Tumours of the Anal Canal

Although incidence rates are still low, there has been a significant increase in squamous cell carcinoma over the last 50 years. HIV infected homosexual men appear particularly at risk, HPV DNA is detectable in most anal squamous cell carcinomas.

Despite its short length, the anal canal produces a variety of tumour types reflecting its complex anatomic and histological structure. Squamous, glandular, transitional, and melanocytic components occur at this site, either alone, or in combination.
### WHO histological classification of tumours of the anal canal

<table>
<thead>
<tr>
<th>Epithelial tumours</th>
<th>Undifferentiated carcinoma</th>
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<tbody>
<tr>
<td>Intraepithelial neoplasia(^1) (dysplasia)</td>
<td>Others</td>
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<td>Squamous or transitional epithelium</td>
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<td>Glandular</td>
<td>Carcinoid tumour</td>
<td>8240/3</td>
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<td>Paget disease</td>
<td>Malignant melanoma</td>
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<td>Carcinoma</td>
<td>Non-epithelial tumours</td>
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<td>Squamous cell carcinoma</td>
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<td>Mucinous adenocarcinoma</td>
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<td>Small cell carcinoma</td>
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\(^1\) Behaviour is coded \(/0\) for benign tumours, \(/3\) for malignant tumours, \(/2\) for in situ carcinomas and grade III intraepithelial neoplasia, and \(/1\) for unspecified, borderline or uncertain behaviour. Intraepithelial neoplasia does not have a generic code in ICD-O. ICD-O codes are available only for lesions categorized as squamous intraepithelial neoplasia, grade III (8077/2), squamous cell carcinoma in situ (8070/2), transitional cell carcinoma in situ (8120/2), glandular intraepithelial neoplasia, grade III (8148/2), and adenocarcinoma in situ (8140/2).

### TNM classification of tumours of the anal canal

<table>
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<th>TNM classification(^2)</th>
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<tr>
<td><strong>T – Primary Tumour</strong></td>
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<td><strong>N – Regional Lymph Nodes</strong></td>
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\(^2\) [1, 66]. This classification applies only to carcinomas.

\(^1\) A help desk for specific questions about the TNM classification is available at http://tnm.uicc.org.

\(^3\) This includes cancer cells confined within the glandular basement membrane (intraepithelial) or lamina propria (intramucosal) with no extension through muscularis mucosae into submucosa.
Tumours of the anal canal

Definition
Tumours that arise from or are predominantly located in the anal canal. The most frequent neoplasms of this region are human papilloma virus (HPV)-associated squamous cell carcinomas and adenocarcinomas.

Topographic definition of anal canal and anal margin
The anal canal is defined as the terminal part of the large intestine, beginning at the upper surface of the anorectal ring and passing through the pelvic floor to end at the anus [68]. The most important macroscopic landmark in the mucosa is the dentate (pectinate) line composed of the anal valves and the bases of the anal columns. Histologically, the mucosa can be divided into three zones. The upper part is covered with colorectal type mucosa. The middle part is the anal transitional zone (ATZ), which is covered by a specialized epithelium with varying appearances; it extends from the dentate line and on average 0.5-1.0 cm upwards [490, 1929]. The lower part extends from the dentate line and downwards to the anal verge and has formerly been called the pecten. It is covered by squamous epithelium, which may be partly keratinized, particularly in case of mucosal prolapse. The perianal skin (the anal margin) is defined by the appearance of skin appendages. There exists no generally accepted definition of its outer limit [62, 66, 845]. The term anus refers to the distal external aperture of the alimentary tract. Anal margin tumours are classified according to the WHO histological typing of skin tumours [682].

Squamous cell carcinoma

Definition
Squamous cell carcinoma (SCC) of the anal canal is a malignant epithelial neoplasm that is frequently associated with chronic HPV infection.

ICD-O code
8070/3

Epidemiology
SCC of the anal canal and anal margin typically occurs among patients in their 6th or 7th decade of life [540]. However, anal SCCs may occur in young adults, particularly in patients with cellular immune incompetence [1212]. Unselected, population-based studies show an approximate 2:1 female predominance among patients with anal SCC [540, 600, 1213]. There are few published, histologically verified incidence rates of anal cancer [540]. Data from most population-based cancer registries worldwide show age standardized incidence rates of anal SCC of between 0.5 and 1.0 per 100,000 in women and between 0.3 and 0.8 per 100,000 in men [1471]. Still a relatively rare disease, anal SCC has shown a remarkable increase in incidence during the past half century [540, 600, 1213]. From being similar in the two sexes until approximately 1960 at 0.2 per 100,000, annual age-adjusted incidence rates in Denmark rose 2.5-fold in men and 5-fold in women during the period 1943-1994. For both men and women, urban populations are at higher risk than rural populations [540, 600, 1213], and there are considerable racial differences in incidence. In the United States, blacks tend to have higher incidence rates than whites [1213], while Asians and Pacific Islanders appear to be at very low risk [70]. Homosexual men appear to constitute a group at particular risk [368, 538, 140, 96, 369, 540, 1213, 1690, 730]. In the United States, the incidence of anal SCC in homosexual men has been estimated to be 11 to 34 times higher than in the general male population and approximately as high as the incidence of cervical cancer before the introduction of cervical cytology screening [369, 1447]. HIV infected homosexual men appear to be at particularly risk [1212, 1449, 598]. Other sexual factors strongly associated with anal SCC include number of sexual partner, receptive anal intercourse, and co-existence of sexually transmitted diseases [368, 538, 730, 733].

Aetiology
Sexually transmittable human papillomaviruses (HPVs) are detected by PCR in the majority of anal SCC [355, 367, 538, 704, 732, 1448]. One large study showed that SCCs involving the anal canal are more often high-risk HPV positive (92%) than lesions confined to the perianal skin (64%) [536], suggesting that HPV-unrelated pathways may apply particularly to cancers of the perianal skin. A strong association with tobacco smoking has been established in women, but the role of smoking in men is less clear [367, 539, 730, 733]. States of cellular immunosuppression are associated
with increased risk of anal squamous cell carcinoma. This has been observed for renal transplant recipients (150, 1494) and for patients with HIV infection and AIDS (1212).

Haemorrhoids and fissures, fistulae and abscesses in the anal region were long considered predisposing factors (192, 198, 1618). However, three case-control studies (368, 537, 733) and two cohort studies (541, 1074) failed to support the association. Crohn’s disease of long duration, which has been implicated in the aetiology of anal SCC based on case reports (992, 1765), was not associated with risk in the only controlled study addressing the issue (537).

Oestrogen and androgen receptors have been found in the anal mucosa and its supportive tissue (1396), suggesting a physiological role of sex hormones in their maintenance. Women who reach menarche late and women with short fertile periods may be at elevated risk of anal SCC (539).

Clinical features

Symptoms and signs

Anal intraepithelial neoplasia is often an unexpected finding in minor surgical specimens. Clinical manifestations of anal cancer are often late and non-specific and are mainly related to tumour size and extent of infiltration. They include anal pruritus, discomfort in sitting position, sensation of a pelvic mass, pain, change in bowel habit, incontinence due to sphincter infiltration, discharge, bleeding, fissure, or fistula. The initial non-specificity of clinical features explains why diagnosis can be delayed (855, 1621, 1719, 1835).

The clinical diagnosis of an anal tumour should always be confirmed by histological examination. A forceps or needle biopsy is usually sufficient to establish the diagnosis. The biopsy should be accompanied by an exact description of location and appearance of the biopsy site. An excisional biopsy is inadvisable, because wound healing delay would postpone optimal chemo-radiotherapy treatment. Enlarged lymph nodes may be excised or biopsied with needle aspiration under radiological control.

Imaging

Computerised tomography (CT) scan, magnetic resonance imaging (MRI), and needle aspiration are used to detect inguinal and pararectal node involvement. Endoanal ultrasonography (EUS) enables assessment of spread in terms of proximal and circumferential extension and infiltration of deep layers. Furthermore, EUS enables the follow-up of irradiated carcinomas (703). CT scan and MRI allow detection of involved lymph nodes and distant metastases (1835).

Exfoliative cytology

In patients with increased risk such as individuals with HIV or women with genital tract SCC, the use of anal smears taken with a cytology brush from the area below the dentate line is recommended (1689).

Macroscopy

The tumour may present as a small ulceration or fissure with slightly exophytic and indurated margins, and irregular thickening of the anoderm and anal margin with chronic dermatitis. The lesion may have a different colour from the surrounding tissue.

If ulceration and infiltration develop, the lesion becomes fixed to the underlying structures and may bleed. In advanced stages, the sphincteric muscles are deeply infiltrated although there may be little mucosal ulceration.
tumour cells may be facilitated by immunostaining for high molecular weight cytokeratins (CKs).

In 15-20% of cases, the lesion may infiltrate the lower rectum and the neighbouring organs including the rectovaginal septum, bladder, prostate and posterior urethra, sometimes with suppuration and fistulas. The vulva is usually spared. Lymphatic spread occurs in up to 40 percent of cases [165, 1174, 1621, 1719, 2033]. Tumours proximal to the pectinate line drain into the pelvis along the middle rectal vessels to the pelvic side walls and internal iliac chains and superiorly via the superior rectal vessels to the periaortic nodes. Tumours distal to the dentate line drain along cutaneous pathways to the inguinal and the femoral nodal chains. Inguinal nodes are involved in about 10-20% of cases [230, 575, 1174, 1650, 1692]. Inguinal lymph nodes can be involved bilaterally in a small number of cases at time of presentation. Retrograde lymphatic drainage occurs in advanced cases when the lymphatics are obstructed by malignant spread [1621, 1719].

**Histopathology**  
*Squamous cell carcinoma of anal canal*

Anal SCC may show a single predominant line of differentiation, but most exhibit a mixture of areas with different histological features. One pattern is that of large, pale eosinophilic cells and keratinization of either lamellar or single cell type. Another is that of small cells with palisading of the nuclei in the periphery of tumour cell islands. The latter often contain necrotic eosinophilic centres. Intermediate stages between these two extremes are often present. Differentiation into tubular or spindle cell configuration may be found. The invasive margin can vary from well circumscribed to irregular, and a lymphocytic infiltrate may be pronounced or absent. None of these features have been shown to have any prognostic significance, but poor keratinization, prominent basaloid features and small tumour cell size are related to infection with ‘high risk’ HPV [536]. The keratin profile of anal SCC is complex and variable [2112, 2113]. The usual immunexpression pattern is shown in Table 7.01. The second edition of the WHO classification of SCC in the anal canal included the large-cell keratinizing subtype, the large-cell non-keratinizing subtype, and the basaloid subtype [845]. The value of this classification of anal SCC has been questioned in recent years. Many tumours show more than one subtype. Thus in a study of 100 cases of anal carcinomas, 99 showed some features of squamous differentiation (keratinisation, stratification and prickles), 65 showed basaloid features (small cell change, palisading, retraction artefact and central eosinophilic necrosis) and 26 showed focal evidence of ductal proliferation and occasionally positive staining for PAS after diastase digestion [2111]. Furthermore, the diagnostic reproducibility of these subtypes is low [492]. This is probably the reason that the proportion of basaloid carcinoma in larger series has varied from 10 to almost 70 %, and that no significant correlation between histological subtype and prognosis has been established. In addition, the histological diagnosis is nowadays nearly always performed on small biopsies, that may not be representative for the whole tumour [492]. Therefore, it is recommended that the generic term ‘squamous carcinoma’ be used for these tumours, accompanied by a comment describing those histopathological features that may possibly affect the prognosis or reflect different aetiologies, i.e. size of predominant neoplastic cell, basaloid features, degree of keratinisation, adjacent squamous intraepithelial neoplasia, or presence of mucinous microcysts.

Apart from the verrucous carcinoma mentioned below, only two rare histological subtypes seem to have a different biological course, both having a less favourable prognosis [1734]. One is characterized by areas with well formed acinar or cystic spaces containing mucin that reacts with Alcian dyes or PAS after diastase digestion. This is termed *squamous cell carcinoma with mucinous microcysts*. The other is characterized by a rather uniform pattern of small tumour cells with nuclear moulding, high mitotic rate, extensive apoptosis and diffuse infiltration in the surrounding stroma. This has been called *small cell (anaplastic) carcinoma*, but should not be confused with small cell carcinoma (poorly differentiated neuroendocrine carcinoma).

**Fig. 7.06** Well differentiated squamous cell carcinoma composed of large cells showing keratinization.

**Fig. 7.07** Squamous cell carcinoma composed of basaloid cells. Central necrosis (N) of tumour nests is typical.

**Fig. 7.08** Squamous cell carcinoma showing a combination of basaloid and squamous features.

**Squamous cell carcinoma of anal margin**

The distinction between anal canal and anal margin SCC may be difficult, as tumours often involve both areas at the time of diagnosis. This may account for the varying data on prognosis, but this is generally better for anal margin SCC than for anal canal SCC, in particular if local resection is possible [392, 530, 1484]. Anal margin SCC is often of the large cell variant [536, 1484].

**Verrucous carcinoma**

In the anogenital area, this tumour is also called giant (malignant) condyloma or Buschke-Lowenstein tumour. It has a cauliflower-like appearance, is larger than the usual condyloma with a diameter up to 12 cm, and fails to respond to
conservative treatment. In contrast to an ordinary condyloma, it is characterized by a combination of exophytic and endophytic growth. Histologically, it shows acanthosis and papillomatosis with orderly arrangement of the epithelial layers and an intact but often irregular base with blunt downward projections and keratin-filled cysts. The endophytic growth is accompanied by destruction of the underlying tissues. Cytologically, the epithelial cells appear benign. Large nuclei with prominent nucleoli may be present, but dysplasia is usually minimal and mitoses are restricted to the basal layers [162]. Some verrucous carcinomas contain HPV, the most common types being 6 and 11. They are regarded as an intermediate state between the ordinary condyloma and SCC, and the clinical course is typically that of local destructive invasion without metastases. Among 33 published anorectal cases, 42 per cent have shown malignant transformation [133]. The presence of severe cytological changes, unequivocal invasion or metastases should lead to the diagnosis of SCC and to the appropriate therapy.

**Grading**

Poor prognosis has been related to poor differentiation [165], especially if this was defined only by the degree of dissociation of tumour cells [599]. However, such differences may be related to tumour stage in multivariate analysis [1734]. Grading on biopsies is not recommended, as these may not be representative for the tumour as a whole.

**Precursor lesions and benign tumours**

**Chronic HPV infection**

Warts in the perianal skin and lower anal canal (condyloma acuminatum) show the same histology as their genital counterparts. Flat koilocytic lesions also occur. They should always be totally embedded and examined histologically for possible presence of intraepithelial neoplasia.

**Intraepithelial neoplasia**

Precancerous anal intraepithelial neoplasia (AIN) in the anal transition zone (ATZ) and the squamous zone, has also been termed dysplasia, carcinoma in-situ and anal squamous intraepithelial lesion (ASIL) [494, 1449]. The corresponding lesions in the perianal skin are commonly referred to as Bowen disease. This terminology is complicated by the fact that the precancerous changes are not always restricted to one area. Leukoplakia is a clinical term and should not be used as a histological diagnosis.

**Anal intraepithelial neoplasia (squamous cell dysplasia in the anal canal).** Most cases of AIN are incidental findings in minor surgical specimens for benign conditions. When macroscopically detected, AIN may present as an eczematoid or papillomatous area, or as papules or plaques. The latter may be irregular, raised, scaly, white, pigmented or erythematous and occasionally fissured. Induration or ulceration may indicate invasion. Histologically, AIN is characterized by varying degrees of loss of stratification and nuclear polarity, nuclear pleomorphism and hyperchromatism, and increased mitotic activity with presence of mitoses high in the epithelium. The surface may or may not be keratinized, and koilocytic changes may be present. AIN has been graded into I, II or III, or into mild, moderate and severe dysplasia [494]. Reproducibility studies have shown considerable observer variation [254]. A two grade system (low- and high-grade) may be more appropriate.

**Squamous dysplasia at the anal margin - Bowen disease.** Clinically, this presents as a white or red area in the perianal skin that may be in continuity with dysplastic lesions in the anal canal. HPV DNA is sometimes identified, including types 16 and 18, among others. Histologically it shows full thickness dysplasia of the squamous and sometimes the pilosebaceous epithelium, with disorderly maturation, mitoses at all levels and dyskeratosis. Occasionally, atypical keratinocytes may resemble Paget cells, but are negative for low molecular weight CKs and for mucin. In pigmented Bowen disease the neoplastic cells are invariably negative.
Bowen disease has a strong tendency to recurrence after local treatment but only a few percent will progress to SCC. It is often associated with genital neoplasia but not with internal malignancies [1161, 1668].

Bowenoid papulosis. This condition presents as multiple 2-10 mm reddish brown papules or plaques, most commonly in sexually active young adults. Aetiologically it is related to HPV infection, usually HPV 16. Bowenoid papulosis is similar histologically to Bowen disease, and the distinction is made on a combination of clinical and pathological observations. Bowenoid papulosis tends to resolve spontaneously, but can recur [635]. It does not progress to carcinoma.

Genetic susceptibility
Human leukocyte antigens (HLAs) are involved in the presentation of viral antigens to the immune system. Since the aetiology of most anal SCCs involves HPV infection [536], susceptibility to cancer development might be HLA type dependent. However, no study has addressed the association between specific HLA class I or II alleles and the risk, and attempts to identify other genetic susceptibility markers for anal SCC have so far been unsuccessful [286, 287].

Genetics
HPV DNA is detectable in most anal SCCs; in a large population-based series of anal SCCs in Denmark and Sweden, 84% contained HPV DNA, with higher proportions of HPV-DNA positive cancers among women and homosexual men than among non-homosexual men [536].

Loss of functional tumour suppressor protein p53 appears to be centrally involved in the development of anal and anogenital SCCs [355, 356, 704, 1040]. Inactivation of p53 may occur at the gene level through point mutations leading to the production of inactive p53 or, less frequently, by means of deletions in the relevant area of chromosome 17p [704]. More typically, p53 inactivation occurs at the protein level through formation of a complex between the viral protein E6 (expressed by ‘high-risk’ HPV types) and a cellular protein, the E6-associated protein, which when bound to p53 leads to rapid proteolytic degradation of p53 [2092]. The level of p53 expression does not correlate with HPV status [704]. The E7 protein of ‘high risk’ HPV types binds to the retinoblastoma protein, pRb [440], disrupting signals that normally restrict proliferation to the basal epithelial layer. The resulting increased proliferation increases the risk of malignant transformation on exposure to DNA damaging stimuli. The combination of increased cell proliferation (pRb inactivation) and impaired ability to induce cell cycle arrest or apoptosis following DNA damage (p53 inactivation) are two central mechanisms through which ‘high risk’ types of HPV increase the risk of anal genital cancer.

Additional gene alterations appear to be involved in malignant progression and invasion. In one study, the c-myc gene was found to be amplified in 30% of anal SCCs [355], while other cellular oncoproteins, including ras and cyclin D, do not seem to be centrally involved [708, 1737]. Several chromosomal aberrations have been observed in anal SCCs [704, 1294]. Using comparative genomic hybridization, one study identified consistent gains in chromosomes 3q, 17, and 19 as well as losses in chromosomes 4p, 11q, 13q, and 18q [704].

Prognosis and predictive factors
The most important prognostic factors in recent larger series of anal canal SCC are tumour stage and nodal status [530, 1483, 1734]. SCC of the anal margin has a slightly better prognosis, which depends only on inguinal node involvement [1484]. DNA ploidy status has only been shown to be of independent prognostic significance in one of three larger series [599, 1702, 1734]. Expression of p53, cathepsin D, c-erb B2 and retinoblastoma gene protein are not predictive factors [169, 731, 784, 1901].

Adenocarcinoma

Definition
Anal canal adenocarcinoma is an adenocarcinoma arising in the anal canal epithelium, including the mucosal surface, the anal glands and the lining of fistulous tracts.

ICD-O code

Clinical features
The clinical features of anal adenocarcinoma of colorectal type do not differ from those of anal SCC. Perianal adenocarcinomas may present as submucosal tumours, sometimes in combination with fistulas. Occasionally, there may be...
associated Paget disease of the anus (see below). Tumour spread and staging largely correspond to anal SCC.

**Histopathology**

**Adenocarcinoma arising in anal mucosa**

Most adenocarcinomas found in the anal canal represent downward spread from an adenocarcinoma in the rectum or arise in colorectal type mucosa above the dentate line. Macroscopically and histologically, they are indistinguishable from ordinary colorectal type adenocarcinoma, and do not seem to represent a special entity except for their low location. Adenocarcinoma in the anal transitional zone (ATZ) may develop after restorative proctocolectomy for ulcerative colitis (1711).

**Extramucosal (perianal) adenocarcinoma**

Approximately two hundred cases of extramucosal adenocarcinoma have been reported, the largest series unfortunately with insufficient histological data (9). A minimum criterion for the diagnosis is an overlying non-neoplastic mucosa, which may be ulcerated. Recent reports indicate that about two thirds of these tumours manifest in men with a mean age about 60 years. Reliable data for the prognosis for such patients have not been identified. Difficulties in establishing the correct diagnosis may delay proper treatment.

Extramucosal adenocarcinoma seem to fall into two groups, based on their association with either fistulae or remnants of anal glands. At present, no laboratory methods can distinguish between these two.

The epithelium of persistent anal fistulae is most often of the same type as found in the anal glands and ATZ (1117), and the epithelium in these two locations show the same profile with regard to mucin composition (491) and keratin expression (2113).

**Adenocarcinoma within anorectal fistula.**

These tumours develop in pre-existing anal sinuses or in fistulae (74). Some are associated with Crohn disease (992). Others may contain epithelioid granulomas, often related to foci of inflammation or extravasated mucin but without other signs of inflammatory bowel disease (863). Rarely, the tumours may be related to fistulae lined by normal rectal mucosa including muscularis mucosae, most likely representing adenocarcinomas arising in congenital duplications (863). Histologically, carcinomas arising in fistulae usually are of the mucinous type, but tubular adenocarcinomas and squamous neoplasia can also be found (992, 2173).

**Adenocarcinoma of anal glands.**

Only a few cases have been reported in which convincing evidence for origin in an anal gland has been demonstrated by continuity between anal gland epithelium and tumour (118, 650, 1472, 2087, 2131). With a single exception (650), these patients have had no history of previous or concomitant fistula. The tumours were all characterized by a combination of ductular and mucinous areas. Pagetoid spread was present in at least one case (2131).
Grading
Anal adenocarcinomas are graded as colorectal adenocarcinomas.

Precursor lesions
Anal adenocarcinomas are thought to arise from glandular intraepithelial neoplasia, which can be graded as in the colorectum.

Prognosis and predictive factors
The prognosis for anal adenocarcinoma seems to be related only to the stage at diagnosis and is poorer than that for SCC (118, 930, 1305).

Basal cell carcinoma of the anal margin
Basal cell carcinoma, the most common skin cancer, is primarily found on sun-exposed areas, and only a few more than a hundred cases have been reported in the anal area. (1353). The aetiology is unknown and there is no evidence of HPV infection (1332). The tumour commonly presents as an indurated area with raised edges and central ulceration, located in the perianal skin but occasionally involving the squamous zone below the dentate line. Histologically, it can show the same variability in morphology as basal cell carcinoma elsewhere, most reported cases having had a solid or adenoid pattern. Basal cell carcinoma is sufficiently treated by local excision and metastases are extremely rare. It is therefore important to distinguish it from squamous carcinoma, and this may be particularly difficult on small biopsies. Both tumours can be found in the squamous zone, and both can show a combination of basaloid, squamous and adenoid features and an inflammatory infiltrate in the stroma (50). Numerous and even atypical mitoses may be present in basal cell carcinomas (1538). However, basaloid areas in squamous carcinoma usually show less conspicuous peripheral palisading, more cellular pleomorphism, and often large, eosinophilic necrotic areas. Immunohistochemistry may be helpful in establishing the diagnosis. Basal cell carcinoma is positive for Ber-EP4 and negative for CKs 13, 19 and 22, and for CEA, EMA, AE 1 and UEA 1, while basaloid variants of squamous cell carcinoma usually show the opposite pattern (50, 1061).

Paget Disease
Extramammary Paget disease usually affects sites with a high density of apocrine glands, such as the anogenital region, where it presents as a slowly spreading, erythematous eczematoid plaque that may extend up to the dentate line (1667). Histologically, the basal part or whole thickness of the squamous epithelium is infiltrated by large cells with abundant pale cytoplasm and large nuclei. Occasional cells have the appearance of signet-rings. Paget cells invariably react positively for mucin stains and nearly always for CK 7, but Merkel cells and Toker cells may also be positive for the latter (120, 1112).

Papillary hidradenoma
This rare tumour arises in the perianal apocrine glands, typically in middle aged women and only exceedingly rarely in men (1082). It presents as a circumscribed nodule approximately 1 cm in diameter and may resemble a haemorrhoid. Histologically, it consists of a papillary mass with a cyst-like capsule. The papillae are lined by a double layer of epithelial cells, the outer layer being composed of cells containing mucin. The tumour does not express the eccrine marker IKH-4, but it must be remembered that adenocarcinoma metastases also are negative (811). Convincing examples of anal apocrine adenocarcinoma have not been published.

Keratoacanthoma
There are a few reports on keratoacanthoma arising in the perianal skin (454).

Neuroendocrine tumours
Neuroendocrine tumours may arise in the anus (493, 744). They are, however, conventionally classified as rectal. An immunohistochemical study of 17 rectal neuroendocrine tumours showed that most were of L-cell type (294). For details, see in chapter 5 the section on endocrine tumours of the colon and rectum.
Malignant melanoma

Anal melanoma is rare. It is a disease of adults with a wide age range; most patients are white [339, 182]. Presentation is usually with mass and rectal bleeding, but tenesmus, pain and change in bowel habit also occur [339].

Macroscopy. Lesions may be sessile or polypoid. Pigmentation of the lesion is often appreciated. Satellite nodules may occur.

Histopathology. The features resemble those of cutaneous melanomas. The majority shows a junctional component adjacent to the invasive tumour, and this finding is evidence that the lesion is primary rather than metastatic. The tumour cells express S-100 and HMB-45.

Prognosis. Anal melanomas spread by lymphatics to regional nodes, and haematogenously to the liver and thence to other organs. Metastases are frequent at time of presentation, and the prognosis is poor; the 5-year survival is less than 10% [339, 157]. The chances of long-term survival are increased if the lesion is small.

Mesenchymal and neurogenic tumours

These are all rare and the exact point of origin may be difficult to establish. Recent reports on tumours in the anorectal and perianal area include haemangioma, lymphangioma [372], haemangiopericytoma [478], leiomyoma, malignant fibrous histiocytoma and leiomyosarcoma [1110], rhabdomyoma in a newborn [1014], rhabdomyosarcoma in childhood [1560] and adulthood [902], fibrosarcoma, neurilemmoma and neurofibroma [571], granular cell tumour (myoblastoma) [862], spindle cell lipoma and aggressive angiomyxoma [503] and extraspinal ependymoma in a newborn [2074]. HIV infected persons may, in addition to the increased risk of squamous neoplasia, develop Kaposi sarcoma in the perianal area [113].

Malignant lymphoma

Primary lymphomas of the anorectal region are rare in the general population, but much more common in patients with AIDS, particularly homosexual men. All are of B-cell type, the most common types being large cell immunoblastic or pleomorphic [687, 786]. Langerhans cell histiocytosis has been described in children [617, 874] and an adult [329].
Secondary tumours

Metastases to the anal canal and perianal skin are rare. Most primaries are found in the rectum or colon, but occasionally also in the respiratory tract, breast and pancreas [157, 182, 379, 888, 1767, 489]. There are few reports of metastatic squamous cell carcinoma [574]. Malignant lymphoma, leukaemia and myeloma may infiltrate the anal canal, and eosinophilic granuloma has also been described [489].

Clinically, anal metastases cause similar symptoms to primary tumours at this site, including pain, bleeding and incontinence.

Neoplasia-like lesions

Fibroepithelial polyp

Also called fibrous polyp or anal tag, this is one of the most frequent anal lesions. It may be found in the squamous zone or the perianal skin in up to half of all individuals [2101]. Grossly, the polyp is spherical or elongated with a greater diameter ranging from a few mm up to 4 cm. The surface is white or grey and may show superficial ulceration. Histologically, it consists of a fibrous stroma covered by squamous epithelium, which usually is slightly hyperplastic and may be keratinized. The stroma may be more or less dense and often contains fibroblastic cells with two or more nuclei and a considerable number of mast cells [630]. Neuronal hyperplasia is a common feature [495]. Fibroepithelial polyps may be associated with local inflammation such as fissure or fistula [1084].

Granulomas can be found in about one third of skin tags in cases of Crohn’s disease [1905]. Others may represent the end stage of a thrombosed haemorrhoid, but remnants of haemorrhoidal vessels or signs of previous bleeding are rarely found. Most are probably of idiopathic nature as the incidence is rather similar in patients with or without anal diseases [2101].

Inflammatory cloacogenic polyp

This polyp was first described in 1981 [1083]. It arises in the ATZ and forms a rounded or irregular mass measuring from 1 to 5 cm in diameter. Histologically, it consists of hyperplastic rectal mucosa, partly covered with ATZ type or squamous epithelium. The surface is typically eroded and the stroma shows oedema, vascular ectasia, inflammatory cells and granulation tissue. Vertically oriented smooth muscle fibres are found between the elongated and tortuous crypts. The inflammatory cloacogenic polyp is commonly associated with mucosal prolapse, sometimes in company with haemorrhoids [296, 1052].

Malacoplakia

Cutaneous malacoplakia may arise in immunocompromised patients and present as perianal nodules [1102].

<table>
<thead>
<tr>
<th>Table 7.01</th>
<th>Anal tumours, immunoreactivity profile (exceptions occur, especially among CK and mucin)</th>
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<tr>
<td></td>
<td>CK 8+18</td>
</tr>
<tr>
<td>Colorectal adenocarcinoma</td>
<td>+</td>
</tr>
<tr>
<td>Squamous cell variants</td>
<td>-</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>-</td>
</tr>
<tr>
<td>Neuroendocrine tumour</td>
<td>+</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>-</td>
</tr>
<tr>
<td>Bowen (also pigmented)</td>
<td>-</td>
</tr>
<tr>
<td>Paget cells, local Paget</td>
<td>+</td>
</tr>
<tr>
<td>Paget cells, from CRC</td>
<td>+</td>
</tr>
<tr>
<td>Prostatic carcinoma</td>
<td>+</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>-</td>
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</tbody>
</table>

Chrom = Chromogranin A
CK = Cytokeratin
CRC = Colorectal carcinoma
GCDPP = Gross cystic disease fluid protein
PSA = Prostate specific antigen
PSAP = Prostate specific acid phosphatase
Synap = Synaptophysin
Vim = Vimentin

**Miscellaneous tumours 155**