adequate. Carcinoembryonic antigen is usually negative in benign mimics, such as microglandular hyperplasia [2780]. In contrast to normal endocervical epithelium, some of the cells of a minimal deviation adenocarcinoma are reactive for serotonin and gastrointestinal tract-pancreatic peptide hormones and uniformly lack immunoreactivity for estrogen and progesterone receptors and CA125.

## Mucinous adenocarcinoma

### Definition

An adenocarcinoma in which at least some of the cells contain a moderate to large amount of intracytoplasmic mucin.

### Endocervical

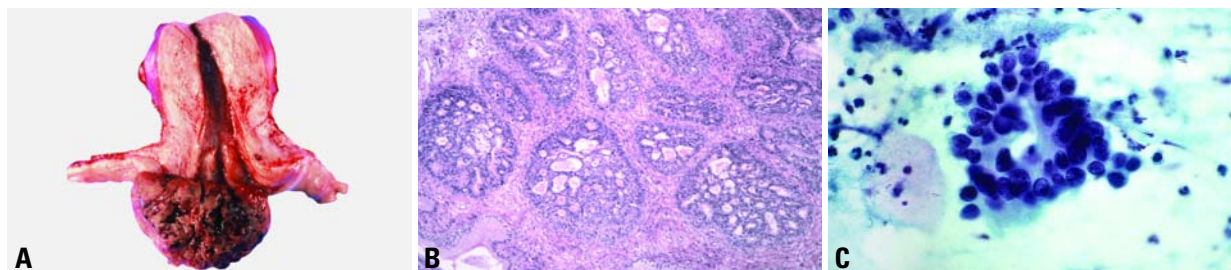
The endocervical type accounts for 70% of cervical adenocarcinomas, and the tumour cells resemble those of the endocervix. Most tumours are well to moderately differentiated. The glandular ele-

ments are arranged in a complex pattern. Papillae may project into the gland lumens and from the surface. At times a cribriform arrangement is observed. A microglandular pattern resembling microglandular hyperplasia of the cervix [3224] and a microcystic variant are rarely seen [2856]. The stroma may be desmoplastic. The cells are typically stratified with basal nuclei and abundant pale granular cytoplasm that stains positively for mucin. They show considerable nuclear atypia with variation in nuclear size, coarsely clumped chromatin and prominent nucleoli. Mitoses are usually numerous. Large amounts of mucin may be found in the stroma forming mucin lakes or pools in the so-called colloid carcinoma [1646,2975]. In poorly differentiated tumours the cells contain less cytoplasm but usually still form recognizable glandular structures. Co-existent CIN occurs in up to 40% of cases [1739], and adenocarcinoma in situ is also common. Synchronous mucinous tumours may be found elsewhere in the female genital tract [1392,3219].

In cytological preparations the cells are arranged in crowded cell aggregates with overlapping nuclei. Gland openings, rosettes, strips with palisading and pseudostratification and cell balls may be seen. The cytoplasm is vacuolated. The nuclei are round, oval or "cigar" shaped and vary in size. The nuclear chromatin is coarse and unevenly distributed with clearing, and nucleoli are present.

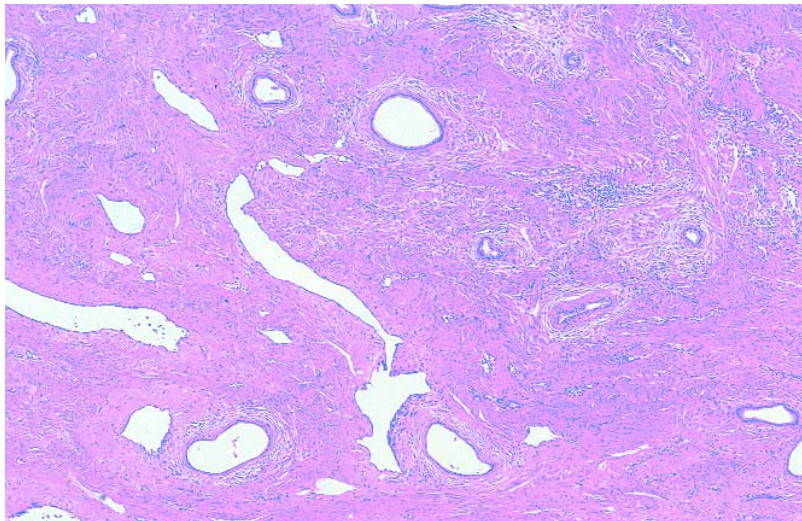
### Intestinal variant

These tumours resemble adenocarcinoma of the large intestine. Intestinal-type change may be found diffusely or only focally within a mucinous tumour. They frequently contain goblet cells and less commonly endocrine and Paneth cells.



**Fig. 520** Adenocarcinoma. **A** A large, polypoid, exophytic tumour arises from the cervix with focal cystic change and necrosis. **B** A cribriform pattern along with other features may indicate an invasive, rather than an in situ, neoplastic glandular process. **C** Endocervical variant. Atypical cells with enlarged nuclei, coarsely granular cleared chromatin and nucleoli form a gland opening.





**Fig. 5.21** Minimal deviation adenocarcinoma of the cervix. Irregular claw-shaped glands infiltrate the stroma.

#### **Signet-ring cell variant**

Primary signet-ring cell adenocarcinoma is rare in pure form {1157,1799,1893, 3013}. Signet-ring cells occur more commonly as a focal finding in poorly differentiated mucinous adenocarcinomas and adenosquamous carcinomas. The differential diagnosis includes metastatic tumours [908,1434] or rare squamous cell carcinomas with signet-ring-like cells that are mucin negative [1533].

#### **Minimal deviation variant**

This is a rare highly differentiated mucinous adenocarcinoma in which most of the glands are impossible to distinguish from normal. Adenoma malignum is a synonym.

**Histopathology.** Most of the glands are lined by deceptively bland, mucin-rich columnar cells with basal nuclei. In the majority of cases, however, occasional glands display moderate nuclear atypia, are angulated or elicit a desmoplastic stromal reaction. The most reliable criteria are the haphazard arrangement of the glands that extend beyond the depth of those of the normal endocervix and the presence of occasional mitoses, which are uncommon in the normal endocervical epithelium. Vascular and perineural involvement is frequent. Transmural and/or parametrial and/or myometrial spread is seen in 40% of cases [1004, 1391]. Because the depth of penetration of the glands is a key histological feature,

the diagnosis cannot be made in punch biopsies in most cases. Minimal deviation adenocarcinoma should be differentiated from the benign conditions of diffuse laminar endocervical glandular hyperplasia [1362], lobular endocervical glandular hyperplasia [2061], endocervicitis [3193] and adenomyoma of endocervical type [1005]. An endometrioid variant of minimal deviation adenocarcinoma has also been described [1391, 1972,3225].

**Somatic genetics.** The genetic locus for the putative tumour suppressor gene is in the region of chromosome 19p 13.3 [1610]. Somatic mutations of the *STK11* gene, the gene responsible for the Peutz-Jeghers syndrome, are characteristic of minimal deviation adenocarcinoma [1397]. They were found in 55% of patients with minimal deviation adenocarcinoma and in only 5% of other types of mucinous adenocarcinoma of the cervix.

**Genetic susceptibility.** These tumours are more likely than any other type of cervical adenocarcinoma to precede or develop coincidentally with ovarian neoplasia, the most common being mucinous adenocarcinoma and sex cord tumour with annular tubules [2769]. The latter is associated with the Peutz-Jeghers syndrome in 17% of cases [453]. A germline mutation of *STK11* was detected in one patient with Peutz-Jeghers syndrome

who had a mucinous adenocarcinoma of the cervix [1397].

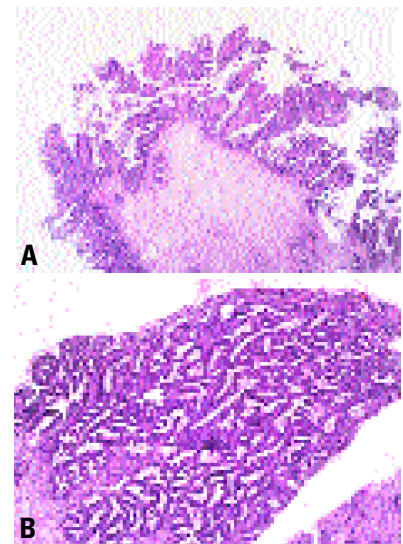
#### **Villoglandular variant**

These have a frond-like pattern resembling villoglandular adenoma of the colon. The tumours generally occur in young women. A possible link to oral contraceptives has been suggested.

The epithelium is generally moderately to well differentiated. One or several layers of columnar cells, some of which contain mucin, usually line the papillae and glands. If intracellular mucin is not demonstrable, the tumour may be regarded as the endometrioid variant. Scattered mitoses are characteristic. Invasion may be absent or minimal at the base; rare neoplasms, however, invade deeply. The invasive portion is typically composed of elongated branching glands separated by fibrous stroma. The non-invasive tumours may, in fact, be examples of papillary adenocarcinoma in situ. Associated CIN and/or adenocarcinoma in situ are common. Lymph node metastases are rare [1366,1387,1391].

#### **Endometrioid adenocarcinoma**

These adenocarcinomas account for up to 30% of cervical adenocarcinomas and have the histological features of an



**Fig. 5.22** Well differentiated villoglandular adenocarcinoma. **A** In the absence of frank invasion, the alternative diagnosis would be papillary adenocarcinoma in situ. **B** The villoglandular growth pattern is prominent.

endometrioid adenocarcinoma of the endometrium; however, squamous elements are less common. Little or no intracellular mucin is present. A distinction from an endocervical type adenocarcinoma is only possible in well differentiated lesions. This neoplasm must be distinguished from one extending into the cervix from the endometrium.

### **Clear cell adenocarcinoma**

An adenocarcinoma that is composed mainly of clear or hobnail cells arranged in solid, tubulocystic or papillary patterns or a combination.

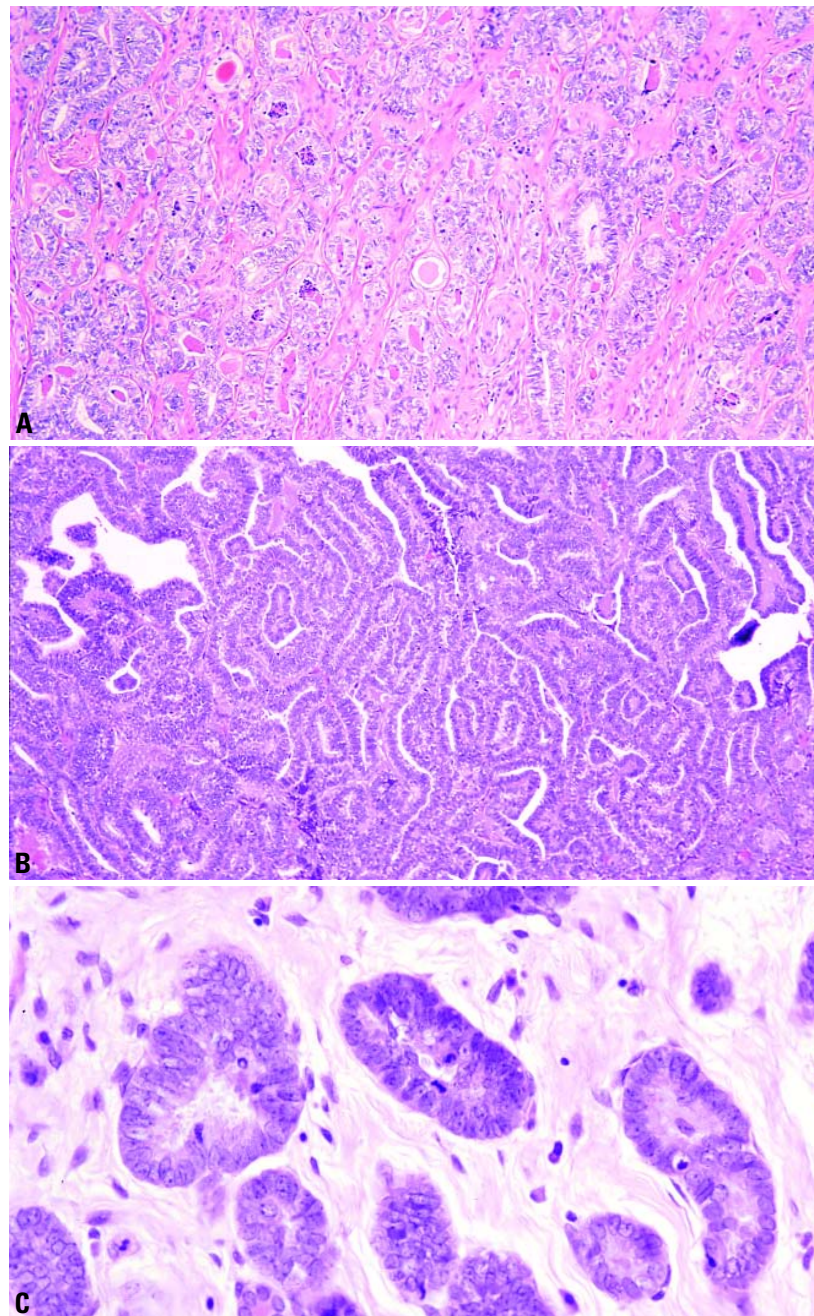
This rare tumour is histologically similar to clear cell adenocarcinoma of the ovary, endometrium and vagina, where they are more common. Although well known because of its association with in utero exposure to diethylstilbestrol (DES) in young women, its peak frequency is at present in the postmenopausal group. Genomic instability has been suggested as a mechanism of DES-related carcinogenesis [330].

### **Serous adenocarcinoma**

A complex pattern of papillae with cellular budding and the frequent presence of psammoma bodies characterize serous adenocarcinoma. Before a diagnosis of primary serous adenocarcinoma of the cervix can be made, spread from the endometrium, ovaries or peritoneum should be excluded. These rare cervical tumours are histologically identical to their ovarian counterparts [565]. A single case was familial. The patient, identical twin sister and mother all had serous tumours of the genital tract [1398].

### **Mesonephric adenocarcinoma**

These adenocarcinomas arise from mesonephric remnants and are most often located in the lateral to posterior wall of the cervix but may involve the cervix circumferentially. Among the 20 reported examples, the patients ranged in age from 33-74 years with a median age of about 52 years. Whereas they often present as exophytic lesions, they may remain completely intramural simply expanding the cervical wall. Histologically, they are commonly characterized by tubular glands lined by mucin-free cuboidal epithelium containing eosino-



**Fig. 5.23** Mesonephric adenocarcinoma. **A** In some areas of the tumour, the proliferation of tubules resembles the diffuse pattern of mesonephric hyperplasia with intraluminal colloid-like secretions. **B** Other areas contain a more complex growth pattern with early formation of papillary structures (same case as in A). **C** The tubules exhibit nuclear atypia and mitotic figures.

philic, hyaline secretion in their lumens in its well differentiated areas or larger glands showing endometrioid differentiation [521], but other patterns including

solid, papillary, ductal and a retiform arrangement may develop. A vast majority arise in a background of mesonephric remnant hyperplasia [850,2036,2679].



The tubular variant is distinguished from focal, florid and diffuse hyperplasia of mesonephric remnants by the presence of cytologic atypia, mitotic activity and the focal presence of intraluminal nuclear debris instead of the colloid-like secretion typical of mesonephric remnants [2679].

Mesonephric adenocarcinomas are immunoreactive for epithelial markers (AE1/3, cytokeratin 1, Cam5.2, cytokeratin 7 and epithelial membrane antigen) in 100% of cases, for calretinin (88%), and vimentin (70%). The absence of immunoreactivity with estrogen and progesterone receptor helps to distinguish the endometrioid variant from endometrioid adenocarcinoma [2679]. Positive immunoreactivity for CD10 may be another helpful feature [2110]. The behaviour of the lesions and prognosis are stage dependent.

### Early invasive adenocarcinoma

#### Definition

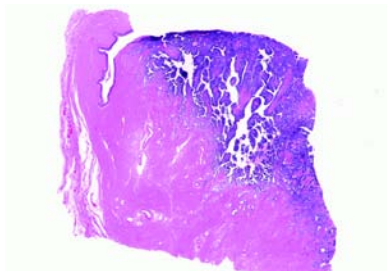
Early invasive adenocarcinoma refers to a glandular neoplasm in which the extent of stromal invasion is so minimal that the risk of local lymph node metastasis is negligible.

#### Synonym

"Microinvasive" adenocarcinoma.



**Fig. 5.25** Early invasive adenocarcinoma. Mounted section shows that its horizontal spread is much greater than the depth of invasion.



**Fig. 5.24** Early invasive adenocarcinoma, mounted section.

#### Tumour spread and staging

Adenocarcinomas of the cervix exist in early and frankly invasive forms [1611, 2139]. The entity of "early invasive" or "microinvasive" carcinoma is controversial. The current, 1995 FIGO staging, omits specific reference to glandular lesions in stage IA [1300]. In addition, there are practical problems in identifying microinvasive adenocarcinoma histologically (see below). Nevertheless, it is recommended that the FIGO classification be adopted.

#### Histopathology

The sine qua non of microinvasive adenocarcinoma is stromal invasion. There may be marked glandular irregularity with effacement of the normal glandular architecture, the tumour extending beyond the deepest normal crypt. Cribri-form, papillary or solid patterns may be present.

There may be a stromal response in the form of oedema, chronic inflammatory infiltrate or a desmoplastic reaction. Lymphatic capillary-like space involvement is helpful in confirming invasion.

Having established the presence of invasion, the depth of invasion and the width of the tumour must be measured. In most cases the depth is measured from the surface rather than the point of origin, which is hard to establish in some cases. Thus, tumour thickness, rather than "depth of invasion", is measured. The width is the greatest diameter of the neoplasm measured parallel to the surface; the measurement should be done by calibrated optics.

#### Prognosis and predictive factors

The prognosis of microinvasive adenocarcinoma (FIGO Stage 1A), as defined above, is excellent and essentially the same as that of its squamous counterpart [768,2143,2573,2732,3076].

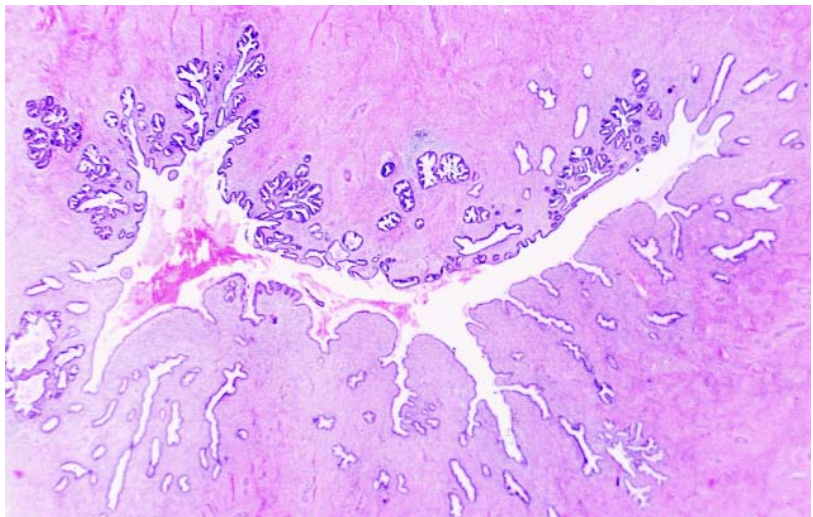
### Adenocarcinoma in situ

#### Definition

A lesion in which normally situated glands are partly or wholly replaced by cytologically malignant epithelium; in the former case the border is characteristically sharp.

#### Histopathology

The epithelium is usually devoid of intracellular mucin and may resemble endo-



**Fig. 5.26** Extensive adenocarcinoma in situ. Note that the neoplastic glands conform to the configuration of normal crypts and do not extend beyond them, and there is no stromal reaction.



metrial epithelium. In some cases the glands are lined by intestinal epithelium containing goblet, neuroendocrine and Paneth cells. The neoplastic glands conform to the expected location of normal endocervical glands and do not extend beyond the deepest normal crypt. A cribriform pattern is common. The epithelium is usually stratified with the long axes of the cells perpendicular to the base. The elongated, pleomorphic and hyperchromatic nuclei are basal in position. Mitoses are common and are disposed on the luminal side [2142]. Apoptosis is prominent [279]. The neoplastic epithelium may affect the surface, where it is often single layered, but more commonly is found in the crypts. These features help to explain the frequent failure of its colposcopic detection. The cell types, in order of frequency, are endocervical, endometrioid and intestinal. A putative tubal variant has also recently been described [2559]. Although the stroma may be intensely inflamed, there is no desmoplastic reaction. Adenocarcinoma in situ is associated with CIN in at least 50% of cases and is immunoreactive for carcinoembryonic antigen in 80% of cases.

#### Prognosis and predictive factors

Evidence supporting the precancerous potential of adenocarcinoma in situ includes its occurrence 10-15 years earlier than its invasive counterparts, its common association with microinvasive or invasive adenocarcinoma, its histological similarity to invasive adenocarcinoma and the frequent occurrence of high-risk HPV types. The transformation of adenocarcinoma in situ into invasive adenocarcinoma over time has also been documented on rare occasions [1224,2076]. Although the treatment of adenocarcinoma in situ is controversial, increasing evi-

dence is available that conservative therapy, such as conization only, is safe and effective in selected cases [1870,2140]

### Glandular dysplasia

#### Definition

A glandular lesion characterized by significant nuclear abnormalities that are more striking than those in glandular atypia but fall short of the criteria for adenocarcinoma in situ.

#### Histopathology

The nuclei are not cytologically malignant, and mitoses are less numerous than in adenocarcinoma in situ. Nuclear hyperchromasia and enlargement identify the involved glands, and pseudostratification of cells is prominent. Cribriform and papillary formations are usually absent. The concept that glandular dysplasia forms a biological spectrum of cervical glandular intraepithelial neoplasia remains unproven [420,1032,1534]. Glandular dysplasia must be distinguished from glandular atypia. The latter is an atypical glandular epithelial alteration which does not fulfil the criteria for glandular dysplasia or adenocarcinoma in situ and which may be associated with inflammation or irradiation.

### Benign glandular lesions

#### Müllerian papilloma

#### Definition

A rare, benign, papillary tumour composed of a complex arborizing fibrovascular core covered by a mantle of single or double-layered mucinous epithelium that may undergo squamous metaplasia.

#### Clinical features

Müllerian papilloma occurs almost exclusively in children typically between 2 and 5 years of age (range 1-9 years), who present with bleeding, discharge or a friable, polypoid to papillary, unifocal or multifocal mass, usually less than 2 cm in greatest dimension.

#### Histopathology

These tumours consist of multiple small polypoid projections composed of fibrous stroma and lined by simple epithelium. Occasional cells may have a hobnail appearance simulating clear cell adenocarcinoma; however, no clear cells, atypia or mitoses are present. The stroma is often inflamed and rarely contains psammoma bodies.

#### Prognosis and predictive factors

Occasional cases recur [2736]. (See chapter on the vagina).

### Endocervical polyp

#### Definition

An intraluminal protrusion composed of bland endocervical glands and a fibrovascular stroma.

#### Epidemiology

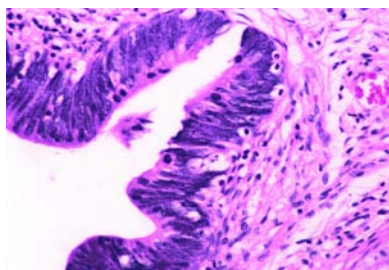
These are very common lesions that rarely are of concern clinically and are easy to diagnose histologically.

#### Clinical features

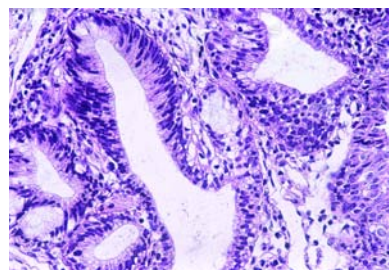
In 75% of cases they are asymptomatic. The rest present with bleeding (especially post-coital) and/or discharge.

#### Macroscopy

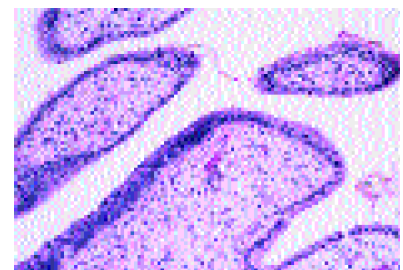
The great majority are less than 1 cm and single [15].



**Fig. 5.27** Adenocarcinoma in situ. High power magnification shows pseudostratified nuclei and a marked degree of apoptosis.



**Fig. 5.28** High grade cervical glandular dysplasia. The histological features are not of sufficient severity to be regarded as adenocarcinoma in situ.



**Fig. 5.29** Glandular dysplasia involving endocervical papillae.

### Histopathology

Endocervical polyps are usually covered by cuboidal and/or columnar epithelium that often shows atypical regenerative changes that may be mistaken cytologically for malignancy. Polyps are often composed of large retention cysts distended by mucus and covered by normal metaplastic squamous epithelium. Ulceration is uncommon, but the stroma is often inflamed.

The presence of bizarre stromal atypia, atypical mitoses or stromal hypercellularity may lead to an unwarranted diagnosis of sarcoma [2067]. Other benign alterations within polyps that may be mistaken for malignancy include florid immature squamous metaplasia, papillary hyperplasia, microglandular hyperplasia and decidual reaction [2930].

### Prognosis and predictive factors

Polyps occasionally recur, even after complete excision.

### Uncommon carcinomas and neuroendocrine tumours

#### Definition

Epithelial tumours of the uterine cervix other than those of squamous or glandular types.

#### ICD-O-codes

Adenosquamous carcinoma	8560/3
Glassy cell variant	8015/3
Adenoid cystic carcinoma	8200/3
Adenoid basal carcinoma	8098/3
Neuroendocrine tumours	
Carcinoid	8240/3
Atypical carcinoid	8249/3
Small cell carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Undifferentiated carcinoma	8020/3

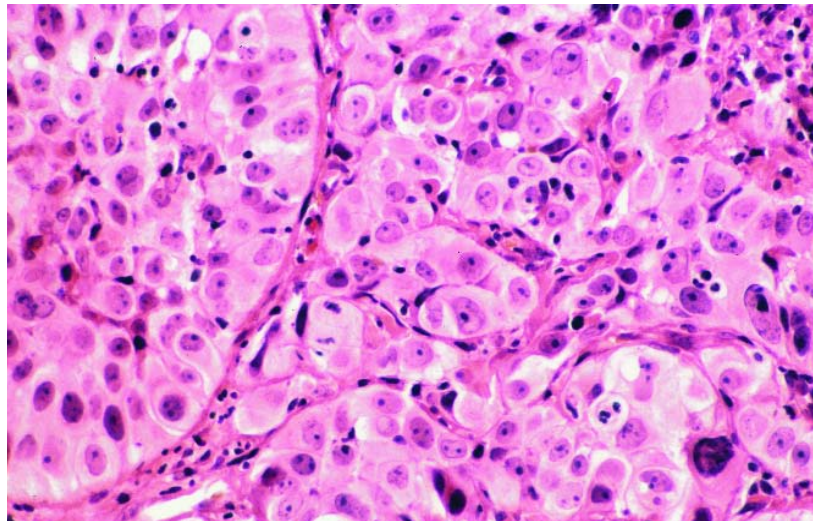
### Adenosquamous carcinoma

#### Definition

A carcinoma composed of a mixture of malignant glandular and squamous epithelial elements.

#### Histopathology

Both elements show atypical features. Scattered mucin-producing cells in an otherwise ordinary looking squamous cell

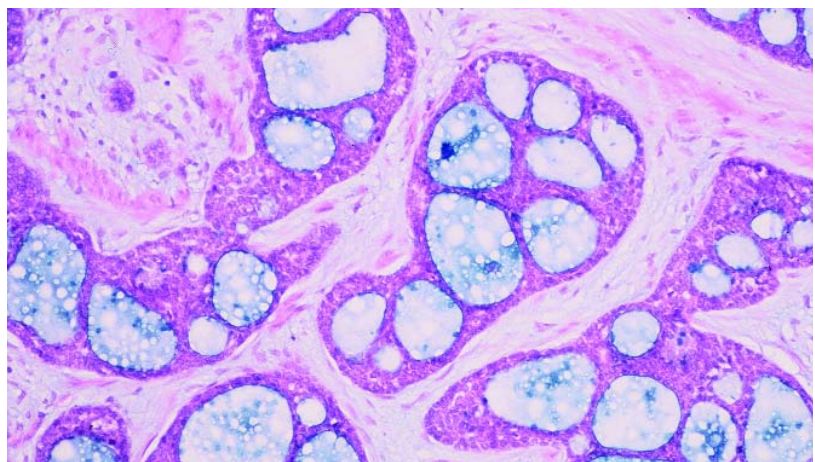


**Fig. 5.30** Glassy cell carcinoma. Note the ground glass appearance of the cytoplasm and the well defined cytoplasmic membranes.

carcinoma have been referred to as mucoepidermoid carcinoma. As there is no convincing evidence that such tumours behave differently, routine mucin staining of squamous cell carcinomas is not recommended, and the former term should no longer be employed. Poorly differentiated tumours resembling poorly differentiated squamous cell carcinoma but with many mucin-producing cells and lacking keratinization or intercellular bridges should be diagnosed as poorly differentiated adenocarcinoma.

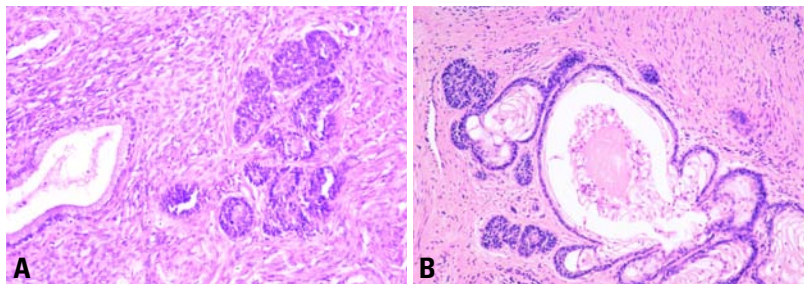
### Glassy cell carcinoma variant

Glassy cell carcinoma is a poorly differentiated variant of adenosquamous carcinoma and accounts for 1-2% of all cervical carcinomas. The tumour occurs in young women, grows rapidly, develops frequent distant metastases and responds poorly to radiotherapy; however, chemotherapy may be promising [1863]. The tumour cells lack estrogen and progesterone receptors [132]. Usually, no preinvasive lesion is seen. The tumour cells are large

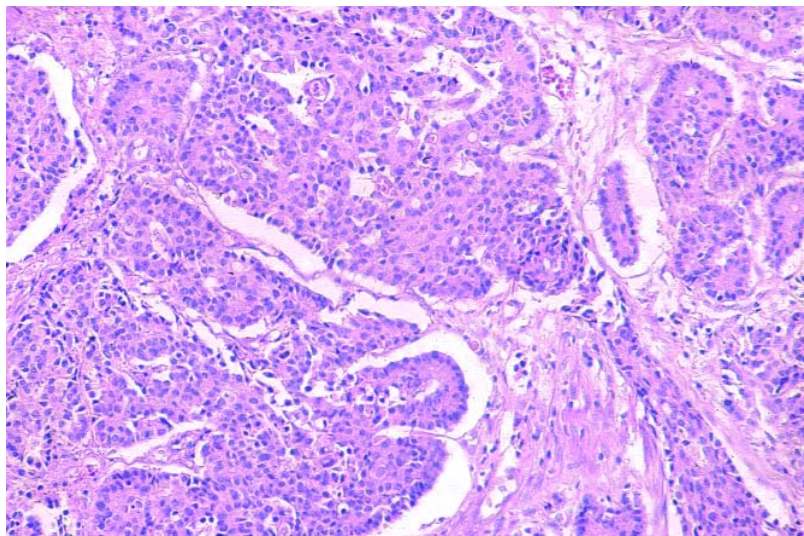


**Fig. 5.31** Adenoid cystic carcinoma. Note the cribriform pattern with abundant luminal mucin.

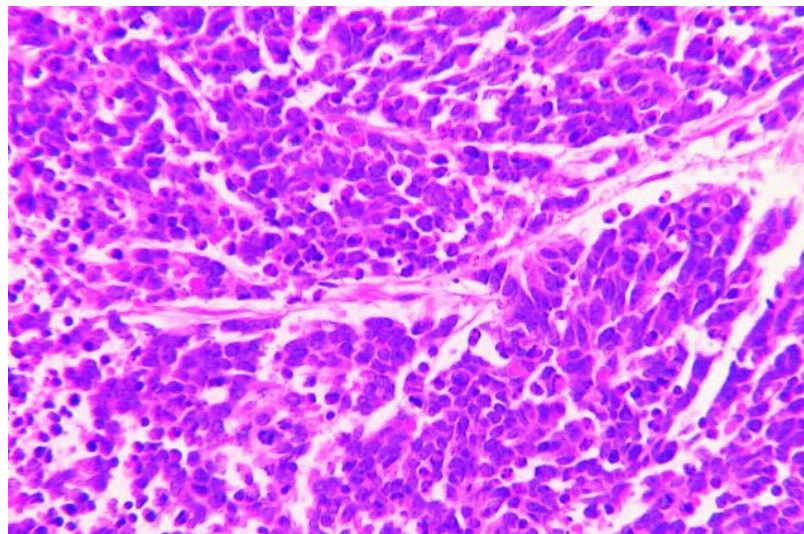




**Fig. 5.32** Adenoid basal carcinoma. **A** Clusters of basaloid cells show mature central squamous differentiation. **B** Note small clusters of basaloid cells adjacent to cystic glands.



**Fig. 5.33** Atypical carcinoid. Islands of tumour cells with moderate nuclear atypia are surrounded by fibrous stroma.



**Fig. 5.34** Small cell carcinoma. Note the loosely packed neoplastic cells with scant cytoplasm.

with distinct cell borders and a ground-glass cytoplasm. A prominent eosinophilic infiltration in the stroma helps to separate the tumour from non-keratinizing squamous cell carcinoma {1701}.

#### **Prognosis and predictive factors**

The prognosis of adenosquamous carcinoma remains uncertain {68}.

#### **Adenoid cystic carcinoma**

##### **Definition**

A carcinoma of the cervix that resembles adenoid cystic carcinoma of salivary gland origin.

##### **Epidemiology**

Most of the patients are over 60 years of age, and there is a high proportion of Black women {849}.

##### **Clinical features**

The majority of patients present with postmenopausal bleeding and have a mass on pelvic examination {849}.

##### **Histopathology**

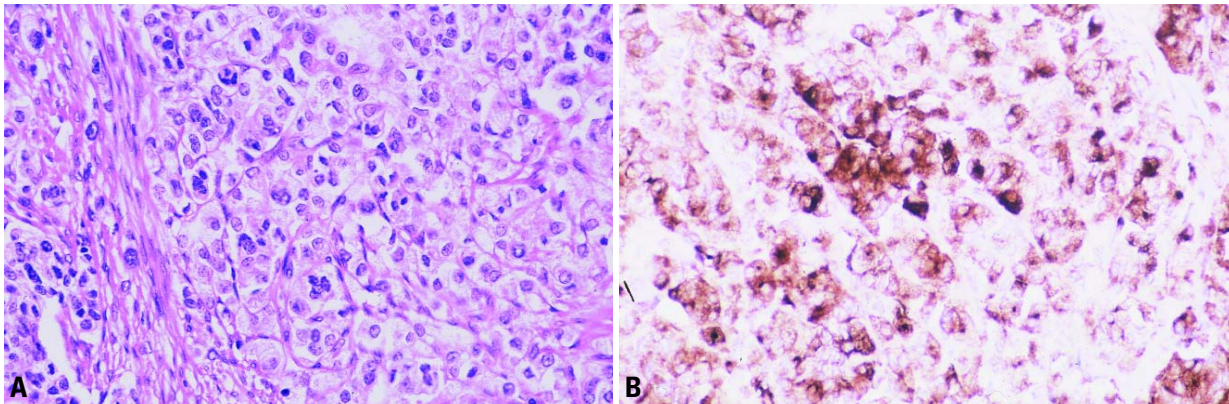
This rare tumour of the cervix has a histological appearance similar to its counterpart in salivary glands. The characteristic cystic spaces are filled with a slightly eosinophilic hyaline material or basophilic mucin and are surrounded by palisaded epithelial cells {849}. In contrast to adenoid cystic carcinoma of salivary gland, the cervical carcinomas show greater nuclear pleomorphism, a high mitotic rate and necrosis {849}. A solid variant has been described {65}. Immunostains for basement membrane components such as collagen type IV and laminin are strongly positive {1918}. In contrast to an earlier study {849}, the majority of the tumours stained for S-100 protein and HHF35 suggesting myoepithelial differentiation {1059}.

The differential diagnosis includes small cell carcinoma, adenoid basal carcinoma and non-keratinizing squamous cell carcinoma.

##### **Histogenesis**

This tumour, basaloid squamous cell carcinoma and adenoid basal carcinoma are part of a morphological and biological spectrum of basaloid cervical neoplasms, and a putative reserve cell origin has been suggested {1059}. Circumstantial evidence suggests that adenoid





**Fig. 5.35** Large cell neuroendocrine carcinoma. **A** The tumour is composed of large cells with pleomorphic nuclei and frequent mitotic figures. **B** Note the strong cytoplasmic immunoreactivity for chromogranin A.

basal carcinoma may be a precursor of adenoid cystic carcinoma [1059].

#### Prognosis and predictive factors

The tumours frequently recur locally or metastasize to distant organs and have an unfavourable prognosis.

### Adenoid basal carcinoma

#### Definition

A cervical carcinoma in which rounded, generally well differentiated nests of basaloid cells show focal gland formation or sometimes central squamous differentiation.

#### Epidemiology

Adenoid basal carcinoma is a rare tumour. The patients are usually more than 50 years old.

#### Clinical findings

Patients are usually asymptomatic and without a clinically detectable abnormality of the cervix. The tumour is often discovered as an incidental finding.

#### Histopathology

The histological appearance shows small nests of basaloid cells, almost always beneath and often arising from CIN or small invasive squamous cell carcinomas [849]. The cells are small with scanty cytoplasm and are arranged in cords and nests with focal glandular or squamous differentiation. There is frequently associated CIN [332,849]. The differential diagnosis includes other small cell tumours [2280].

#### Histogenesis

This tumour, basaloid squamous cell carcinoma and adenoid cystic carcinoma are part of a morphological and biological spectrum of basaloid cervical neoplasms and a putative reserve cell origin has been suggested [1059].

#### Prognosis and predictive factors

The tumour is low grade and rarely metastasizes.

### Neuroendocrine tumours

The group of neuroendocrine tumours includes carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma and small cell carcinoma [63,2803].

Neuroendocrine differentiation is demonstrated with pan-neuroendocrine markers such as chromogranin A, synaptophysin and neuron specific enolase. A variety of peptides and hormones are also present, such as calcitonin, gastrin, serotonin, substance P, vasoactive intestinal peptide, pancreatic polypeptide, somatostatin and adrenocorticotrophic hormone [22], but their clinical significance is limited [2612].

#### Carcinoid

Generally benign, carcinoids have the same characteristic organoid appearance as observed in other sites. The degree of nuclear atypia and mitotic activity are important in the differential diagnosis between typical and atypical carcinoids.

#### Atypical carcinoid

An atypical carcinoid is a carcinoid with cytologic atypia that exhibits increased mitotic activity (5-10 per high power field) and contains foci of necrosis [63].

#### Small cell carcinoma

Small cell carcinomas account for 1-6% of cervical carcinomas [22]. Squamous or glandular differentiation may be present [22,248,830,1761,2219]. The 5-year survival rate is reported to be 14-39% [22,248,2803].

#### Large cell neuroendocrine carcinoma

Large cell neuroendocrine carcinoma is a rare tumour that often has focal adenocarcinomatous differentiation [592a, 1521a, 2361a]. The tumour cells have abundant cytoplasm, large nuclei and prominent nucleoli. Mitoses are frequent. The differential diagnosis includes non-neuroendocrine undifferentiated carcinoma, adenocarcinoma with neuroendocrine features, metastatic neuroendocrine carcinoma and undifferentiated sarcoma. The tumours are aggressive and appear to have a similar outcome to small cell carcinoma [1006].

#### Undifferentiated carcinoma

Undifferentiated carcinoma is a carcinoma lacking specific differentiation. The differential diagnosis includes poorly differentiated squamous cell carcinoma, adenocarcinoma, glassy cell carcinoma and large cell neuroendocrine carcinoma.

# Mesenchymal tumours

M.L. Carcangiu

## Definition

A variety of rare benign and malignant mesenchymal tumours that arise in the uterine cervix and which exhibit smooth muscle, skeletal muscle, vascular, peripheral nerve and other types of mesenchymal tissue differentiation. Smooth muscle tumours are the most common.

## Malignant mesenchymal tumours

### ICD-O codes

Leiomyosarcoma	8890/3
Endometrioid stromal sarcoma, low grade	8931/3
Undifferentiated endocervical sarcoma	8805/3
Sarcoma botryoides	8910/3
Alveolar soft part sarcoma	9581/3
Angiosarcoma	9120/3
Malignant peripheral nerve sheath tumour	9540/3

### Epidemiology

Sarcomas are extremely rare. Of 6,549 malignant tumours arising in the uterine cervix reported in the United States in a 5 year period (1973-1977), only 36 (0.5%) were sarcomas [3191]. Leiomyosarcoma is the most common primary sarcoma, although less than thirty cases have been

described in the literature [25,212, 543,912,927,1045,1058,1405,2473]. About 100 cases of sarcoma botryoides of the cervix have been reported [170, 333,642,1041,1898,3250]. Fifteen cases of undifferentiated endocervical sarcoma [20,25,1324], ten cases of alveolar soft part sarcoma and six of malignant peripheral nerve sheath tumour primary in the uterine cervix are on record [21,892, 901,1056,1375,1424,1504,1916,2017, 2507,2721]. All the other types of mesenchymal tumours have been case reports. Cervical mesenchymal tumours affect adult patients with the exception of sarcoma botryoides, which usually occurs in children and young women (mean age 18 years) [642]. The prognosis of cervical sarcomas as a group is poor with the exception of sarcoma botryoides.

### Clinical features

Most patients with these cervical tumours present with vaginal bleeding or discharge. Large tumours may compress adjacent organs or, if polypoid, protrude through the cervical os into the vagina. Less frequently, the passing of tissue through the vagina is the presenting symptom.

At operation sarcomas may be seen to infiltrate the entire thickness of the cervical wall. Pelvic recurrences or regional

lymph node metastases are the most common late events.

## Leiomyosarcoma

### Definition

A malignant tumour composed of smooth muscle cells.

### Clinical features

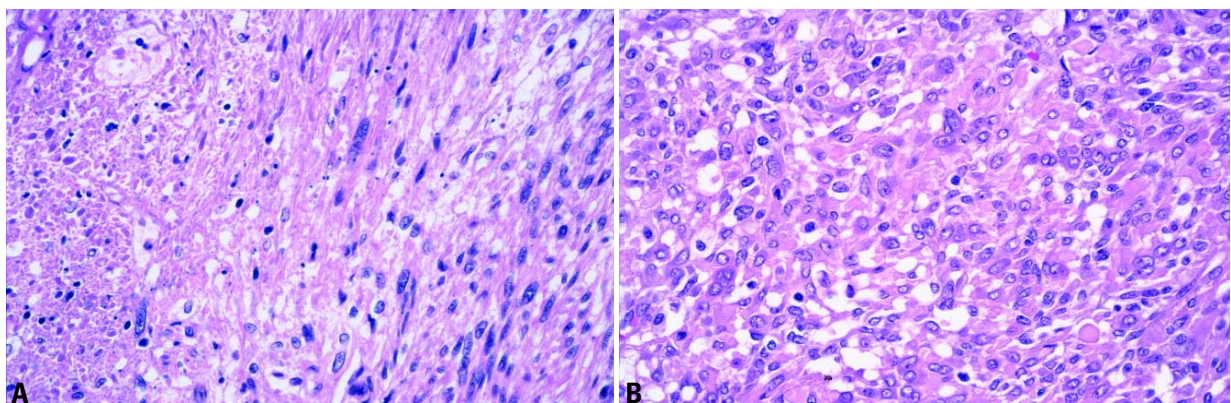
Leiomyosarcoma presents as a mass replacing and expanding the cervix or as a polypoid growth.

### Macrosocopy

The tumours have a soft and fleshy consistency and often contain areas of necrosis or haemorrhage. The rare myxoid variant of leiomyosarcoma has a typical gelatinous appearance.

### Histopathology

Leiomyosarcomas show hypercellular interlacing fascicles of large spindle-shaped or round cells with diffuse moderate to marked nuclear atypia, a high mitotic rate, atypical mitoses, single or multiple prominent nucleoli and tumour cell necrosis. Infiltrative borders and vascular invasion are also frequently seen. Cervical epithelioid leiomyosarcoma, and one case each of myxoid and xanthomatous cervical leiomyosarcoma



**Fig. 5.36** Cervical leiomyosarcoma. **A** Typical variant. The neoplasm shows marked nuclear atypia and coagulative necrosis. **B** Epithelioid variant. The tumour cells are round and uniform.

have been reported {543,912,927,1045,1058}.

#### Differential diagnosis

The criteria used in the distinction from leiomyoma are the same as those for smooth muscle tumours of the uterine corpus. At least two of three features (marked nuclear atypia, a mitotic rate higher than 10 mitoses per 10 high power fields and tumour necrosis) are required for the diagnosis of leiomyosarcoma {211}. For epithelioid leiomyosarcoma a mitotic count higher than 5 mitoses per 10 high power fields is considered diagnostic of malignancy. A low mitotic count is typical of the myxoid variant {912}. Antibodies to smooth muscle actin and/or desmin may be used to demonstrate smooth muscle differentiation in these tumours.

Leiomyosarcoma should be differentiated from postoperative spindle cell nodule {1420}. The latter is mitotically active and may infiltrate the underlying tissue. The distinction from leiomyosarcoma or other malignant spindle cell tumour depends to a large extent on the history of a recent operation at the same site.

#### Endometrioid stromal sarcoma, low grade

##### Definition

A sarcoma arising outside of the fundus composed of cells resembling endometrial stromal cells.

##### Epidemiology

Very rarely, tumours with the features of low grade endometrial stromal sarcoma arise in the cervix {295,437}.

##### Histopathology

This tumour may arise from cervical endometriosis and must be distinguished from stromal endometriosis and primary endometrial stromal sarcoma that has invaded the cervix. The term undifferentiated endocervical sarcoma is preferred for high grade lesions.

#### Undifferentiated endocervical sarcoma

##### Definition

An endocervical sarcoma lacking endometrial stromal or other specific differentiation {20,1324}.

#### Histopathology

Tumours described in the literature as undifferentiated endocervical sarcoma are characterized by a polypoid or infiltrative cervical growth similar to that exhibited by malignant peripheral nerve sheath tumours arising in the uterine cervix {25,1424}.

The tumour is composed of spindle or stellate-shaped cells with scanty cytoplasm, ill defined cell borders and oval hyperchromatic nuclei arranged in a sheet-like, fasciculated or storiform pattern {25}. The prominent vascular pattern typical of endometrioid stromal sarcoma is not a characteristic of these tumours, and the stromal proliferation tends to encircle the endocervical glands creating a focal resemblance to adenosarcoma. Nuclear atypia and markedly increased mitotic activity are seen in all cases, as well as areas of haemorrhage, necrosis and myxoid degeneration.

#### Sarcoma botryoides

##### Definition

A tumour composed of cells with small, round, oval or spindle-shaped nuclei, some of which show evidence of differentiation towards skeletal muscle cells.

##### Synonym

Embryonal rhabdomyosarcoma.

##### Macroscopy

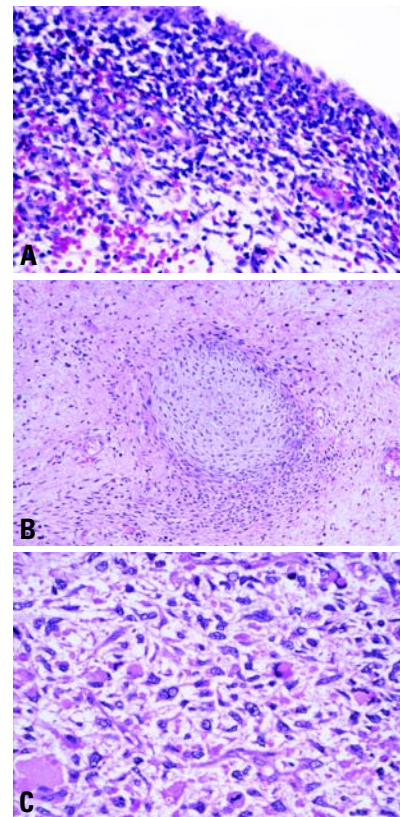
Embryonal rhabdomyosarcoma usually grows in a polypoid fashion. The grape-like type of growth classically exhibited by vaginal sarcoma botryoides is only rarely seen in cervical tumours. The polypoid masses have a glistening translucent surface and a soft consistency and may be pedunculated or sessile. Their size ranges from 2-10 cm {642}. The sectioned surface of the tumour appears smooth and myxoid with small haemorrhagic areas.

##### Histopathology

The histological features are described in the section on the vagina. Islands of mature neoplastic cartilage are more frequently seen in cervical than in vaginal tumours {642}.

##### Somatic genetics

In one case of sarcoma botryoides chromosomal analysis has demonstrated deletion of the short arm of chromosome 1,



**Fig. 5.37** Cervical sarcoma botryoides. **A** The subepithelial cambium layer is prominent. **B** Note the focus of neoplastic cartilage. **C** Tumour cells with eosinophilic cytoplasm exhibit myoblastic differentiation.

and trisomies 13 and 18 {2156}, and in another a point mutation in exon 6 of *TP53* was found, but no *KRAS* point mutations at codons 12,13 and 61 were detected {2627}.

##### Genetic susceptibility

An association between ovarian Sertoli-Leydig tumour and cervical sarcoma botryoides has been described {1026}

##### Prognosis and predictive factors

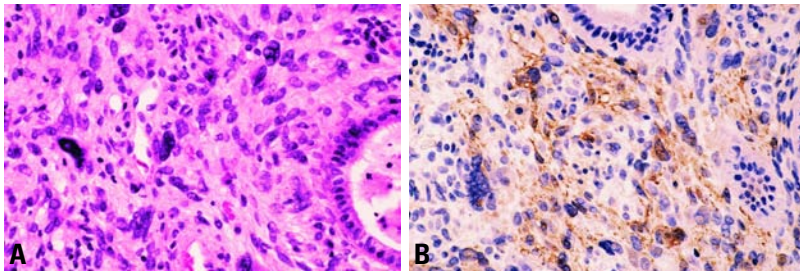
The use of neoadjuvant chemotherapy allows a more conservative approach for these neoplasms {170,1041,3250}.

#### Alveolar soft part sarcoma

##### Definition

A sarcoma characterized by solid and alveolar groups of large epithelial-like cells with granular, eosinophilic cytoplasm.





**Fig. 5.38** Malignant peripheral nerve sheath tumour (MPNST). **A** Atypical tumour cells are adjacent to an endocervical gland in a MPNST presenting as an endocervical polyp. **B** Tumour cells are positive for S-100 protein.

### Macroscopy

These appear macroscopically as a polyp or an intramural nodule measuring less than 5 cm and have a friable or solid consistency.

### Histopathology

They are histologically similar to their counterparts in other sites. Most of the tumours exhibit an alveolar architecture, where nests of tumour cells with central loss of cellular cohesion are supported by thin-walled, sinusoidal vascular spaces. A solid pattern of growth may also be present. The tumour cells have an abundant eosino-philic cytoplasm, large nuclei, prominent nucleoli and contain PAS-positive, diastase-resistant, rod-shaped crystals [1056]. A predominantly clear cytoplasm may characterize some neoplasms, and some cells may exhibit prominent nuclear atypia. Electron microscopy shows characteristic intracytoplasmic crystals, electron-dense secretory granules, numerous mitochondria, prominent endoplasmic reticulum, glycogen and a well developed Golgi apparatus [1937].

### Prognosis and predictive factors

Alveolar soft part sarcomas of the female genital tract, including those primary in the uterine cervix, appear to have a better prognosis than their counterpart in other sites [2017].

### Angiosarcoma

#### Definition

A malignant tumour the cells of which variably recapitulate the morphologic features of endothelium.

The macroscopic appearance of angiosarcoma is similar to that in other sites forming a haemorrhagic, partially cystic or necrotic mass [2551], and the neoplastic cells are

immunoreactive for CD31, CD34, and factor VIII-related antigen [2551].

### Malignant peripheral nerve sheath tumour

#### Definition

A malignant tumour showing nerve sheath differentiation.

#### Histopathology

Cervical malignant peripheral nerve sheath tumour (MPNST) is similar to MPNST arising in other sites including the occurrence of less common variants such as epithelioid and melanocytic types [2721]. The tumour is composed of fascicles of atypical spindle cells invading the cervical stroma and surrounding endocervical glands with a pattern reminiscent of adenosarcoma. Myxoid paucicellular areas are characteristically intermixed with others with a dense cellularity [1375]. Mitoses are common. The tumour cells are positive for S-100 protein and vimentin and negative for HMB-45, smooth muscle actin, desmin and myogenin [1424].

### Other malignant tumours

Other malignant mesenchymal tumours include alveolar rhabdomyosarcoma

{781}, liposarcoma {2840,3016}, osteosarcoma {289,588} and malignant fibrous histiocytoma {308}.

## Benign mesenchymal tumours and tumour-like lesions

### Definition

Benign mesenchymal tumours and tumour-like lesions that arise in the uterine cervix.

### ICD-O codes

Leiomyoma	8890/0
Genital rhabdomyoma	8905/0

### Leiomyoma

#### Definition

A benign tumour composed of smooth muscle cells.

#### Epidemiology

Leiomyoma is the most common benign mesenchymal tumour of the cervix. It has been estimated that less than 2% of all uteri contain cervical leiomyomas, and that about 8% of uterine leiomyomas are primary in the cervix [2020,2925].

#### Histopathology

Cervical leiomyoma is histologically identical to those that occur in the uterine corpus.

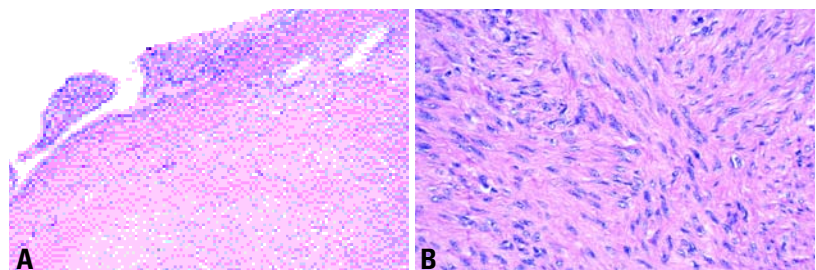
### Genital rhabdomyoma

#### Definition

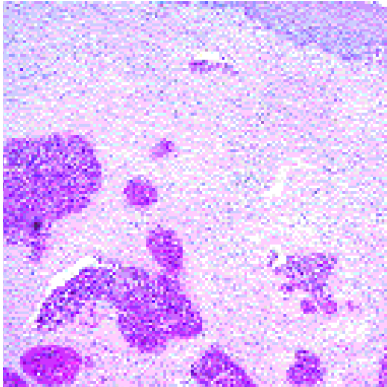
A rare benign tumour of the lower female genital tract composed of mature striated muscle cells separated by varying amounts of fibrous stroma.

#### Clinical features

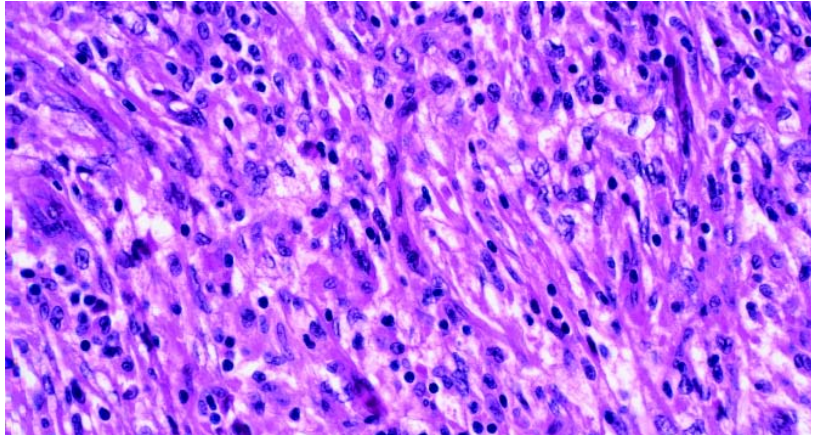
Cervical rhabdomyoma presenting as a polypoid lesion has been rarely reported [690].



**Fig. 5.39** Cervical leiomyoma. **A** Note the endocervical glandular mucosa overlying a leiomyoma. **B** The tumour is composed of interlacing fascicles of uniform spindle-shaped cells.



**Fig. 5.40** Venous haemangioma. Vascular channels of variable size occupy the cervical stroma. Note a portion of the ectocervical squamous epithelium in the right upper corner of the field.



**Fig. 5.41** Postoperative spindle cell nodule. The lesion is composed of spindle-shaped mesenchymal and inflammatory cells..

#### **Histopathology**

The tumour is composed of rhabdomyoblasts with small, uniform nuclei dispersed in a myxoid and oedematous stroma. The typical cambium layer of sarcoma botryoides is absent {690}.

#### **Postoperative spindle cell nodule**

##### **Definition**

A localized, non-neoplastic reactive lesion composed of closely packed proliferating spindle cells and capillaries simulating a leiomyosarcoma occurring at the site of a recent excision.

#### **Clinical features**

The lesion develops at the site of a recent operation several weeks to several months postoperatively {1420,2020}.

#### **Histopathology**

The lesion is composed of closely packed, mitotically active, spindle-shaped mesenchymal cells and capillaries often with an accompaniment of inflammatory cells, and may infiltrate the underlying tissue.

#### **Differential diagnosis**

Postoperative spindle cell sarcoma may closely resemble a leiomyosarcoma or other malignant spindle cell tumours, but

the history of a recent operation at the same site facilitates its diagnosis.

#### **Other benign tumours**

Rare examples of cervical lipoma {334,1910}, haemangioma {47,629}, glomus tumour {64}, localized neurofibromatosis {381,986}, schwannoma {1093}, pigmented melanocytic schwannoma {2900}, granular cell tumour {553,952,1101}, ganglioneuroma {858} and paraganglioma {3229} have been reported.

# Mixed epithelial and mesenchymal tumours

W.G. McCluggage  
R.A. Kubik-Huch

## Definition

Tumours composed of an admixture of neoplastic epithelial and mesenchymal elements. Each of these components may be either benign or malignant.

## ICD-O codes

Carcinosarcoma	8980/3
Adenosarcoma	8933/3
Wilms tumour	8960/3
Adenofibroma	9013/0
Adenomyoma	8932/0

## Epidemiology

These neoplasms are much less common than their counterparts in the uterine corpus. They may occur in any age group, but carcinosarcomas most commonly involve elderly postmenopausal women [527,1060].

## Clinical features

The presenting symptom is usually abnormal uterine bleeding. In some cases, especially in cases of carcinosarcoma, a friable mass may extrude from the vaginal introitus. The tumour may be identified following an abnormal cervical smear.

## Carcinosarcoma

### Definition

A neoplasm composed of an admixture of malignant epithelial and mesenchymal elements.

### Synonyms

Malignant müllerian mixed tumour, malignant mesodermal mixed tumour, metaplastic carcinoma.

### Epidemiology

Carcinosarcomas most commonly involve elderly postmenopausal women [527,1060]. These neoplasms are much less common than their counterparts in the uterine body.

### Aetiology

An occasional case of cervical carcinosarcoma has been associated with

prior radiation treatment. HPV infection, especially HPV 16, has been found in the epithelial and mesenchymal components suggesting a role in the evolution of these neoplasms [1060].

## Histopathology

The histological features are similar to its counterpart in the uterine corpus. However, the epithelial elements are more commonly non-glandular in type and include squamous (keratinizing, non-keratinizing or basaloid), adenoid cystic, adenoid basal or undifferentiated carcinoma [527,1060,1757,1785,3177]. Adjacent severe dysplasia of the squamous epithelium has also been described. Mesonephric adenocarcinomas of the cervix with a malignant spindle cell component have been reported, representing an unusual subtype of cervical carcinosarcoma [521]. Before diagnosing a cervical carcinosarcoma, ex-

tension from a primary uterine corpus neoplasm should be excluded [960, 3245].

## Prognosis and predictive factors

Cervical carcinosarcomas are aggressive neoplasms, and treatment is usually radical hysterectomy followed by chemotherapy and/or radiotherapy. The prognosis may be better in small tumours with a polypoid appearance. Although aggressive, these neoplasms appear to be more often confined to the uterus compared to their counterparts in the corpus and may have a better prognosis [527,1060].

## Adenosarcoma

### Definition

A neoplasm composed of an admixture of benign epithelial and malignant mesenchymal elements.



**Fig. 5.42** CT scans of malignant müllerian tumour (T) of the cervix, extensively involving uterine corpus. On the sagittal image (left) note a large leiomyoma (LM) of the uterine fundus. The coronal reconstruction (right) shows the large extension of the tumour (T). Note the hydronephrosis of the left kidney.



### Epidemiology

Cervical adenosarcomas are much less common than their counterparts in the uterine corpus.

### Histopathology

The histological features are similar to its counterpart in the corpus. However, the epithelium is more likely to be squamous or mucinous. Adenosarcomas may or may not invade the underlying cervical stroma.

### Prognosis and predictive factors

Because these neoplasms are rare, management is individualized. The therapy is usually simple hysterectomy, and radiation may be considered for deeply invasive neoplasms. They may recur following conservative therapy by simple excision or polypectomy. The prognostic features are not well established. The prognosis is much better than that of cervical carcinosarcoma [848].

### Wilms tumour

#### Definition

A malignant tumor showing blastema and primitive glomerular and tubular differentiation resembling Wilms tumour of the kidney.

#### Epidemiology

Occasional cases of Wilms tumour arising within the cervix have been described, usually in adolescents [155, 215, 1302].

#### Macroscopy

Macroscopically, these neoplasms are composed of polypoid masses that protrude through the vagina.

#### Histopathology

Histologically, the classic triphasic pattern of epithelial, mesenchymal and blastemal elements may be present.

### Prognosis and predictive factors

In two cases prolonged survival has been reported following local excision and chemotherapy [155, 206, 215, 1302].

### Adenofibroma

#### Definition

A mixed neoplasm composed of benign epithelial and mesenchymal components.



**Fig. 5.43** Adenosarcoma. Leaf-like glands are surrounded by a cuff of cellular mesenchyme.

### Epidemiology

These are uncommon in the cervix and are more commonly found within the uterine body [3245].

### Macroscopy

Cervical adenofibromas are polypoid neoplasms that usually protrude into the endocervical canal. On sectioning small cystic spaces may be identified.

### Histopathology

Histologically, adenofibroma is a benign papillary neoplasm composed of fronds lined by benign epithelium that is usually glandular in type. The epithelium may be cuboidal, columnar, attenuated, ciliated or mucinous.

Occasionally, benign squamous epithelium may be present. The mesenchymal component shows little mitotic activity and is usually composed of non-specific fibrous tissue. The main differential diagnosis is a low grade adenosarcoma; the latter, however, exhibits malignant mesenchymal features including hypercellularity with condensation around glands, nuclear atypia and increased mitotic activity.

### Prognosis and predictive factors

The therapy is usually local excision or simple hysterectomy.

Local excision is usually curative, although recurrence may follow incomplete removal.

### Adenomyoma

#### Definition

A tumour composed of a benign glandular component and a benign mesenchymal component composed exclusively or predominantly of smooth muscle. These tumours are rare within the cervix. A variant is the atypical polypoid adenomyoma.

#### Macroscopy

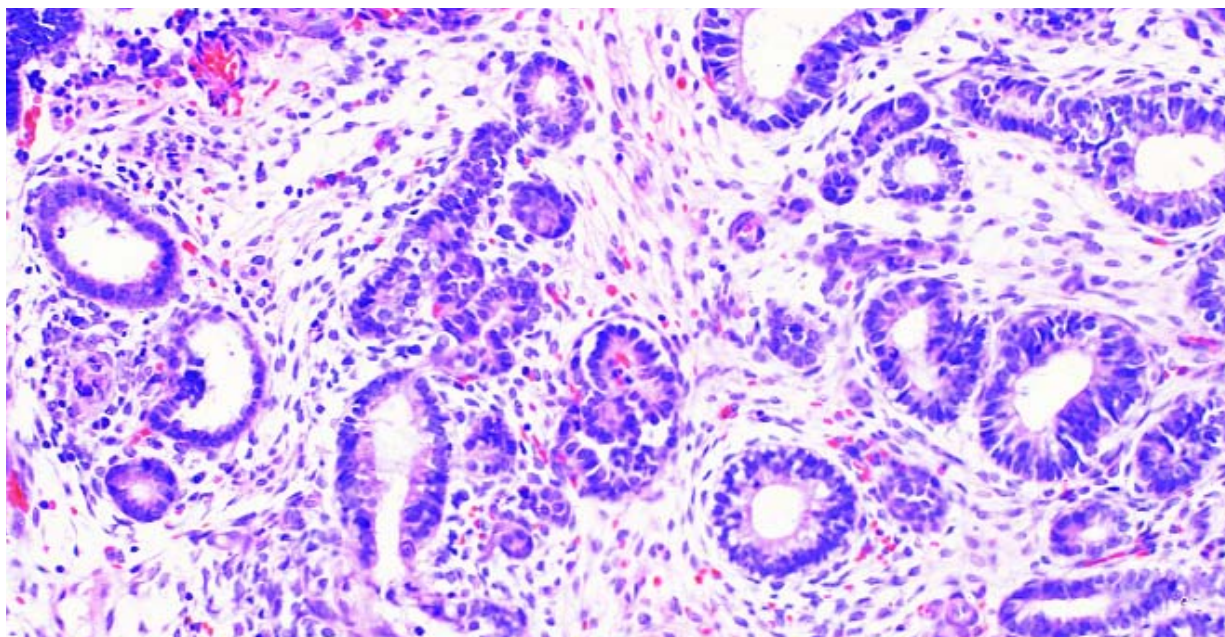
Cervical adenomyomas are usually polypoid lesions with a firm sectioned surface. In some cases small cystic areas may be seen that may contain abundant mucin. Rare tumours are entirely intramural.

#### Histopathology

Three variants of cervical adenomyoma have been described, the endocervical type, the endometrial type and atypical polypoid adenomyoma.

#### Endocervical type

The endocervical type, which may be confused with minimal deviation adenocarcinoma, is composed largely of endocervical mucinous glands surrounded by a mesenchymal component consisting predominantly of smooth muscle [1005]. The glands are lined by tall mucin-secreting cells and are typically irregularly shaped with papillary infoldings. Occasionally, tubal-type epithelium or endometrial-type glands surrounded by endometrial-type stroma are focally present.



**Fig. 5.44** Wilms tumour. The tumour is composed of primitive tubules set in a background of renal blastema.

ent. Both the epithelial and smooth muscle components are uniformly bland without any significant mitotic activity. Differentiating features from minimal deviation adenocarcinoma include the well circumscribed nature of adenomyoma and the absence of a desmoplastic stromal reaction or focal atypia [1005].

#### **Endometrial type**

Another variant of cervical adenomyoma is similar to that found within the corpus [1002]. It is composed of endometrial-type glands surrounded by endometrial-type stroma that is, in turn, surrounded by smooth muscle that predominates. The glands and stroma are bland. Minor

foci of tubal, mucinous or squamous epithelium may be found. These adenomyomas may or may not be associated with uterine adenomyosis. The most likely differential diagnoses are atypical polypoid adenomyoma and low grade adenosarcoma.

#### **Atypical polypoid adenomyoma**

In atypical polypoid adenomyoma the glandular component exhibits architectural complexity that is usually marked. It is similar to the corresponding tumour within the uterine corpus and usually involves the lower uterine segment or upper endocervix (see chapter on uterine corpus).

#### **Prognosis and predictive factors**

Simple polypectomy or local excision cures most cervical adenomyomas. However, recurrences have been described following local excision, and residual tumour may be found at hysterectomy.



# Melanotic, germ cell, lymphoid and secondary tumours of the cervix

C.B. Gilks  
S. Carinelli

### Definition

A variety of primary benign or malignant tumours of the uterine cervix that are not otherwise categorized as well as secondary tumours.

### ICD-O codes

Malignant melanoma	8720/3
Blue naevus	8780/0
Yolk sac tumour	9071/3
Dermoid cyst	9084/0
Mature cystic teratoma	9080/0

### Malignant melanoma

#### Definition

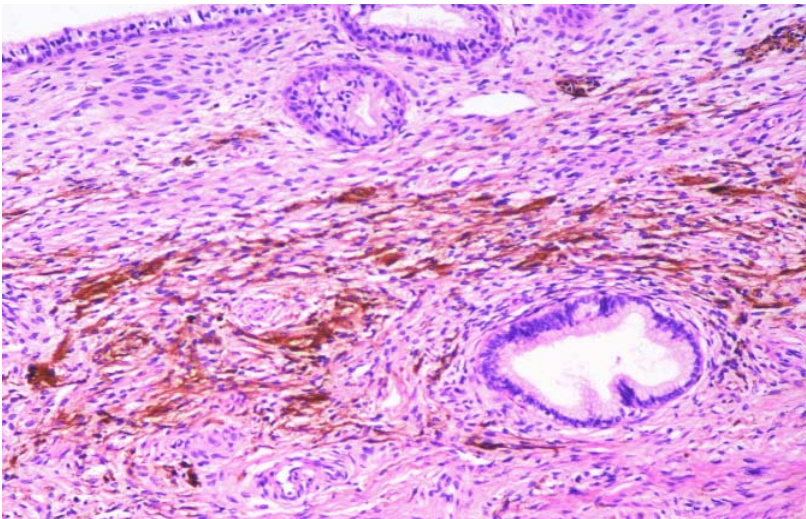
A malignant tumour of melanocytic origin.

#### Epidemiology

Malignant melanoma of the cervix is considerably less common than vulvar or vaginal melanoma with fewer than 30 well documented cases reported {396, 667,940}. All occurred in adults, and approximately one-half had spread beyond the cervix at the time of presentation {396}.

#### Clinical features

These tumours commonly present with abnormal vaginal bleeding. Malignant melanomas are typically described as polypoid or fungating, pigmented masses. However, they may be amelanotic and non-specific in appearance.



**Fig. 5.45** Blue naevus of the cervix. Note the aggregates of heavily pigmented dendritic melanocytes within the endocervical stroma.

#### Tumour spread and staging

Spread to the vagina is often present at the time of presentation {396}.

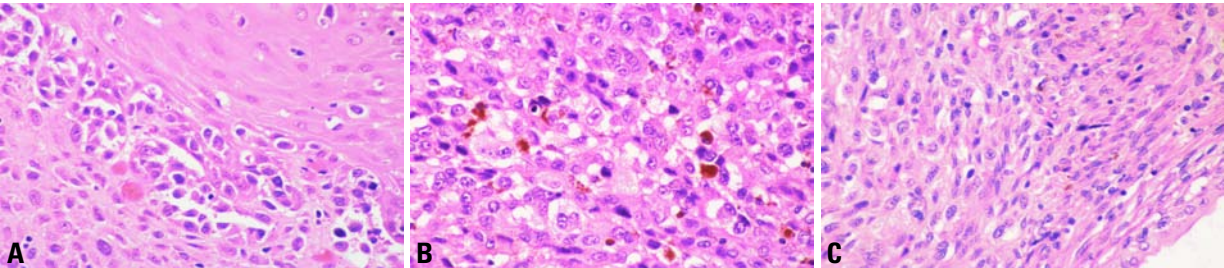
#### Histopathology

A junctional component was reported in approximately 50% of cases. In tumours lacking a junctional component, exclusion of the possibility of metastatic melanoma to the cervix requires clinical correlation. The histological appearance of cervical melanomas is noteworthy for the frequent presence of spindle-shaped cells. Desmoplastic and clear cell variants have also been reported {940, 1306}. The immunophenotype of cervical melanoma is indistinguishable from that of other sites.

ants have also been reported {940, 1306}. The immunophenotype of cervical melanoma is indistinguishable from that of other sites.

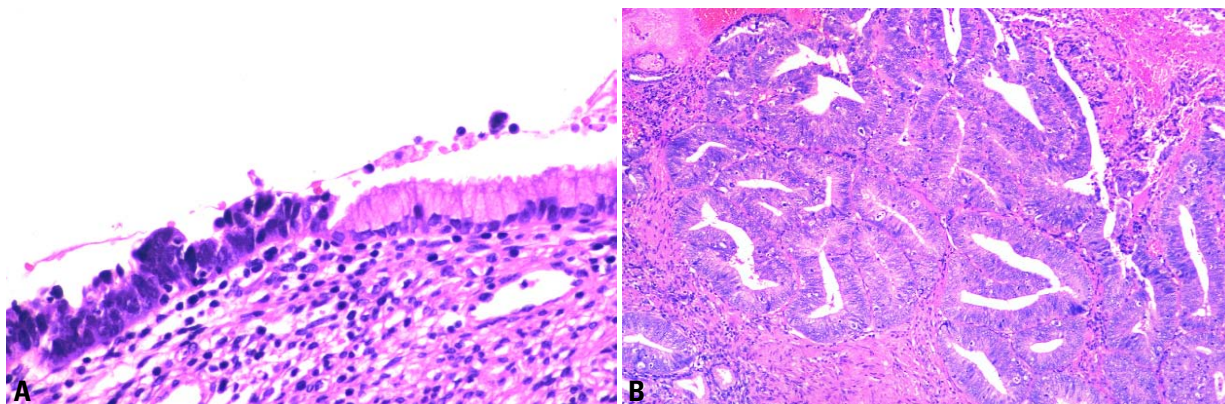
#### Prognosis and predictive factors

The prognosis for patients with cervical melanoma is dismal, with only two reports of patients surviving more than 5 years {1360,2893}.



**Fig. 5.46** Malignant melanoma of the cervix. **A** The tumour shows junctional growth and transepidermal migration. **B** This tumour is composed of large epithelioid cells with pleomorphic nuclei in association with melanin pigment. **C** Note the spindle cell growth pattern of malignant melanocytes.





**Fig. 5.47** Implant of endometrial carcinoma. **A** Non-invasive implant. To the right is the mucinous epithelium of the endocervix; to the left the epithelium has been replaced by malignant epithelium of endometrioid type. **B** Invasive implant. Note the aggregates of well differentiated endometrioid carcinoma in the stroma that do not conform to the pattern of endocervical glands.

### Blue naevus

#### Definition

A naevus composed of dendritic melanocytes that are typically heavily pigmented.

#### Clinical features

Benign pigmented lesions are asymptomatic and are typically incidental findings in hysterectomy specimens [2972, 2973]. As most blue naevi occur in the endocervical canal, they are not visible colposcopically [2972, 2973]. Occasional examples are visible as pigmented macules on the ectocervix with a smooth overlying mucosa [1744].

#### Histopathology

Blue naevi are recognized histologically by the presence of poorly circumscribed collections of heavily pigmented, bland, spindle-shaped cells with fine dendritic processes in the superficial cervical stroma. They are most commonly located under the endocervical epithelium, but examples that involved the ectocervix have been reported [1744].

#### Differential diagnosis

The differential diagnosis includes other benign melanocytic lesions. In contrast to the frequency with which blue naevi are encountered, the cervical equivalent of common junctional, compound or intra-dermal naevi of skin is vanishingly rare in the cervix, with no convincing examples reported. Benign melanosis [3182] and lentigos [2568] of the ectocervical squamous mucosa are, however, occasionally encountered.

### Yolk sac tumour

#### Definition

A primitive malignant germ cell tumour characterized by a variety of distinctive histological patterns, some of which recapitulate phases in the development of the normal yolk sac.

#### Synonym

Endodermal sinus tumour.

#### Epidemiology

The cervix is the second most common site in the lower female genital tract for yolk sac tumour after the vagina. It may be difficult or impossible to determine the primary site (vagina vs. cervix) in some cases [557].

#### Clinical features

These tumours commonly present with abnormal vaginal bleeding. Yolk sac tumours are polypoid, friable masses, protruding into the vagina [557].

#### Histopathology

The histological features are the same as for vaginal yolk sac tumours [557, 3213].

#### Prognosis and predictive factors

The prognosis for patients with cervico-vaginal yolk sac tumours is good with modern chemotherapy [1794].

### Dermoid cyst

#### Definition

A mature teratoma characterized by a predominance of one or a few cysts lined

by epidermis accompanied by its appendages.

#### Synonym

Mature cystic teratoma.

#### Clinical features

Cervical teratomas appear as smooth cervical polyps that may be pedunculated [1451].

#### Histopathology

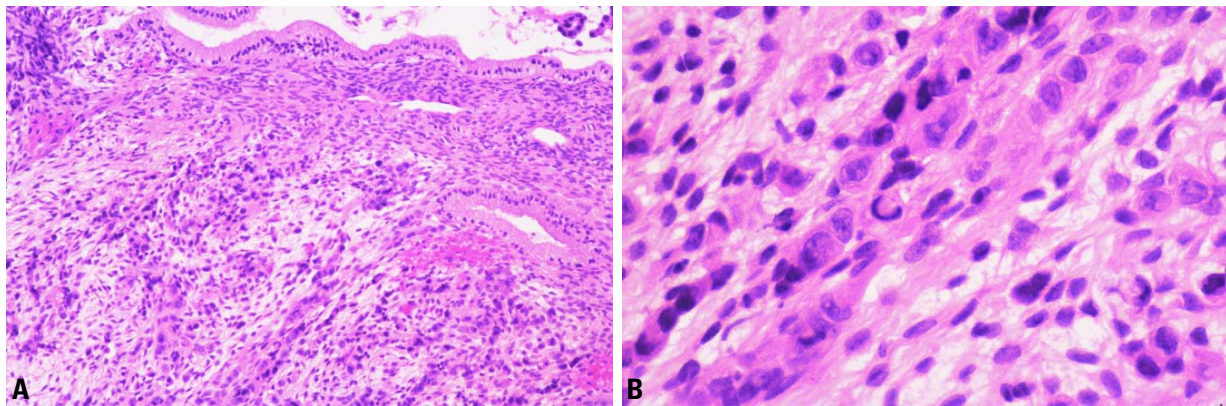
The histological appearance is indistinguishable from mature teratomas at other sites. Glial and squamous epithelial elements are common, but a wide range of mature tissue types have been reported [1451].

#### Differential diagnosis

The differential diagnosis includes benign glial polyp of the cervix, a polypoid mass of mature glial tissue in women of reproductive age that is probably closely related to the cervical dermoid cyst. The former is thought to most probably arise from implantation of fetal tissue [1069, 1711, 2396].

#### Histogenesis

It has been proposed that these are not true neoplasms but are implanted fetal tissues [2968]; molecular studies to determine whether the cells of cervical teratomas are genetically identical to the host and, thus, neoplastic rather than fetal in origin have not been performed.



**Fig. 5.48** Metastatic gastric carcinoma to the uterine cervix. **A** Solid aggregates of metastatic carcinoma occur within the endocervical stroma. Note the surface endocervical mucinous epithelial lining and the endocervical glands in the upper portion of the field. **B** Note the cords of highly pleomorphic neoplastic cells within the endocervical stroma.

## Lymphoma and leukaemia

### Definition

A malignant lymphoproliferative or haematopoietic neoplasm that may be primary or secondary.

### Epidemiology

Involvement of the cervix by lymphoma or leukaemia may rarely be primary but is more commonly part of systemic disease with no specific symptoms referable to the cervix [1145].

### Clinical features

With cervical involvement by lymphoma or leukaemia the cervix appears enlarged and barrel-shaped, although polypoid or nodular masses may be seen [1145,2457,3000]. For the histological description see chapter on the vagina.

## Secondary tumours

### Definition

Tumours of the uterine cervix that originate outside the cervix.

### Incidence and origin

The majority of clinically significant secondary tumours of the cervix originate in the female genital system (endometrium ovary, vagina and fallopian tube in that order) [1625,1939]. Endometrial carcinoma presents with stage II disease in 12% of patients [576]. Secondary cervical involvement is more common with high grade endometrial carcinoma, including serous carcinoma [576]. Extragenital pri-

mary sites include the breast, stomach and large bowel [1625,2608]. Cervical involvement by an extragenital tumour is almost always associated with disseminated disease and rapid progression to death. In occasional cases, however, cervical involvement may be the only evidence of disease at presentation or the first sign of recurrence [1087,1625,1802,2892].

### Clinical features

The most common symptom of secondary cervical tumour is abnormal bleeding [1625,1939,2608]. Malignant cells may be detected on cervical cytologic preparations [1087]. On examination there are usually no abnormalities of the cervix [1939]. Occasionally, the cervix may appear enlarged, nodular or distorted, tumour may protrude from the os, or the cervix may be abnormally firm on palpation [1625,1802,2608,3179].

Secondary cervical involvement by endometrial carcinoma may present as raised nodules of tumour in the endocervical canal and have a similar appearance to the primary endometrial tumour. In most cases of stage II endometrial carcinoma, however, no clinical abnormality is evident [2608].

### Histopathology

Secondary involvement of the cervix by endometrial carcinoma may be superficial with replacement of normal cervical epithelium by neoplastic cells of endometrial carcinoma (Stage IIA) or tumour may invade the underlying stroma (Stage IIB). The assessment of possi-

ble invasion into the cervical stroma poses the same problems in cases of secondary involvement of the cervix by endometrial carcinoma as for primary cervical adenocarcinoma. The cervical tumour may be either discontinuous or contiguous with the dominant endometrial tumour [2608]. Metastases of endometrial carcinoma to the cervix by lymphatic spread are less common than superficial mucosal implants and are present in only 6% of stage II endometrial carcinomas [2608]. The distinction of primary cervical adenocarcinoma from secondary involvement may be difficult or impossible in a small biopsy, as the different histological subtypes of adenocarcinoma seen in the female genital tract are not site-specific. Metastases from extragenital primary tumours may be suspected based on the submucosal location of tumour cells with a normal overlying cervical epithelium. Widespread lymphatic dissemination is also suggestive of a secondary origin. In the case of metastatic lobular carcinoma of the breast or diffuse gastric carcinoma, small nests, cords and individual cells infiltrate the cervical stroma, an appearance not characteristic of primary cervical adenocarcinoma.