Cervical Cancers: Varieties and the Lower Anogenital Squamous Terminology

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1. George N. Papanicolaou: A Tribute
2. Epidemiology and Disease Burden
3. The ’Why and How’ of Cervical Cancers and Genital HPV Infection
4. Screening Technologies: Overview
5. Pap Smear Collection and Preparation: Key Points
6. Nonneoplastic Cervical Cytology
7. The Bethesda System for Reporting Cervical Cytology
8. The Pap Smear in Inflammation and Repair
9. Cytologic Diagnosis of Squamous Intraepithelial Lesions
10. The Gray Zone Squamous Lesions: ASC-US/ASC-H
11. Atypical Glandular Cells (AGC)
12. Radiation and Other Therapy Effects
13. Cervical Precancers: Biopsy and Immunohistochemistry
14. Cervical cancers: Varieties and The LAST Terminology
15. Abnormal Cytology and Colposcopy
16. Liquid Based Cytology: Technical Aspects
17. Role of Immunocytochemistry?
18. The Pap Stain: Technical Nuances

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Cervical cancers: Varieties and the LAST terminology

**ABSTRACT**

Carcinoma of cervix is classified as per the WHO classification into primary tumors which are predominantly epithelial tumors, mesenchymal tumors and tumor like lesions, mixed epithelial stromal tumors, melanocytic, germ cell, and lymphoid tumors. Secondary tumors are uncommon. Squamous cell carcinoma (SCC) in various morphological forms needs to be separated from other epithelial tumors for treatment modality selection. Majority of SCC are human papilloma virus (HPV) positive. The histological pattern, HPV type, and grading do not affect prognosis. Mixed mesenchymal and epithelial tumors are of Mullerian origin. Among sarcomas, Botryoid rhabdomyosarcoma needs to be looked for, as a small biopsy may miss it. Carcinoma cervix is not the only cancer caused by HPV. High-risk HPV is implicated in causation of various other cancers such as anal cancers, oropharyngeal cancers, vulval cancers, vaginal cancers, and penile cancers. Low-risk HPV viruses similarly cause infections of perianal and genital region in males and females. The terminology for these lesions has evolved before understanding of pathogenesis of low- and high-risk HPV. The lower anogenital squamous terminology (LAST), an acronym for LAST, incorporates the low- and high-grade squamous intraepithelial lesion (HSIL) terminology. In invasive cancers, a superficially invasive SCC is a well-defined entity. LAST outlines areas where p16 use is recommended. No benefit of addition of other biomarkers like p63 or ki67 is found in problem-solving in differentiation of HSIL from mimics or low-grade squamous intraepithelial lesion. Routine use of biomarkers is not advocated.

**Keywords:** Carcinoma, Squamous cell, Epithelial tumors, Papilloma virus infections, Glandular tumors

**INTRODUCTION**

**Anatomy**

Cervix is the distal tubular portion of uterus. Cervix protrudes into vaginal vault and thus anterior and posterior fornices are formed. Lower most opening is the external os, from where endocervix begins as a narrow canal up to internal os or isthmus, from where endometrial cavity begins. Space between uterus and rectum is pouch of Douglas. Immediately posterior and inferior to urinary bladder are anterior part of cervix. The endocervix is lined by columnar mucinous epithelium and in continuity with vaginal mucosa, the ectocervix is lined by squamous epithelium. The region where there is a transition from squamous to columnar epithelium in cervix is transformation zone. Most of the cervical epithelial neoplasms and their precursors occur at the squamocolumnar junction or within the transformation zone. Squamous epithelium comprises superficial, intermediate, and basal layer. The one cell thick basal layer has high nucleocytoplasmic ratio which progressively decreases from basal to superficial layer.

**WHO CLASSIFICATION OF MALIGNANT TUMORS OF THE CERVIX IS AS FOLLOWS**

- **Squamous cell tumors**
  - Squamous cell carcinoma, HPV associated
  - Squamous cell carcinoma, HPV independent
  - Squamous cell carcinoma, NOS.

- **Glandular tumors**
  - Adenocarcinomas, NOS
  - Adenocarcinoma, HPV associated
  - Adenocarcinoma, HPV independent, gastric type
  - Adenocarcinoma, HPV independent, clear cell type
  - Adenocarcinoma, HPV independent, mesonephric type

- **Mixed epithelial and mesenchymal tumors**
  - Adenosarcoma.

- **Germ cell tumors**
  - Germ cell Tumour NOS
  - Yolk Sac Tumour NOS
  - Choriocarcinoma NOS

**SQUAMOUS CELL CARCINOMA (SCC)**

SCC – An invasive carcinoma composed of squamous cells of varying differentiation.\(^1\) It is the most common form of cervical cancer.

**Histopathology**

Most invasive SCCs of cervix infiltrate as network of anastomosing bands or single cells with intervening inflammatory or desmoplastic stroma. A number of grading systems have been used depending on the type and differentiation of predominant cells.\(^2\) The most commonly used classification is modification of Broder’s\(^3\) in which SCC is divided into well differentiated, moderately differentiated, and poorly differentiated. However, no grading system has found universal acceptance in cervical carcinoma. Cervical stroma in the tumor is usually infiltrated by lymphocytes and plasma cells. A markedly eosinophilic response\(^4\) and a foreign body type giant cell reaction are occasionally seen.
Cervical carcinoma is classified as
- SCC, HPV associated
- About 80–90% of the cervical cancers are SCC and 90–95% of cervical SCCs are HPV associated.\(^1\)
- SCC, HPV independent
- SCC, NOS.

HISTOLOGICAL SUBTYPES OF SCC ARE AS FOLLOWS

**Keratinizing SCC**\([\text{Figure 1a and b}]\)

SCC composed of whorls of squamous cells with keratin and epithelial pearls. Tumor cells show mature appearance with intercellular bridges and individual cell keratinization is usually seen. The nuclei show atypia, hyperchromasia, and are large with coarse chromatin. Mitosis may not be frequent and is usually seen in less differentiated cells.

**Figure 1**: (a) Keratinizing squamous cell carcinoma showing epithelial pearls with keratinization of squamous cells at the center (H&E, ×40). (b) Keratinizing SCC showing individual cell keratinization (H&E, ×40).

**Non-keratinizing**

Tumor cells are composed of nests or sheets of recognizable squamous cells. Cells may show individual cell keratinization or intercellular bridges; however, keratin pearls are not seen. Obvious cellular atypia is seen and mitosis is usually numerous \([\text{Figure 2a and b}]\).

**Figure 2**: (a) Non-keratinizing squamous cell carcinoma, squamous cells in islands infiltrating deeper tissue with individual cell keratinization but lack epithelial pearls (H&E, ×40). (b) Mitosis seen in non-keratinizing squamous cell carcinoma (×40).

**Basaloid**

Tumor is composed of nests of immature basal type of squamous cells. Cytoplasm is scanty. Some foci of keratinization may be seen; however, keratin pearls are usually absent. When seen in vulva, association with HPV Type 16 is frequently encountered \([\text{Figure 3}]\).\(^3\)

**Figure 3**: Basaloid squamous cell carcinoma showing small hyperchromatic basaloid cells in sheets with focal squamous differentiation (H&E, ×40).

**Warty (condylomatous) SCC**

This has an exophytic surface and cellular features of HPV infection, that is, koilocytic changes. High-risk HPV DNA is typically detected.

**Papillary SCC**

Papillary SCC has an exophytic appearance with papillae and a fibrovascular core bordered by many layers of atypical squamous cells. Superficial biopsy may not reveal evidence of invasion; however, underlying tumor is a typical SCC. The tumors are usually positive for HPV Type 16. This differs from warty type by inconspicuous keratinization and lack of cellular features of HPV infection.\(^6\)

**Verrucous**

This is a highly differentiated SCC with hyperkeratotic undulating surface. The tumor invades the stroma with a pushing border. Nuclei show minimal atypia. HPV infection is usually not seen. This tumor has a tendency to recur locally after excision. However, usually they do not metastasize. This tumor is distinguished from condyloma by the presence of broad papillae and lack of fibrovascular cores.

**Squamotransitional carcinoma**

Rarely, transitional cell carcinomas of cervix are described. These tumors may be pure transitional or may have squamous component. Detection of HPV Type 16 and presence of allelic losses at chromosome 3p with infrequent involvement of chromosome 9 suggest that this tumor is more closely related to squamous carcinoma than to primary...
urothelial carcinoma. Furthermore, these tumors are more likely to express cytokeratin 7 than CK20 which suggest only histological rather than immunophenotypic resemblance to transitional epithelium.

**Lymphoepithelioma like**

This tumor is strikingly similar to nasopharyngeal tumor by the same name. It is composed of poorly defined islands of undifferentiated cells, in a dense lymphocytic background. The tumor cells have uniform vesicular nuclei with prominent nucleoli and mildly eosinophilic cytoplasm. EBV is not involved in these tumors of the cervix. The most common patterns in HPV associated SCC are non-keratinizing and basaloïd patterns.

**IMMUNOHISTOCHEMISTRY**

The majority of SCC are positive for p16, and p16 testing/molecular typing is recommended for the diagnosis of HPV-associated SCC [Figure 4]. If the test is not available, the term SCC NOS should be used.

**Figure 4:** Keratinizing squamous cell carcinoma showing diffuse block positivity for p16, ×40.

**PROGNOSIS**

Histological patterns, HPV types, and grading do not affect the prognosis.

**HPV-INDEPENDENT SCC**

- These are HPV-independent squamous tumors with stromal invasion and/or exophytic type of invasion. They constitute 5–7% of SCC cervix and are negative for HPV even when very sensitive techniques are used. They cannot be distinguished from HPV-associated SCC by only morphology and absence of HPV by highly sensitive molecular testing for the detection of HPV or mRNA is necessary for diagnosis. p16-negative IHC is also acceptable but it should be remembered that occasional HPV-associated SCC shows loss of p16 in the invasive component.

- These SCCs are diagnosed at an advanced stage, have a higher rate of node metastases, and reduced disease-free and overall survival.

**SCC NOS**

This is the term recommended in case p16 IHC or HPV testing is not available.

**ADENOCARCINOMA**

**Adenocarcinoma, HPV associated**

- These are tumors composed of glands with stromal invasion and/or expansile invasion. These are caused by high-risk HPV, HPV 18, 16, and 45.
- These are classified into three patterns (Silva System) which have shown association with risk of nodal metastases, recurrence, and survival. Pattern A has non-destructive invasion whereas Patterns B and C are associated with destructive invasion. In Pattern B, there is early/focally destructive invasion, and in Pattern C, there is diffusely destructive invasion.
- Atypical mitosis and apoptotic bodies are seen at low power.

**Histological subtypes of HPV-associated adenocarcinoma**

a. **Usual type:** Constitutes about 75% of endocervical adenocarcinoma. Mucinous cells comprise up to 50% of all cells [Figure 5a-c].

b. **Mucinous type:** Cells with mucinous cytoplasm comprise equal or more than 50% of all cells. It comprises of about 10% of all endocervical carcinomas.

The subtypes are as follows: [1]

- **Mucinous NOS adenocarcinoma:** Cells have mucinous cytoplasm-like normal endocervix
- **Intestinal adenocarcinoma:** Goblet cells and/or enteroendocrine differentiation in ≥50% of the tumor
- **Signet-ring cell adenocarcinoma:** Non-cohesive cells with mucinous vacuoles displacing the nucleus in ≥50% of the tumor
- **Stratified mucin producing carcinoma:** Invasive nests of stratified epithelium with intracytoplasmic mucin
- **Immunohistochemistry:** 95% of the tumors show diffuse block positivity for p16 [Figure 5d].
Adenocarcinoma, HPV independent

Gastric type

Adenocarcinoma exhibiting gastric type differentiation is unrelated to HPV. They account for 10–15% of all endocervical adenocarcinomas. Features include:

- Glands lined by large cells with pale to eosinophilic cytoplasm
- P16 is negative or patchy and/or negative HPV
- These tumors are more aggressive with significantly poor prognosis
- These have a higher stage at diagnosis, more extraterine spread, and are associated with higher prevalence of destructive invasion.

Clear cell type [Figure 6a and b]

- This type of adenocarcinoma is composed of uniform clear or eosinophilic cells in tubulocystic, papillary, or solid patterns
- These comprise 3–4% of all endocervical adenocarcinomas
- These can develop sporadically or with DES exposure
- Immunohistochemistry: Can be p16 positive in the absence of HR-HPV infection.

Mesonephric type

- A malignant neoplasm with the tumor exhibiting mesonephric differentiation
- These are very rare comprising <1% of cervical adenocarcinomas
- This tumor is associated with mesonephric remnants of mesonephric duct
- They arise in the cervical wall and may extend to the mucosa
- Tubular morphology with back-to-back tubules lined by cuboidal cells and lumina is filled with eosinophilic material which is PAS positive
- Other patterns which may be seen are ductal, papillary, retiform, sex cord-like, hobnail, spindled, and glomeruloid. Nuclei are clear and grooves may be seen
- Immunohistochemistry: P16 positivity is not diffuse and HPV is not detected.

OTHER ADENOCARCINOMAS

Endometrioid adenocarcinoma diagnosis can be made only after primary adenocarcinoma of the endometrium and HPV infection have been ruled out.

Adenosquamous and mucoepidermoid carcinomas

They account for 5–6% of cervical carcinomas.

Adenosquamous carcinoma

- This variant is composed of glandular and squamous elements [Figure 7]
- Both elements show atypical features
- The two components should be intimately mixed and one should be able to identify both on morphology
- These tumors do not behave differently from conventional squamous carcinoma
- Routine mucin staining is not recommended. 

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Adenoid cystic carcinoma

- Most common tumor occurring in patients over 60 years of age
- Most present with post-menopausal bleeding and have a mass on pelvic examination
- Histopathologically, it is similar to its counterpart in salivary gland
- The characteristic cystic spaces are filled with slightly eosinophilic hyaline basophilic mucin and are surrounded by palisading epithelial cells
- In contrast to salivary gland counterpart, these tumor cells show more nuclear pleomorphism, high mitosis, and necrosis\[9\]
- Immunostain for basement membrane component (collagen type V) and laminin is strongly positive
- Prognosis is poor with tumor recurring locally frequently and showing metastasis.

Adenoid basal carcinoma

A cervical carcinoma in which rounded generally well-differentiated nests of basaloid cells show focal gland formation or sometimes central squamous differentiation.\[1\]

- Patient is usually more than 50 years old and has a clinically detectable abnormality of cervix. Often, the tumor is discovered incidentally [Figure 8]
- Histopathologically small nests of basaloid cells are seen almost always beneath or arising from CIN/small invasive squamous carcinoma.\[9\] Cells are small with scanty cytoplasm and are arranged in cords nests and focal glandular or squamous differentiation
- Prognosis of this tumor is good as this is a low-grade tumor and rarely metastasizes.

Carcinoma of the uterine cervix, unclassifiable

This epithelial tumor of the cervix cannot be classified further as there are no differentiating features.

Germ cell tumors

Germ cell tumors of the uterine cervix are composed of primitive or mature germ cell elements similar to the germ cell tumors of the ovary. Metastasis from the ovary should be excluded.

Mesenchymal tumors

Leiomyosarcoma

- This is a malignant tumor composed of smooth muscle. Macroscopically, it is soft and fleshy, often with areas of hemorrhage and necrosis. Myxoid variant has a typical gelatinous appearance
- Histopathologically, spindle cell hypercellular areas are seen showing interlacing fascicles, diffuse marked nuclear atypia, high mitotic activity, and atypical mitosis
- Infiltrative border and vascular invasion is frequently seen
- Epithelioid, myxoid, and xanthomatous types have been reported
- At least two of the three criteria i.e. marked nuclear atypia, mitotic rate higher than 10/hpf and tumor necrosis are required for the diagnosis of leiomyosarcoma\[10\]
- A low mitotic count is typical of myxoid variant
- Antibodies to smooth muscle actin and/or desmin may be used to demonstrate smooth muscle cell differentiation
- These tumors should be differentiated from post-operative spindle cell nodule, diagnosis of which depends largely on history of recent surgery.

Endometroid stromal sarcoma (low grade)

- This is a sarcoma arising outside of uterine fundus composed of cells resembling endometrial stromal cells
- The tumor may arise from cervical endometriosis and must be distinguished from stromal endometriosis and endometrial stromal sarcoma which has infiltrated cervix.

Undifferentiated endocervical sarcoma

- An endocervical sarcoma lacking stromal and other specific differentiation
- This tumor is composed of spindle or stellate cells with scanty cytoplasm and hyperchromatic nuclei\[11\]
- Tumor cells are arranged in fascicles, storiform, or sheet-like pattern

Figure 8: Adenoid basal carcinoma: Rounded sheets of basaloid cells with glandular lumina or squamous differentiation in center (H&E, ×40).
Mitotic figures are noted with >10 mitotic figures in 10 hpf in most tumors.

**Sarcoma botryoides**

- This tumor is composed of cells with round, oval, or spindle-shaped nuclei some of which show differentiation toward skeletal muscle fibers
- Macroscopically, these tumors are usually polypoid and are penduculated or sessile. They have a glistening surface and soft consistency
- Cut section is smooth and myxoid with areas of hemorrhages
- Typically, there is a dense cambium layer composed of closely packed cells with small hyperchromatic nuclei
- Nuclei have open chromatin and inconspicuous nucleoli. Mitotic rate is high. Foci of mature cartilage may be seen \[12\]
- Immunohistochemistry against actin, desmin, or myoglobin is positive. Although first two antibodies are not specific for skeletal muscle differentiation, they are more sensitive than myoglobin
- Ultrastructural examination may reveal characteristic rhabdomyoblastic differentiation such as thin filaments with z band material
- An association with ovarian Sertoli-Leydig cell tumor and cervical sarcoma botryoides has been described [Figure 9].

**Angiosarcoma**

Malignant tumor cells of which recapitulate the morphological features of endothelium. Neoplastic cells are immunoreactive for CD31, CD34, and Factor VIII-related antigen.

**Malignant peripheral nerve sheath tumor (MPNST)**

It is also similar to MPNST occurring at other sites. These cells are positive for S100 and negative for HMB45, SMA, desmin, and myogenin. Other malignant tumors include alveolar rhabdomyosarcoma, liposarcoma, epithelioid sarcoma, osteosarcoma, and malignant fibrous histiocytoma. Mixed epithelial and mesenchymal tumors of cervix resemble those at other sites. These include adenosarcoma, carcinosarcoma, Wilms tumor, adenofibroma, and adenomyoma.

**Adenosarcoma**

This is a biphasic tumor with a benign epithelial and a malignant mesenchymal component. This is a rare tumor.

**Carcinosarcoma**

This is a biphasic malignant neoplasm with epithelial and mesenchymal components. Epithelial components may be squamous, adeno, mesonephric, or neuroendocrine.

Mesenchymal element can be homologous (fibrosarcoma and endometrial stromal sarcoma) or heterologous (rhabdomyosarcoma).

**NEUROENDOCRINE TUMORS**

These are uncommon tumors with 1–6% of all cervical tumors.[14]

This group includes carcinoid, atypical carcinoid, large-cell neuroendocrine carcinoma, and small-cell carcinoma.

**Carcinoid (Grade 1)**

These are generally benign showing characteristic organoid arrangement of cells as observed in other sites. Degree of nuclear atypia and mitosis, both typical and atypical, is important to diagnose carcinoid and atypical carcinoid.

**Atypical carcinoid (Grade 2)**

It is a carcinoid with cytological atypia and increased mitosis (5–10/10 HPF 0.5 mm in diameter and 0.2 mm² in area) \[1\] and foci of necrosis.

**Small-cell carcinoma (Small-cell neuroendocrine carcinoma)**

It accounts for 1–6% of cervical cancer. The cells are small and show characteristic nuclear molding with high N: C ratio.
Large-cell neuroendocrine carcinoma

This tumor shows focal adenocarcinomatous differentiation.\[13\] Tumor cells are large with abundant cytoplasm, large nuclei, prominent nucleoli, and frequent mitosis. These tumors are aggressive and appear to have same outcome as small-cell carcinoma. Neuroendocrine differentiation can be demonstrated in all these tumors by chromogranin A, synaptophysin, and neuron-specific enolase.\[14\]

THE LOWER ANOGENITAL SQUAMOUS TERMINOLOGY (LAST) TERMINOLOGY

Carcinoma cervix is not the only cancer caused by HPV. High-risk HPV is implicated in causation of various other cancers such as anal cancers, oropharyngeal cancers, vulval cancers, vaginal cancers, and penile cancers. Low-risk HPV viruses similarly cause infections of perianal and genital region in males and females. At present, the histopathological terminology for describing the lesions caused by low- and high-risk HPV viruses does not reflect either the HPV type or the risk prognostication. This is due to fact that the terminology has evolved before understanding of role of HPV and is a descriptive terminology for the lesion as seen grossly or under the microscopy. Thus, we have terms such as Wart, Bowen’s disease, and erythroplasia of Queyrat, which are used by dermatologists. The Bethesda classification incorporated understanding of HPV biology and mechanism of pathogenesis, and cytologically, the intraepithelial lesions were divided into two tiers.\[16\] Those are of Low-grade squamous intraepithelial lesion and High-grade squamous intraepithelial lesion. However, histologically, we still have three grades of dysplasia: Mild, moderate, and severe. Recently, the terminology of The Bethesda System is also being applied to biopsy interpretations.

To address all these issues, a project was undertaken by College of American Pathologists and American Society for Colposcopy and Cervical Pathology. The consensus of all working groups is that the LAST should be used for histopathology of tissues from anogenital region. The report hopefully has the LAST word, considering numerous changes and classifications evolved so far. The recommendations encompass the HPV associated lesions of squamous epithelium of cervix, vagina, and vulva in females, penis and scrotum in males, and anal region and perianal skin in both genders.

Biologically, HPV infects squamous epithelium in two basic ways.\[17,18\] In first, the virus often of Type 6 and 11 completes its life cycle in the squamous epithelium, produces virions and while growing inside the epithelium, it produces changes secondary to infection, seen histologically as Grade 1 squamous intraepithelial lesions or low-grade squamous intraepithelial lesion (LSIL). The condyloma of skin and genital organs is another manifestation of this type of infection. In the second way, the virus integrates with the host genome with overexpression of viral oncogenes, leads to epithelial cell proliferation and expansion of relatively undifferentiated clone, expressing persistent viral antigens. These are caused by oncogenic viruses of Type 16 and 18, mediated through two viral proteins E 6 and E7 which interfere with cell cycle regulation and unlock the regulatory mechanisms. These proliferating cells evade apoptosis, proliferate, and gather further mutations to develop into cancer. A hallmark of these lesions is persistence and overexpression of viral antigens which potentially can differentiate the pre-cancer from other lesions that mimic dysplasia.

RATIONAL FOR UNIFIED TERMINOLOGY FOR LOWER ANOGENITAL REGION IS AS FOLLOWS

1. Epithelial infections of HPV are biologically similar
2. Each cytological or histological sample is a representation of true biology of viral infection at that point of time and in the epithelium studied. Thus, over period of time and in multiple biopsies true biological picture of viral infection will emerge
3. The diagnostic variations due to these facts can be improved by the use of biomarkers and by assigning terminology that correlates with biologically relevant categories.

THE RECOMMENDATIONS OF LAST PROJECT GROUP ARE AS FOLLOWS

Squamous intraepithelial lesion: All pre-invasive lesions of lower anogenital tract which are HPV associated, to be called intraepithelial neoplasia with IN suffix and labeled as per site [Table 1]. The intraepithelial neoplasia is to be reported as a two-tier system: Low grade and high grade.

Rationale for recommending a two-tier nomenclature

a. The current understanding of HPV biology does not support a three-tier nomenclature. The -IN2 is an admixture of low and high grade of SIL that cannot be separated by morphology in H and E sections. Biomarkers can help to classify this accurately. The use of IN2 category is retained in young girls and adolescents as this category is managed conservatively in these patients. Thus, a high-grade squamous intraepithelial
lesion (HSIL) in cervix will be reported as HSIL-CIN3
b. Low SIL is defined as a proliferation of squamous or metaplastic cells with abnormal nuclear features of increased nuclear size, irregular nuclear membrane, increased N/C ratio, and little cytoplasmic maturation in lower third. Mitosis is seen in lower third
c. Koilocytic cells which show nuclear pleomorphism, multinucleation, and perinuclear halo [Figure 10]
d. HSIL is defined as proliferation of squamous or metaplastic cells with abnormal nuclear features of increased nuclear size, irregular nuclear membrane, increased N/C ratio, and little cytoplasmic maturation in middle third/superficial layers. Mitosis is not confined to lower third [Figure 11].

| S. No. | Organ/site | Prior terminology                  | SIL    | SISCCA                           | Remarks                                      |
|--------|------------|------------------------------------|--------|----------------------------------|----------------------------------------------|
| 1      | Cervix     | Dysplasia carcinoma in situ        | CIN    | 3 mm depth 7 mm wide             | LVI, multiplicity commented on               |
|        |            |                                    |        | No gross lesion                  |                                               |
| 2      | Vagina     | ValIN                              | NA     |                                  | Terminology not recommended                  |
| 3      | Vulva      | Bowen's disease Bowenoid Papulosis | VIN    | 2 cm or less Stromal invasion<1 mm| The criteria same as AJCC T1a/FIGO 1 A        |
|        |            | Condyloma acuminata flat kondyloma |        | Confined to vulva or perineum    |                                               |
| 4      | Anus       | Bowen's disease                    | AIN    | 3 mm depth 7 mm wide             |                                               |
|        |            |                                    |        | No gross lesion                  |                                               |
| 5      | Penis      | Erythroplasia of Queyrat Bowen's   | PeIN   | Invasion of only subepithelial   | AJCC T1a                                      |
|        |            | disease Bowen's disease Condyloma  |        | connective tissue                |                                               |
| 6      | Perineum   | Bowen's disease Condyloma          | PAIN   | 3 mm depth 7 mm wide             |                                               |
|        |            |                                    |        | No gross lesion                  |                                               |

**Table 1:** The lower anogenital squamous terminology.\[26,27\]

Figure 10: Low-grade squamous intraepithelial lesion of vagina showing anisonucleosis, loss of polarity, and mitosis in lower one-third with koilocytic change in the upper part (H&E, ×40) (Pic Courtesy – Dr. MM Kamal).

Figure 11: High-grade squamous intraepithelial lesion of anal canal showing near full-thickness nuclear atypia showing high N:C ratio, nuclear pleomorphism, loss of polarity, and mitosis. (H&E; ×40) (Pic Courtesy – Dr. MM Kamal).
SPECIAL CIRCUMSTANCES: WHERE P16 STAINING IS RECOMMENDED

1. Marked atypia in a low SIL
2. In thin (<10 layer thick) epithelium [Figure 12]

![Figure 12: Thin epithelium <10 cells in thickness, showing marked nuclear atypia, loss of polarity, and mitosis, consistent with high-grade squamous intraepithelial lesion. These need confirmation with p16 immunostaining (H&E; ×40) (Pic Courtesy – Dr. MM Kamal).](image)

3. Atypia in keratinizing epithelium is considered high grade
4. Full-thickness dysplasia extending into endocervical glands
5. Superficially invasive SCC: This term is reserved for minimally invasive squamous cancers which are excised and do not show positive resection margins.

SUPEFICILY INVASIVE SCC OF CERVIX (SISCCA OF CERVIX)

It is defined as an invasive SCC that is not a grossly visible lesion and has an invasive depth of 3 mm from the basement membrane of the point of origin, and has a horizontal spread of 7 mm in maximal extent, and has been completely excised.

A report of Superficially Invasive SCC of Cervix should include

a. Presence or absence of lymphovascular invasion
b. Presence of number and size of independent multifocal carcinoma
   - In a biopsy, if the invasive carcinoma exceeds dimensions of SISCCA, it should be reported as such
   - In a biopsy showing SISCCA and the dimensions of SISCCA within the parameters, if the margins are positive, then it is reported as at least a SISCCA
   - In carcinoma cervix, multiple biopsies reveal a true picture of biological behavior of squamous intraepithelial lesion. These biopsies should be properly numbered as per location and colposcopic findings and documented
   - The criteria for anal intraepithelial lesion and perianal SISCCA are same as those for carcinoma cervix
   - The morphological hallmark of SCC in these lesions is abnormal cellular proliferation with nuclear atypia, enlargement, pleomorphism, change in nuclear chromatin texture, and irregular nuclear borders
   - No recommendation of the use of term SISCCA is made for early invasive vaginal carcinoma due to rarity and lack of separate treatment modality for early lesions
   - Vulvar SISCCA is defined as an T1a American Joint Committee on Cancer (AJCC) (FIGO 1A) vulvar cancer, that is, tumor 2 cm or less size, confined to the vulva or perineum AND stromal invasion of 1 mm or less.[21,22] No change in the current definition of T1a vulvar cancer is recommended.[23-25]
   - Anal and perianal SISCCA has definition same as cervical SISCCA
   - SISCCA of penis is defined as T1a of AJCC, that is, tumor invading only the subepithelial connective tissue. There is no lymphovascular invasion, and morphologically, it is not poorly differentiated.

The calculation of depth of invasion is defined as distance from epidermal stromal junction of adjacent most dermal papilla to deepest point of tumor invasion. When HSIL colonizes an endocervical gland, the depth should be measured from basement membrane of the gland.

BIOMARKER RECOMMENDATIONS

Biomarker recommended is p16INK4a.[28] No benefit of addition of other biomarkers like p63 or ki67 is found in problem solving in differentiation of HSIL from mimics or LSIL. The positivity of p16 should be strong and block like. Routine use of biomarkers is not advocated.

Use of p16 is recommended in the following situations: [28-31]

1. To differentiate HSIL from morphological mimics such as squamous metaplasia, atrophy, and reparative changes
2. When lesion is diagnosed as CIN 2, to better classify it as LSIL or HSIL for further management, p 16 can be useful [Figure 13]
3. To resolve professional disagreement due to interobserver variation
4. In high-risk colposcopy referral situations where biopsy shows a lesion LSIL or lower but colposcopy, cytology, or clinical features indicate a higher lesion
5. There is no role of use of p16 to differentiate between LSIL and its mimics
6. There has been a more accurate classification of HSIL with the use of biomarkers in these situations
7. The proliferation marker ki67 which trends with p16 is not recommended unless p16 is inconclusive.[32,33]

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Nil.

LIST OF ABBREVIATIONS (In Alphabetic Order)
AJCC – American Joint Committee on Cancer
CIN – Cervical intraepithelial neoplasia
HPV – Human papillomavirus
HSIL – High-grade squamous intraepithelial lesion
LAST – Lower anogenital squamous terminology
MPNST – Malignant peripheral nerve sheath tumor
PAS – Periodic acid-Schiff
SCC – Squamous cell carcinoma
SISCCA – Superficially invasive squamous cell carcinoma
WHO – World Health Organization

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