NCPTS
National Cervical Pathology Training Service

INVASIVE SQUAMOUS CELL CARCINOMA (SCC)
Cytomorphology for Year 1-2 Registrars

Overview

- Invasive SCC can be difficult to diagnose accurately by cytology. Bleeding, inflamed, ulcerated or necrotic lesions do not provide ideal material.
- Features of invasion can be subtle. Where features of invasion are poorly developed and suspicious but not diagnostic, cases can be reported as “HSIL with features suspicious of invasion”, with urgent referral for colposcopy.
- There is no single feature that determines that a case is invasive so the diagnosis is made by taking all features observed into account. LSIL and HSIL cells can be present but malignant squamous cells usually predominate.
- Malignant squamous cells show more extreme aberrations both in the nucleus and cytoplasm than HSIL. Some features such as nuclear pleomorphism are similar to HSIL but may be more extreme in SCC, whereas other features such as clumping and clearing of nuclear chromatin are not seen in HSIL and when present, are more specific for SCC.

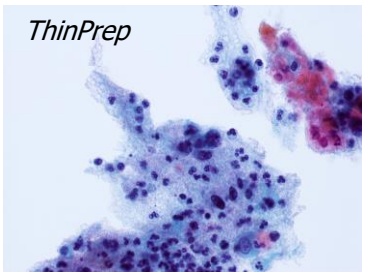
While background and cytoplasmic features may raise the possibility of invasion, **identifying malignant nuclei is essential** in making the diagnosis. Features suggesting invasion include:

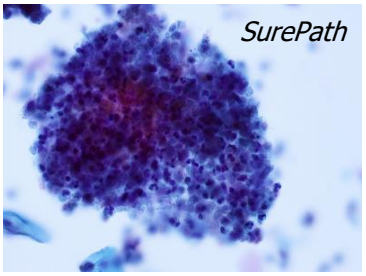
- marked cell and nuclear pleomorphism and hyperchromasia
- usually more cytoplasm than is seen in HSIL. Some SCC cells may show very high N:C ratios
- Coarse clumped irregularly distributed chromatin alternating with irregularly distributed hypochromatic areas. (“clumping and clearing”)
- Irregular angular thick nuclear membranes
- Large, prominent, often irregular nucleoli which may be multiple
- Bizarrely shaped keratinised squamous cells including spindle, caudate/tadpole forms
- Tumour diathesis consisting of degenerate blood, disintegrating leucocytes and necrotic debris.
- Abundant blood in the background.

CYTOLOGICAL FEATURES OF INVASIVE SCC

General features

1. Number of abnormal cells can vary greatly, from a few cells/groups to all the material on the slide.
    - Anatomical location, histological type, surface necrosis/ulceration all influence this.
2. Cells can be arranged as isolated cells, sheets and/or crowded groups.
3. Background: *Blood* – very common.
   Inflammation – may impair screening even with LBC.
   Tumour diathesis – a granular proteinaceous precipitate of necrotic cell debris, degenerating neutrophils and blood.

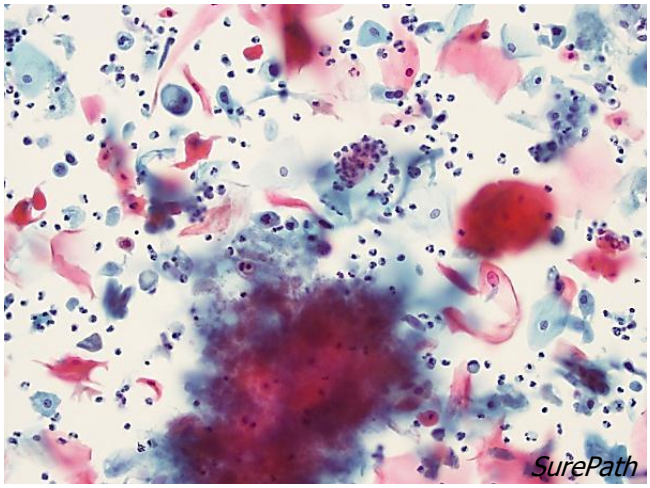


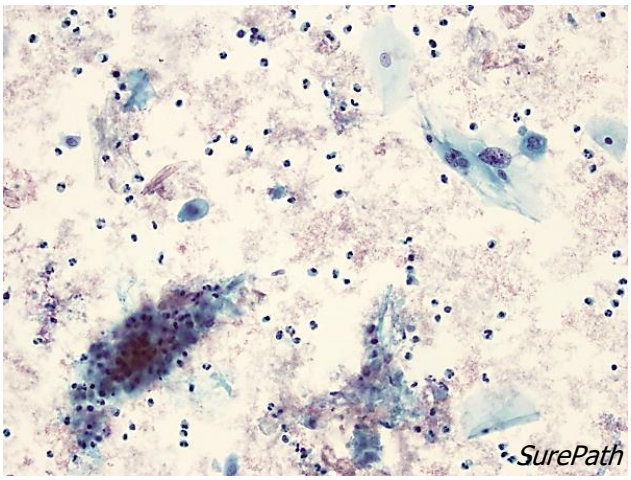


Low-power features

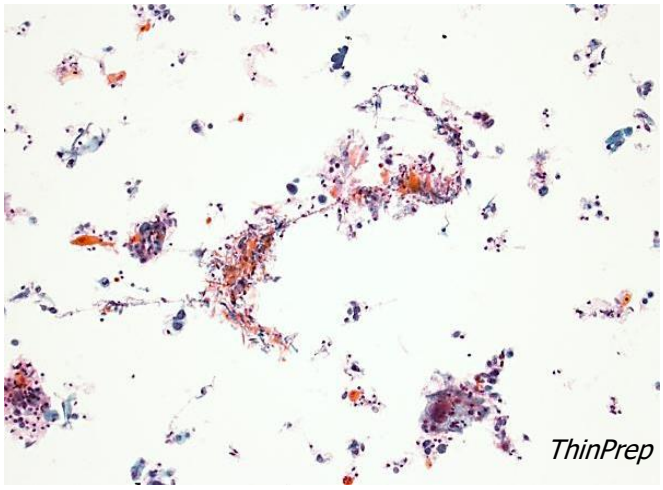
The low power appearance is not diagnostic, but can raise the possibility of an invasive lesion. The first impression is often of a “dirty background”. The SCC cells are often single or in small groups. There may be clumped and dissociated cells, cell fragments and inflammatory cells, all of which are may be partly degenerate. There may be fresh or degenerate red blood cells or granular debris, either in irregular clusters

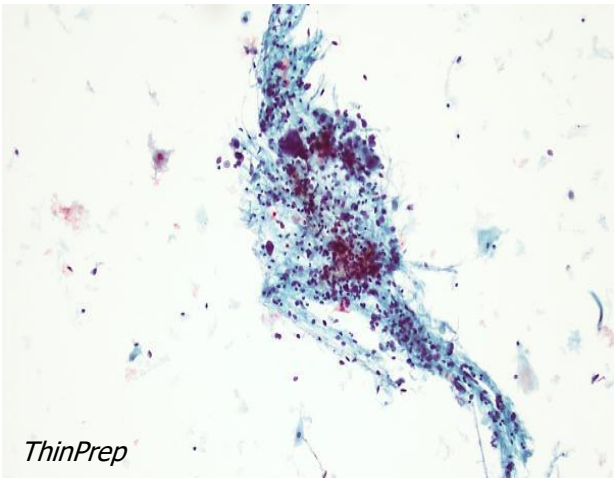
or around the edges of cell groups (“clinging diathesis”). Examination of the cells at high power is essential to confirm or refute a suspicion of invasive malignancy.





Left: SCC with keratinised spindle cells and a clump of degenerate cells
Right: Abundant blood, debris, neutrophils and suspicious squamous cells

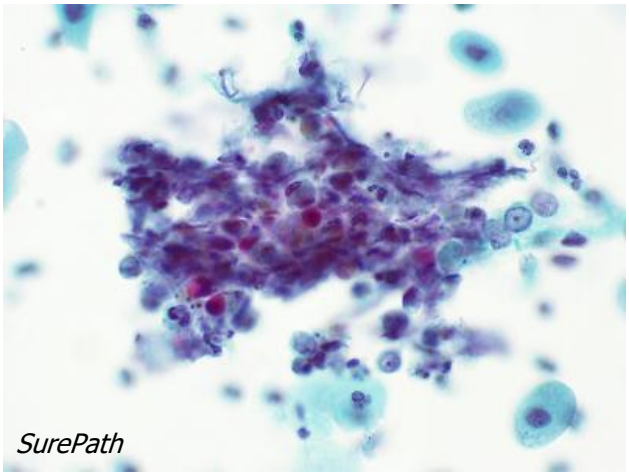


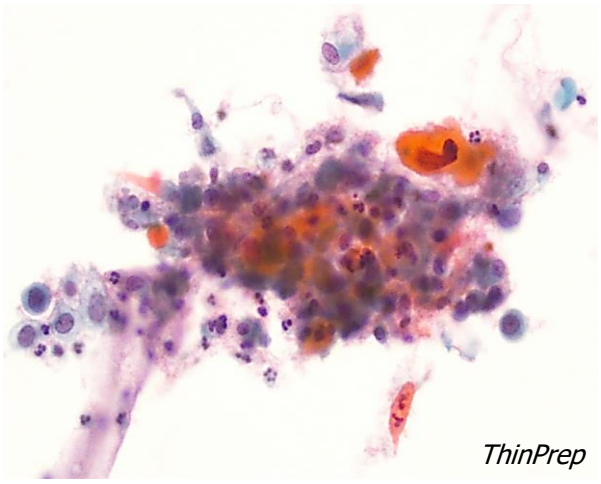


Left: Keratinising SCC with tumour cells, inflammatory cells, debris and blood
Right: Non-keratinising SCC with a ragged clump of debris requiring closer inspection

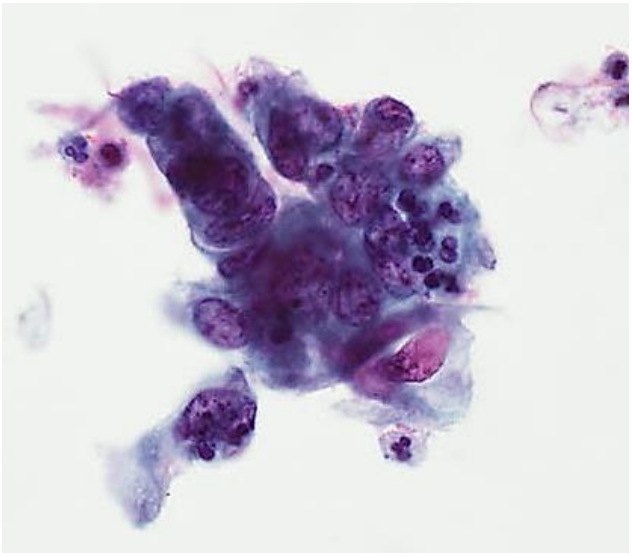
Tumour Diatheses and blood

Tumour diathesis consists of blood, leucocytes, and malignant cellular material in various stages of degeneration, often resulting in granular proteinaceous debris. Viable or degenerate tumour cells may be visible within the material. Tumour diathesis is not always present and abundant blood is at least as common as tumour diathesis in SCC.



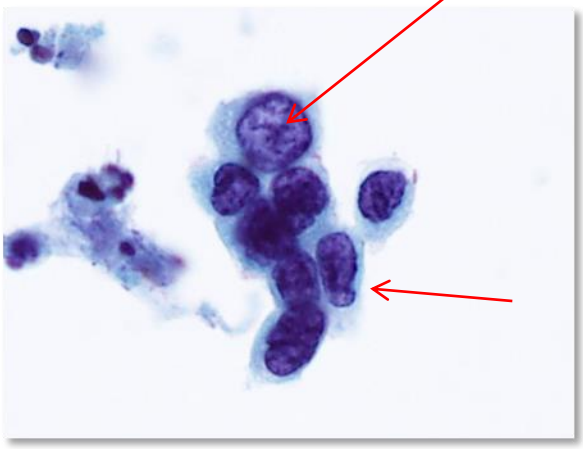


High power features: ThinPrep

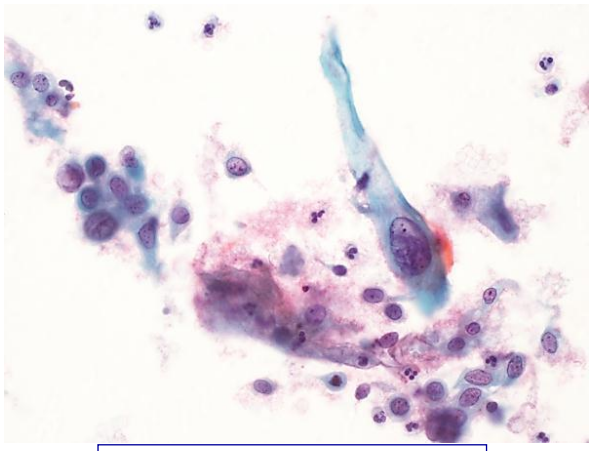


Cluster of malignant squamous cells in SCC

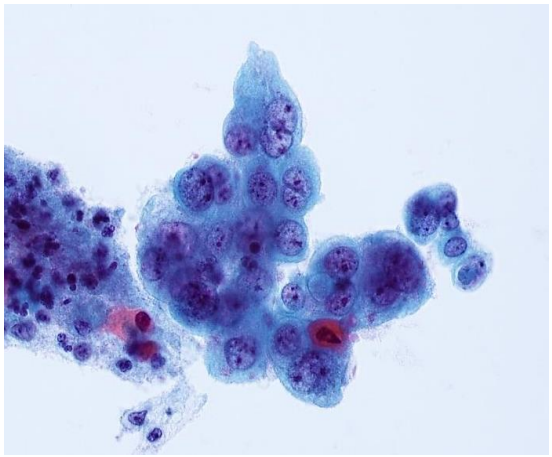
Chromatin clumping and clearing



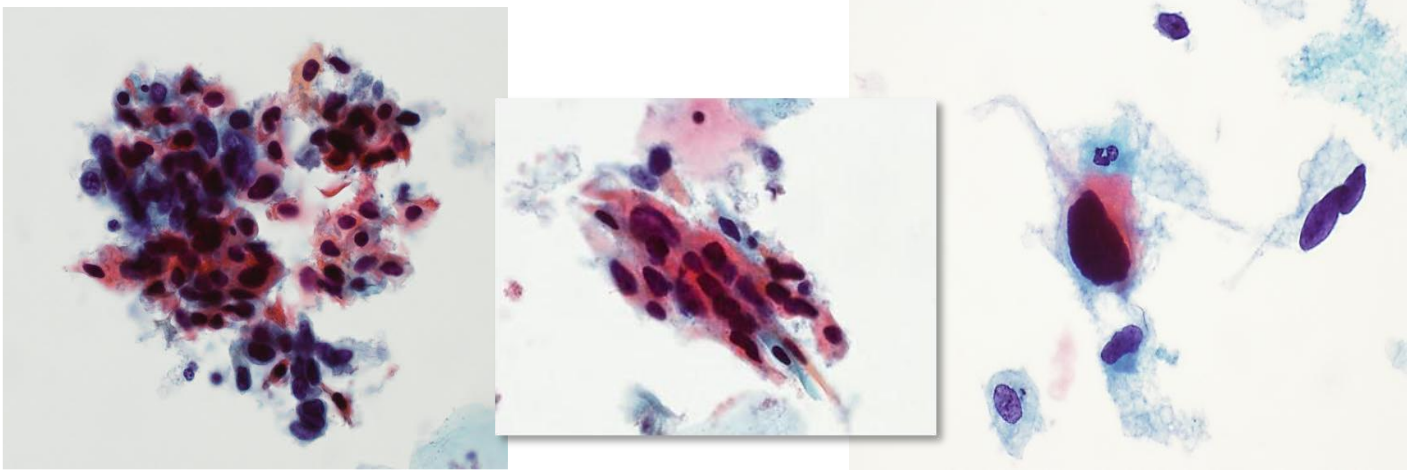
Thickened angular nuclear membranes



Marked pleomorphism

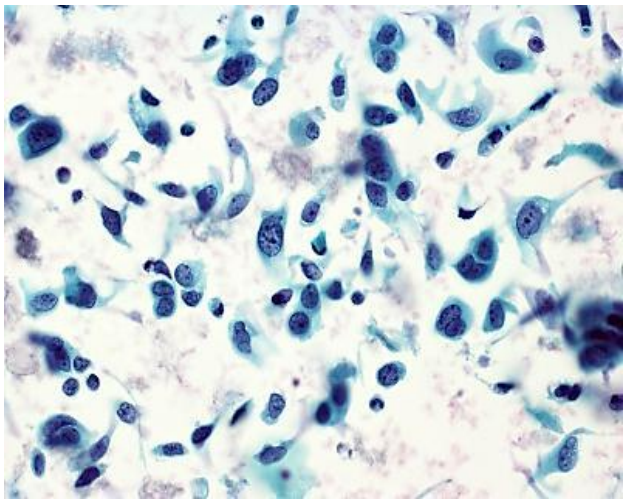


Prominent nucleoli which vary in size and number

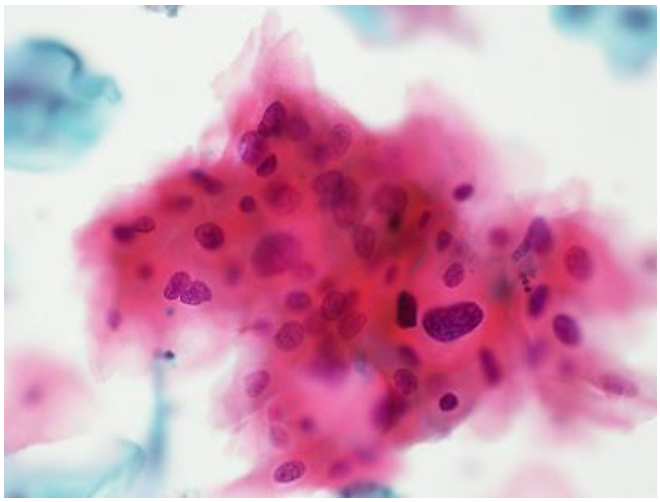


Keratinising SCC showing inky black hyperchromatic nuclei, spindle cells (centre), marked pleomorphism and keratinised cytoplasm.

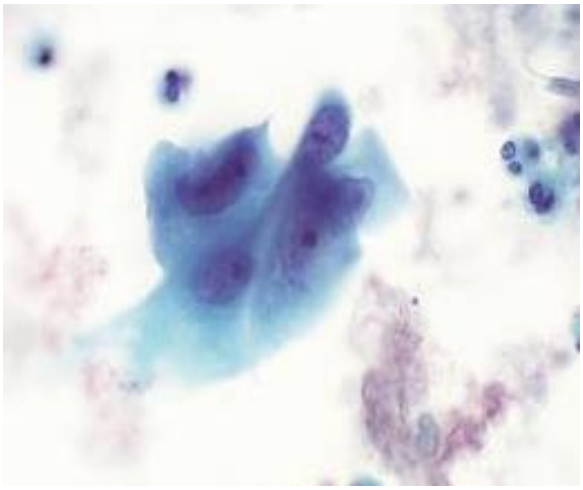
High power features: SurePath

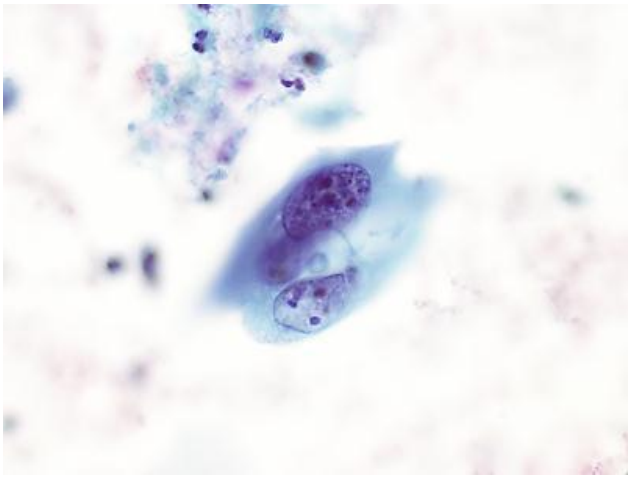


Dissociated malignant squamous cells in SCC

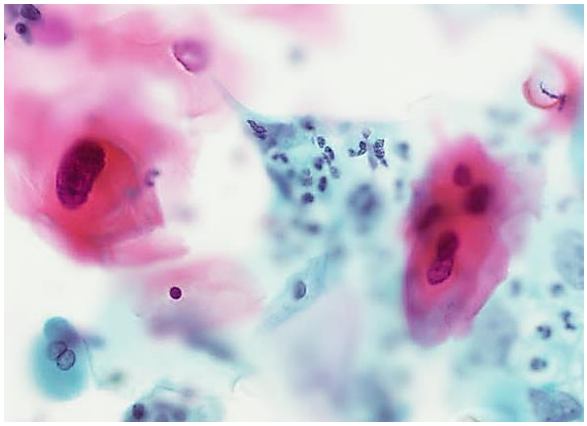


Cluster of keratinising malignant squamous cells

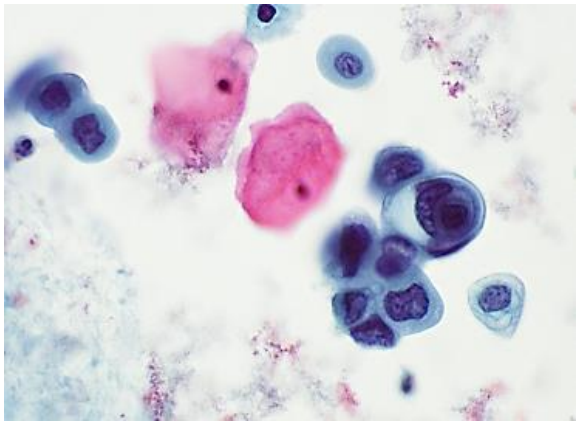




Malignant squamous cells with large nuclei, irregularly distributed chromatin (right image), prominent nucleoli and moderately abundant cytoplasm



Large malignant squamous cells with large hyperchromatic nuclei and abundant well-keratinised cytoplasm



Small malignant squamous cells with high N:C ratios, irregular nuclear membranes, hyperchromasia and cell-in-cell engulfment

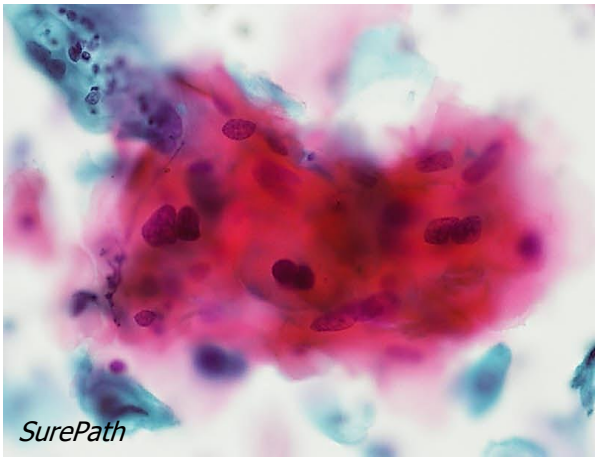
Presentation of SCC in cytology samples

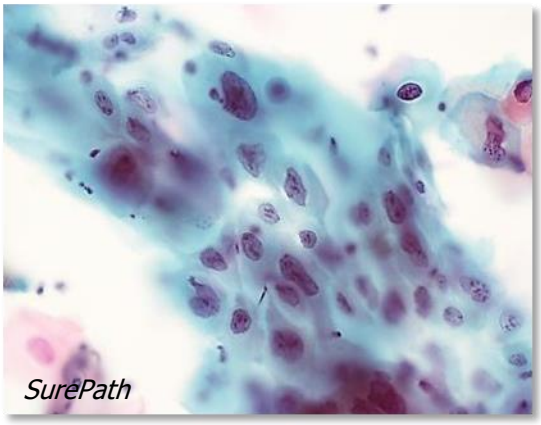
There are two cytologic presentations of SCC. These types are not identified in cytology reports and are of no clinical relevance but are useful to consider because each type has a particular cytologic appearance and is associated with particular diagnostic problems. Both types may be present but one type tends to predominate in cytology samples.

Keratinising SCC

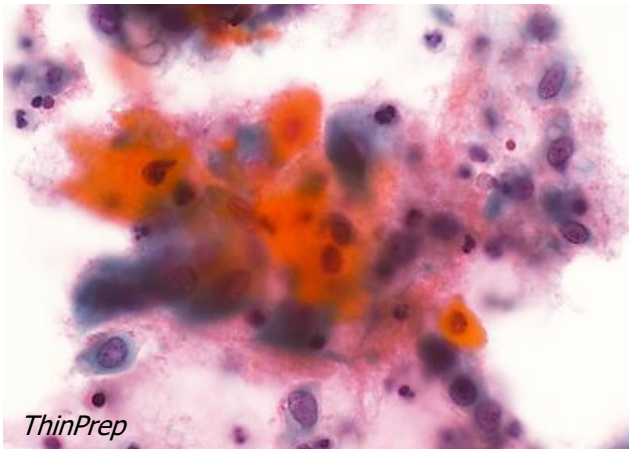
This is classic keratinising SCC as seen at many different body sites. Cytology samples typically contain many bizarrely shaped orangeophilic cells with large pyknotic/hyperchromatic irregular nuclei.

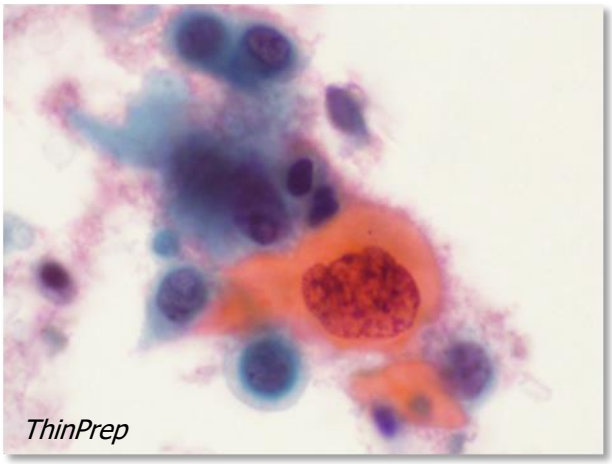
- keratinisation usually results in a brilliant dense glassy eosinophilic/orange cytoplasm.
- cells vary greatly: may be very large or very small, round or irregular or bizarre in shape
- nuclei are usually large for the cell size but the N:C ratio is often lower than is seen in HSIL
- nuclei may be pyknotic and karyorrhexis may be present
- nucleoli are frequent
- background may contain keratin and hyaline debris (eosinophilic/basophilic).





Malignant squamous cells. The cytoplasm is abundant and dense and may stain an intense orange (left) or a thick hyalinised blue colour (right).





A mix of keratinised and non-keratinised squamous cells is often seen in SCC.

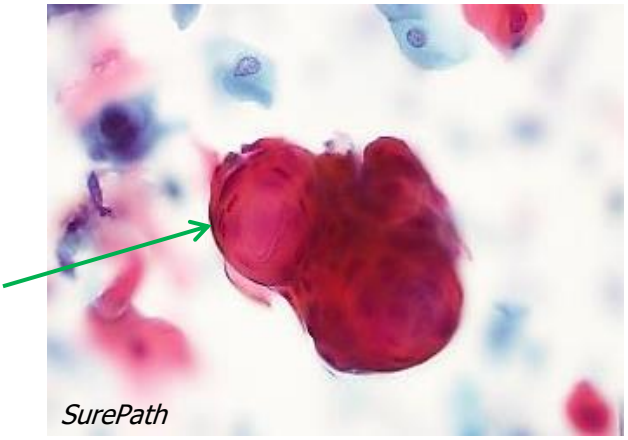
Specific cellular and cytoplasmic features are well described for keratinising SCC. All of the following cytoplasmic forms can also be seen in some benign conditions. It is essential that the cell be classified as malignant based on nuclear criteria.

Keratin Pearls

Pearl formation is a feature of squamous differentiation and may be seen in normal (reactive) or abnormal (neoplastic) cells. Squamous pearls are round structures of stratified squamous epithelial cells that form and

radiate out from a central single initial cell. The “newest” or “most recent” cells are on the outer edge of the pearl. For SCC look for:

- Concentrically arranged clusters of malignant squamous cells
- Enlarged, hyperchromatic nuclei
- A deposit of acellular keratin can be observed at the centre of the pearl

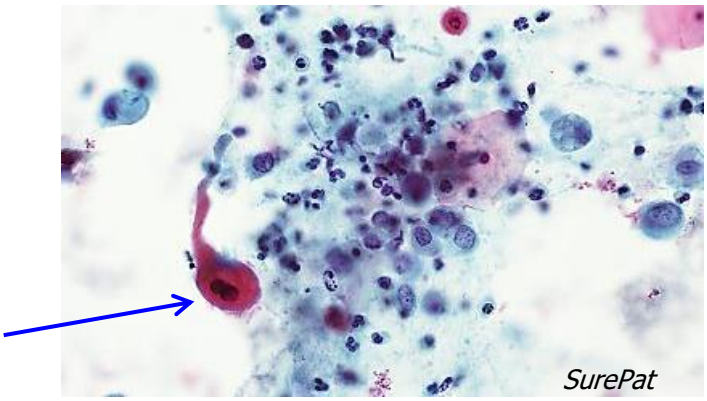


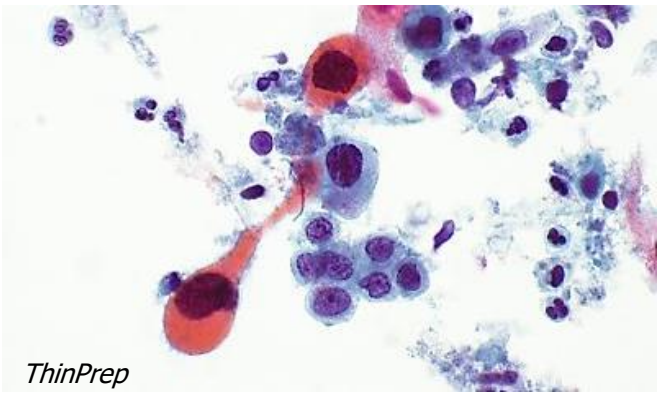
A fragment of keratinised squamous cells in a case of SCC.

The pearl has a dense keratinised centre with peripheral nucleated cells (green arrow).

Tadpole/caudate cells

Malignant tadpole cells (caudate cells) have the nucleus at the head of the cell with a long elongated, thinned tail of cytoplasm that may have a bulbous end. The nucleus is generally rounded.

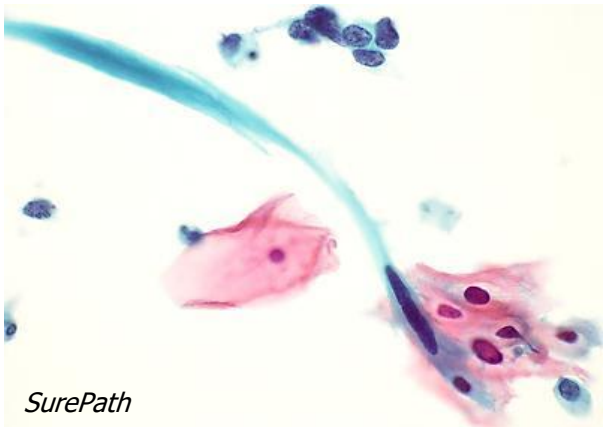


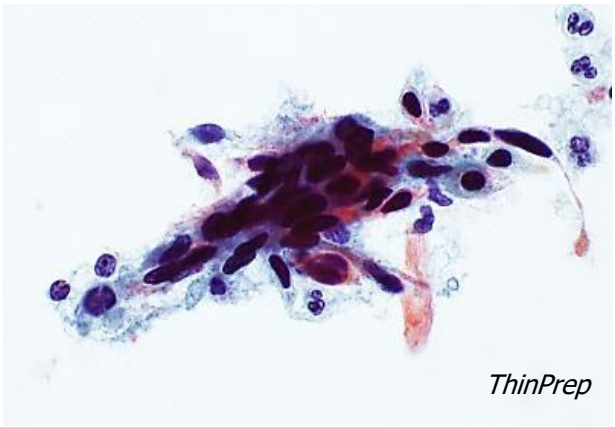


Two images showing keratinised tadpole/caudate forms in SCC. The left image shows a binucleate cell (blue arrow) with a low N:C ratio. Although atypical, this individual cell does not have the criteria of malignancy. The right image has a tadpole cell with a grossly abnormal hyperchromatic nucleus with a high N:C ratio consistent with malignancy.

Spindle or fibre cells

- Narrow, elongated spindle shaped varying in length from10-40μm.Keratinization is variable (cyanophilic or eosinophilic).
- Nuclei are elongated (cigar shaped) and hyperchromatic with a high N/C ratio

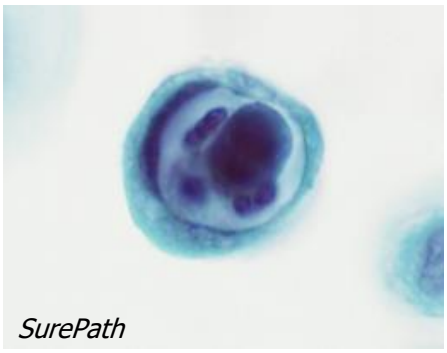


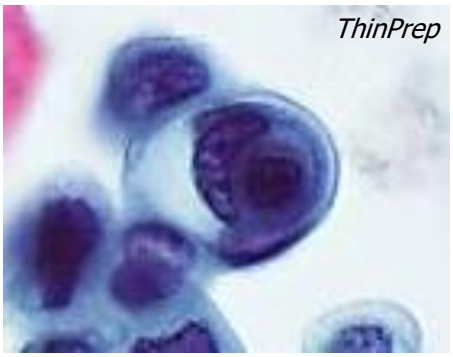


Spindle cells in SCC

Cell-in-cell engulfment (cannibalism)

A malignant cell may engulf another cell producing a “cell-in-cell” appearance. This appearance may be observed in HSIL as well as in invasive squamous cell carcinoma.



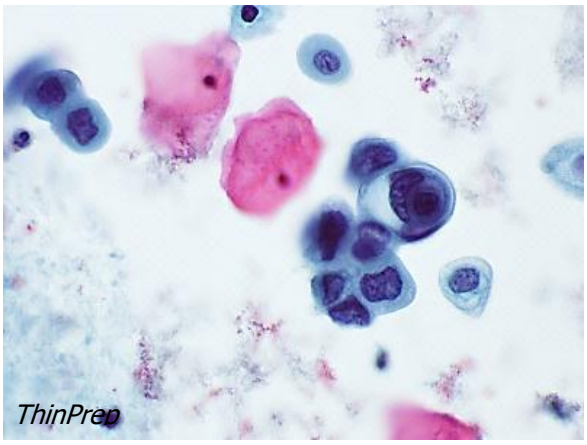


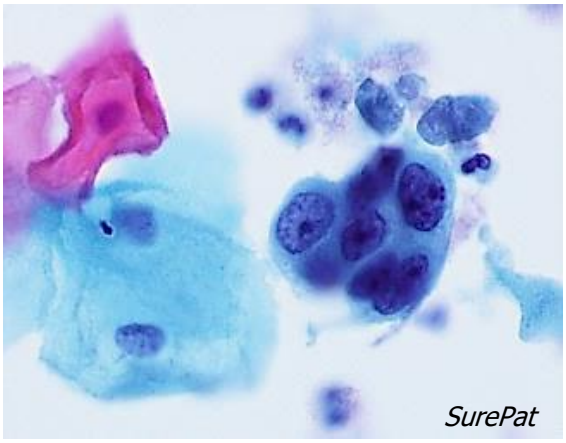
Cell-in-cell engulfment in cases of SCC

Non-keratinising SCC

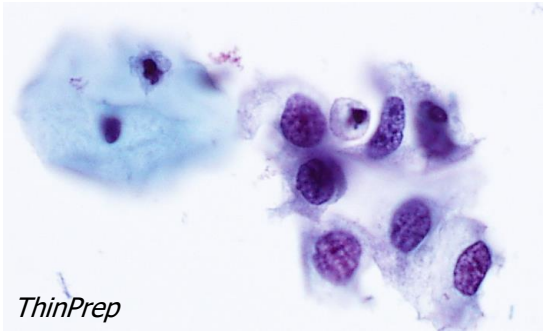
This is the most common subtype of SCC.

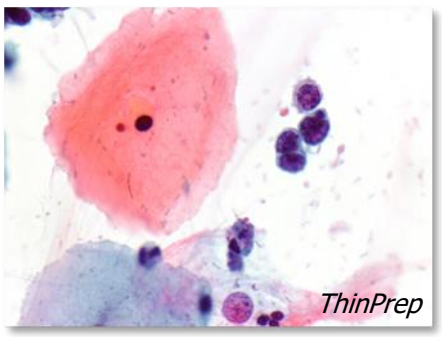
- Classic features of keratinisation are not or only focally present: individual keratinised cells may be seen.
- Nuclei are large, pleomorphic and hyperchromatic and contain prominent, irregular nucleoli.
- The cell size can vary considerably from large non-keratinised cells to small cells that closely resemble HSIL.
- Tumour diathesis is more common than with keratinised SCC.





Non-keratinising SCC





Malignant squamous cells: Cell size can vary considerably in non-keratinised tumours. Large malignant squamous cells (left) contrast with small malignant cells (right) which closely resemble HSIL. The uneven distribution of nuclear chromatin indicates invasive SCC.

SUMMARY:

1. Keratinising (differentiated) SCC

- *Background:* can be clean or may be a diathesis
- *Number of abnormal cells:* few to many. May be very small numbers of abnormal cells.
- *Cell type:* classically large squamous cells with prominent cellular pleomorphism and marked cell size variation including spindle and tadpole (club-shaped) forms. May see small highly keratinised cells with very dark dense pyknotic nuclei. Cell aggregates less common.
- *Nuclei:* large for the degree of cytoplasmic maturation. Dense opaque nuclei often numerous.
- *Chromatin:* mainly coarsely granular and irregularly distributed.
- *Prominent nucleoli:* may be present. Macronucleoli less common *c.f.* non-keratinising SCC
- *Cytoplasm:* Dense glassy bright orange keratinised appearance

2. Non-keratinising (poorly differentiated) SCC

- *Background:* fresh blood more common than diathesis
- *Number of abnormal cells*: usually many. Single cells or sheets.
- *Cell type:* large or intermediate size, uniform squamous type. Frequently looks very like HSIL but cells somewhat smaller.
- *Nuclei:* size of nucleus varies depending on degree of differentiation.
- *Chromatin:* coarsely granular and hyperchromatic. Markedly irregular in distribution.
- *Prominent nucleoli:* often multiple and irregular. Can be single and round.
- *Cytoplasm:* often poorly defined cell borders. Individual cell keratinisation seen occasionally.

- which does occur rarely as a primary cervical tumour. Term “small cell carcinoma” is now restricted to neuroendocrine small cell carcinoma.

Note: Superficially invasive SCC (formerly called microinvasive)

- this is a histological diagnosis: it is not reproducibly accurate in cytology
  - do sometimes see a “halfway house” between HSIL and SCC in cytology samples e.g. typical HSIL with one or two groups showing features of SCC
- a report of “HSIL with features suspicious of invasion” will ensure the woman is managed appropriately.

The appearance of SCC varies greatly between cases: See as many cases as you can

Notes prepared by:
Margaret Sage
NCPTS Cytopathologist
Updated 3/3/25