Neoplasia I: Benign and malignant neoplasms in glandular epithelium and mesenchyme

1.0. Aims

1. To understand the distinction between benign and malignant neoplasms
2. To understand the nomenclature for neoplasms, based on benign versus malignant and tissue of origin (histogenesis)
3. To study multistage development of glandular epithelial neoplasia in the colon
4. To study invasion and metastasis
5. To consider presentation and screening
6. To study benign and malignant neoplasms of the mesenchyme

2.0. Benign versus malignant

The most important feature of a neoplasm is whether it is **benign** or **malignant.** Malignant tumours are capable of invasion and metastasis, i.e. spreading to other tissues, whereas benign tumours do not invade and cannot metastasize. This is crucial for the patient, since it is usually metastases rather than primary tumours that kill. We do not yet understand mechanistically what it is that makes a cell malignant, but benign and malignant tumours can be distinguished by their histological appearances as illustrated by the slides of colorectal epithelial neoplasms and uterine smooth muscle neoplasms.

3.0. Classification, histogenesis and nomenclature

Solid tumours are classified according to whether they are benign or malignant, but also by their **histogenesis** (cell or tissue of origin). Benign tumours are often called [tissue]-**oma**, e.g. lipoma (fat cell benign tumour), leiomyoma (*leio*-smooth, *myo*-muscle benign tumour), adenoma (glandular tissue benign tumour). A glossary of these words is provided at the end of the sheet. Malignant epithelial tumours are mostly called [tissue] **carcinoma** or [tissue] adenocarcinoma (if from glandular epithelial tissue) e.g. colorectal adenocarcinoma. Malignant connective tissue tumours are mostly called [tissue]- **sarcoma,** e.g. liposarcoma (fat cell malignant tumour) or leiomyosarcoma (*leio*-smooth, *myo*-muscle malignant tumour). The common malignant tumours in humans are mostly carcinomas or adenocarcinomas.

3.1. Tumours of epithelium:

Tissue	**Benign**	**Malignant**
Glandular epithelium	Adenoma	Adenocarcinoma
Squamous epithelium	Papilloma	Squamous Carcinoma

3.2. Tumours of Connective Tissues / Mesenchyme:

Tissue	Benign	Malignant
Fibrous tissue	Fibroma	Fibrosarcoma
Bone	Osteoma	Osteosarcoma
Cartilage	Chondroma	Chondrosarcoma
Fat	Lipoma	Liposarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Striated muscle	Rhabdomyoma	Rhabdomyosarcoma

4.0. Colorectal cancer

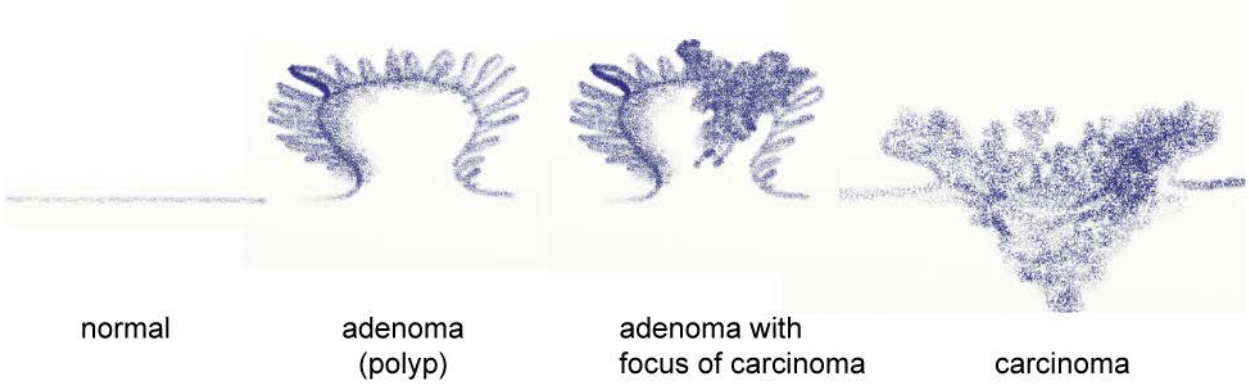
Colorectal neoplasia is one of commonest and best understood cancers. It illustrates well:

- The multistage development of neoplasms
- The difference between benign and malignant neoplasms
- Spread of cancer to other organs, leading to death
- The early detection of cancer or its precursors and possible screening strategies
- The molecular basis of cancer (which we will explore in Practical 25).

Colorectal neoplasia comprises colonic and rectal adenoma (benign) and adenocarcinoma (malignant).

4.1. Multistage development

Cancers develop by accumulating genetic and epigenetic changes that alter the behaviour of the cell. On the way to becoming a cancer, a neoplasm therefore passes through various abnormal precursor states, some of which we can recognize by their microscopic appearances. Early on, an abnormal proliferation of cells in the glandular epithelium of the colon often forms a 'polyp' (polyp is a descriptive term [not a diagnosis] and refers to a head of abnormal cells on a stalk). If the abnormal cells are a **benign (non-invasive)** neoplasm, it is called an **adenoma** or adenomatous polyp. Somewhere in this adenomatous polyp a fully malignant clone may eventually develop, which will gradually take over and grow down into the underlying tissue. This is called an adenocarcinoma.



We will look at four stages: an adenomatous polyp; an adenomatous polyp with a focus of invasive adenocarcinoma in it, where an adenoma cell has converted to

malignancy; an established primary adenocarcinoma invading into the bowel wall; and finally a metastasis to the liver.

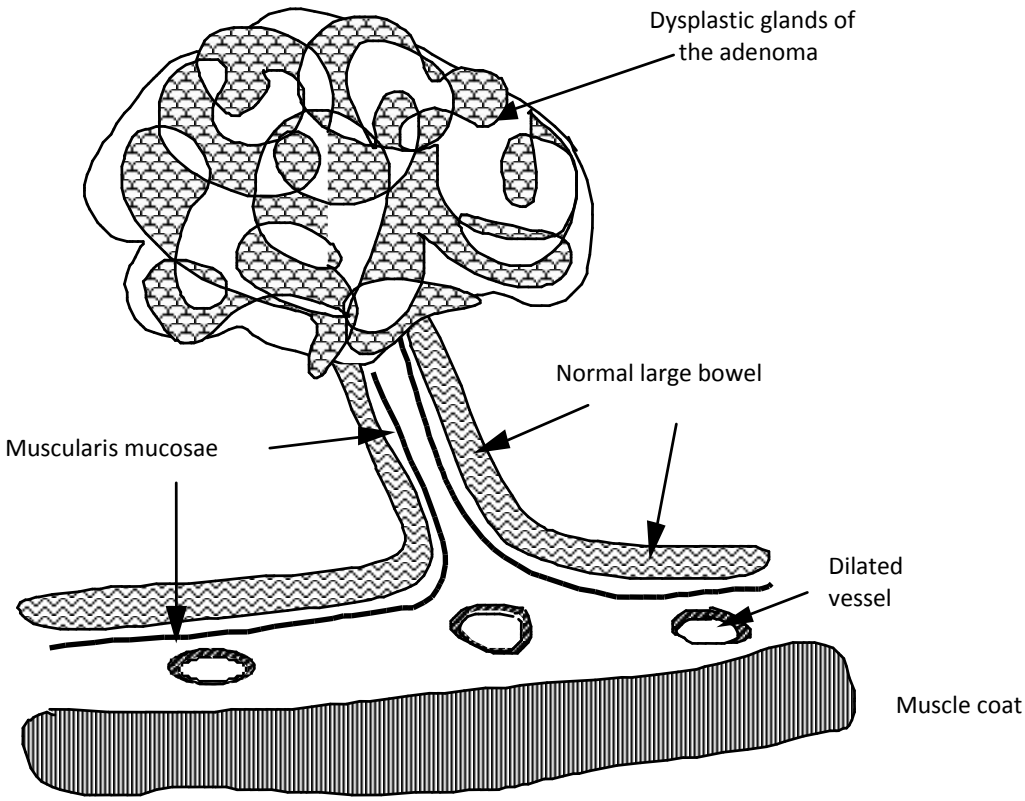
4.2. Colon: Adenoma - a benign precursor of cancer

NDP Images: 23.1: 77.270
Glass Slides: 23.1: 77.270
Image Map: A_NP_PQ_LI_07

Excessive unregulated proliferation of the columnar epithelium has given rise to a **polyp** of branching, tubular pattern on a stalk of normal mucosa. The polyp behaves like a lump that peristalsis tends to pull down the gut, dragging out the normal wall to form the stalk. This is an **adenoma** or **adenomatous polyp** (polyp = head on a stalk). An example is shown in museum specimen I.

The cells of the adenoma are taller, more crowded and contain less mucin than the normal cells, i.e. have lost some differentiated features. The nuclei are seen towards the base of the cells, but show variation in nuclear size, shape and chromatin staining pattern (**pleomorphism**) and stain darkly (**hyperchromasia**). A small number of mitotic figures can be seen. However, this is a benign growth: there is **no invasion** through the muscularis mucosae into the stalk.

Colon : Adenoma
77.27



4.3. Colon: Transition to malignancy – a focus of adenocarcinoma developing in an adenoma

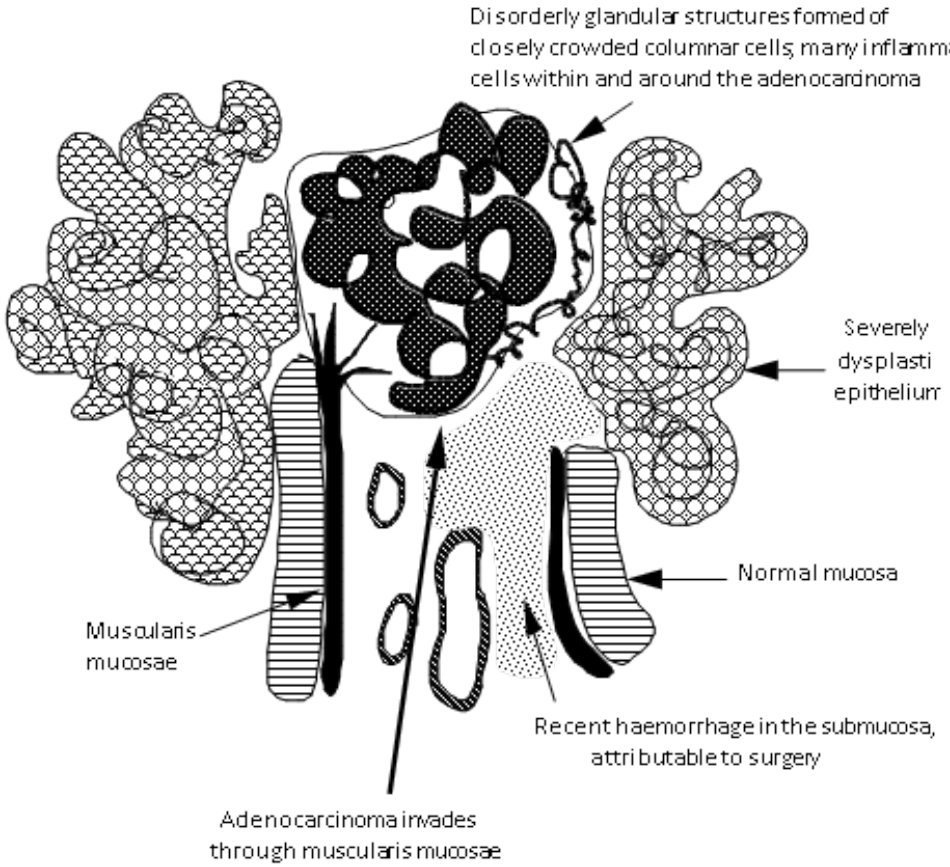
NDP Images: 23.2: 80.280
Glass Slides: 23.2: 80.280
Image Map: A_NP_CA_LI_11

This slide is best understood by reference to the diagram below. Most of it is adenoma, like the preceding example, with a short stalk of normal mucosa at the bottom, but it has a focus of invasive malignant cells in the top centre, a cancer arising from a cell in the adenoma. Even the adenoma part shows more severe (high grade) dysplasia than the preceding example: the glandular pattern is **more complex** and the cells are taller, more densely packed and the epithelium looks darker because many of the nuclei are larger and more hyperchromatic.

The cells in the centre of the polyp show signs of malignancy. They are no longer part of an epithelial sheet resting on a basement membrane, however elaborately folded, but are chaotic, and they are spreading or **invading** down into the stalk (having invaded through the basement membrane and through the muscularis mucosae). The cells show even more pronounced morphological features of neoplasia: they have a greater increase in nuclear/cytoplasmic ratio (bigger nuclei), greater pleomorphism and hyperchromatism, with little or no evidence of mucin storage. Mitotic figures can be seen quite easily. The gland-like structures appear as disorganized islands with irregular lumens and there is some epithelial budding into the lumen.

Consider the relationship of this central area to the normal tissue. Note that the muscularis mucosae which underlies the normal mucosa is frayed and split beneath the central area and that the budding glandular structures have penetrated it. A clone of cells has acquired **invasive properties** and the result is a small focus of **adenocarcinoma** which is **invading through the muscularis mucosae into the stalk**.

Adenocarcinoma developing from an adenoma
80.28



4.4. Colon: typical malignant tumour, an adenocarcinoma

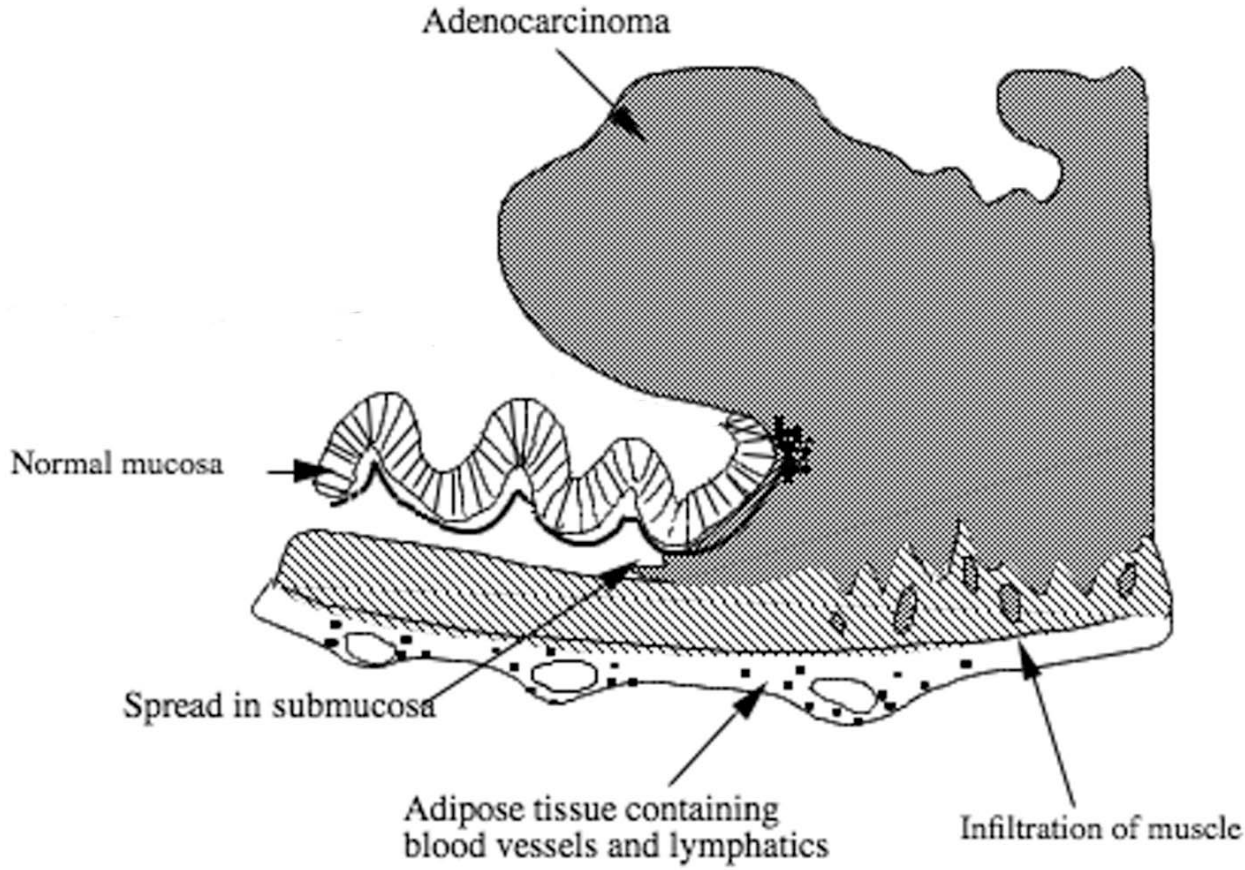
NDP Images: **23.3: 71.663 B**
Glass Slides: 23.3: 71.663 B
Image Maps: **A_NP_CA_LI_18** ; **A_NP_CA_LI_19**
A_NP_CA_LI_20 ; **A_NP_CA_LI_21**

This is a colonic adenocarcinoma, clearly showing the malignant cells invading the underlying muscle and under the neighbouring normal epithelium. It is easy to imagine that it may have developed from a lesion like the preceding one, overgrowing it and gradually replacing the adenoma tissue.

Examine the tumour tissue and note how chaotic it is, but particularly zoom in to see the invasion marked in the diagram: the spread into the submucosa, under the adjacent normal epithelium, and infiltration into the muscle wall (muscularis propria) below the tumour. You should be able to see islands of cells forming ragged glandular structures, growing in between the muscle fibres. This is classical **malignant invasion**. Although we cannot yet see it, you can easily imagine that given time the malignant cells will reach beyond the muscle and also start to enter vessels, allowing dissemination around the body.

The cells in the tumour are glandular in type and are forming easily recognized glandular structures (the glandular spaces vary in shape and size). Therefore, it is a

moderately differentiated adenocarcinoma. Many inflammatory cells are also present in the surrounding stroma which contains plump fibroblasts synthesising fibrous tissue, sometimes called a desmoplastic stroma.



Questions:

Q1 What is the significance of the occurrence of adenocarcinoma within an adenoma?

Q2 What do you think is the most significant difference in the behaviour of adenomas and adenocarcinomas?

Q3 What do you understand by the term moderately differentiated adenocarcinoma?

Q4 Which features in the adenocarcinoma section would help you in predicting the behaviour of this neoplasm?

4.5. Metastasis

It is generally the spread or **metastasis** of cancer to other organs that causes illness (morbidity) and death (mortality). For example, spread to the liver, lung, brain or bone / bone marrow can prevent them from performing their normal functions.

4.5.1. Liver: spread of cancer to another organ, metastatic colonic adenocarcinoma in otherwise normal liver

NDP Images: 23.4: 64-705
Glass Slides: 23.4: 64-705
Image Maps: **A_NP_MT_LV_06**; **A_NP_MT_LV_08**

This slide shows metastasis from a primary colonic adenocarcinoma to the liver (commonly called secondary tumours or secondaries). Tumour cells from an adenocarcinoma such as the preceding one got into the circulation and have colonised other tissues, including liver, a common site of metastasis for colorectal cancers. The normal liver is made up of hepatocytes (with much pink cytoplasm and small nuclei) in plate-like structures surrounding sinusoids, central veins and portal triads. The tumour occupies most of the slide. It consists of irregular glandular structures, which have cells with very large nuclei and mitotic figures (compare tumour nuclei with adjacent hepatocyte nuclei). The tumour has a dense fibrous-tissue background (pale pink material). In the centre of the tumour there is bright pink material, which is a combination of dense fibrotic tissue, oedema fluid and necrotic tumour cells. Normal large arteries and bile ducts are trapped within the tumour.

Questions:

Q5 What are the routes of spread of metastasising adenocarcinoma of the large intestine?

Q6 Why is there necrosis within the tumour deposit?

5.0. Presentation and screening strategies

One reason why colorectal cancer can be fatal is that it is only discovered after it has metastasised. Colorectal cancer may **present** (i.e. the patient visits a GP to complain about a problem) in various ways. One is chronic bleeding, leading to anaemia. Look again at the adenocarcinoma slides and the museum specimens: the luminal surface is chaotic and ulcerated, which can lead to bleeding over a prolonged period of time. Another reason for presentation is obstruction of the bowel lumen leading to a change in bowel habit.

Museum specimen **S61.2560** shows an example where fibrosis around the cancer has led to obstruction. Adenomas can also bleed or partially obstruct if large enough.

Two strategies are currently in use to attempt earlier detection by screening. One is testing for blood in faeces, using the faecal occult blood test (FOBt). The other is endoscopy to find cancers early, but, even better, to find adenomas before they become malignant and remove them. What do you think the relative merits of these strategies might be?

6.0. Grading of malignant tumours

Neoplastic cell nuclei are often enlarged, abnormal and variable (**pleomorphic**) in size, shape, and chromatin staining pattern, and this tends to be more pronounced in malignant cells than benign cells. Malignant cells often have nuclei that are darkly staining (**hyperchromatic**). There is disordered architecture with the relative positions and arrangements of tumour cells to one another often variable or abnormal, with more haphazard arrangements in malignant than benign neoplasms. The disordered architecture in glandular epithelial neoplasms may vary from well-formed glands seen in some tumours to either poorly formed glandular lumen or solid sheets of tumour cells seen in other tumours. These features can be used to grade malignant tumours as either well differentiated (grade 1), if there are well formed glands with mild nuclear enlargement, pleomorphism and hyperchromasia, through moderate differentiation (grade 2), to poorly differentiated (grade 3), if there are mostly solid sheets with few glands with severe/marked nuclear enlargement, pleomorphism and hyperchromasia. These features together illustrate the aberrant growth patterns of neoplasms.

6.1. Breast: invasive adenocarcinoma

NDP Images: 23.5: 96.359
Glass Slides: 23.5: 96.359

This section of breast tissue is composed of fatty tissue around the periphery and a central star-shaped region of dense fibrous tissue that contains an invasive adenocarcinoma. Within the stellate scar, there are variably sized clusters, irregular cords and islands of cancers cells with a surrounding fibrous (desmoplastic) stroma. More peripherally, the islands and tongues of tumour cells infiltrate outwards into the fatty connective tissue of the breast. At the left side of the section, there are areas of normal breast glandular tissue, with a duct and some breast lobules. In the centre of the breast cancer, there are a few dilated breast ducts containing neoplastic glandular cells (an example of the precursor – ductal carcinoma *in situ*). The appearances of some of the tumour islands show gland lumen formation with variable sizes and shapes of glandular lumen. Much of the tumour is formed of more solid-appearing cords and clusters of cancer cells. This gland formation represents clear evidence of glandular differentiation in the tumour, indicating its glandular (adeno-) histogenesis. This represents an example of a commonly occurring adenocarcinoma and its benign precursor in a different tissue, breast glandular epithelium, where the precursor-to-cancer sequence can be summarised as: **ductal carcinoma *in situ* – to – adenocarcinoma**. Breast cancers such as this can spread by lymphatic metastasis to local lymph nodes in the axilla (armpit) and by haematogenous metastasis to lung, liver, bone or other sites.

7.0. Mesenchymal tumours

You have seen the contrast between the benign *adenoma* and malignant *adenocarcinoma* in a glandular epithelium. To see another, rather different, comparison of a benign and a malignant tumour, this time in a mesenchymal / connective tissue, compare the next two slides.

7.1. Benign and malignant smooth muscle tumours of the uterus

The contrast between a benign and a malignant tumour in the same tissue can be seen in uterine muscle wall. Compare a leiomyoma, a benign smooth muscle tumour of the uterus, and its malignant counterpart, a leiomyosarcoma.

These slides illustrate how benign tumours are confined to their normal position in tissue and often can be quite easily separated from surrounding normal tissue. In contrast, malignant tumours are usually disorganized in three dimensions, with ragged invasive edges, and may be seen to have spread into, and through, neighbouring layers of tissue.

7.1.1. Uterus with multiple fibroids

Image and museum specimen: 23.6A: S77.4368 & 77.4349

Leiomyomas of the uterus are very common benign tumours often referred to as fibroids. A macroscopic image of a uterus with multiple leiomyomas is shown in the photograph. Note that the tumours are distinct, round, circumscribed bodies in the uterine wall with a whorled cut surface.

7.1.2. Myometrium: Leiomyoma, a benign smooth muscle tumour

NDP Images: 23.6B: 58.521
Glass Slides: 23.6B: 58.521
Image Map: A_NP_TU_UT_07 ; A_NP_TU_UT_10

The section includes part of a leiomyoma, like the ones in the macroscopic picture. The tumour is a round ball of cells in a swirling pattern. It shows several features characteristic of a benign tumour, but the most important is that the tumour remains a **separate mass of cells, distinct and usually separated from the surrounding normal tissue**. Indeed in this example, shrinkage during tissue preparation has split the tissue along the junction between tumour and normal, emphasizing their separate nature. The tumour appears to have a distinct “capsule”, the connective tissue pressed into a layer over the expanding and slowly growing tumour. The benign smooth muscle tumour cells appear very similar to their normal counterparts in the surrounding tissue, with little nuclear pleomorphism and almost no mitotic figures.

7.1.3. Myometrium: Leiomyosarcoma, a malignant smooth muscle tumour –

NDP Images: 23.7A: 82.225
Glass Slides: 23.7A: 82.225
Image Map: A_NP_TU_UT_03; A_NP_TU_UT_05

Uterine leiomyosarcomas are much less common. Try and work out where the malignant cells and the normal cells are - it is much more difficult than in the benign tumour because the malignant cells are invading into the surrounding normal smooth muscle of the myometrial wall, and tongues of malignant cells are spreading between strands of normal muscle. This is the clearest sign that this tumour is malignant: it is not confined to a defined place but invades into surrounding tissues. The malignant smooth muscle tumour cells appear different from their normal counterparts in the surrounding tissue, with marked nuclear enlargement and pleomorphism. Note that the leiomyosarcoma shows more nuclear pleomorphism than the leiomyoma (which shows very little nuclear pleomorphism). In fact, some of the leiomyosarcoma nuclei are very large and odd-looking or bizarre, forming so-called tumour giant cells. The leiomyoma nuclei are much more like those of normal smooth muscle cells. Mitotic figures are frequent in this leiomyosarcoma, while it is unlikely you will find mitoses in the leiomyoma.