

CAP-ASCCP LAST Work Group 3: Terminology for Minimally Invasive Cancers, Integrating Morphology, Biology, and Clinical Management

Recommendations and Rationale

WG3 was tasked with performing a formal literature review regarding definitions in current use for minimally invasive HPV-related squamous cell carcinoma of the lower anogenital tract, to identify areas of confusion or misunderstanding in histologic terminology, and to make recommendations to clarify terminology for HPV-related invasive squamous carcinomas of the lower anogenital that potentially can be managed conservatively through minimal or local surgery only.

Using pre-specified criteria focused on terminology and following an organized title/abstract and full text review process, 1675 articles were identified from the targeted literature search; this number was culled to 193 from which complete data extraction was performed. The vast majority of the articles dealt with cervical disease; however, some articles did address disease of vulvar/penile and anal/perianal sites. This literature review was supplemented with information from articles culled from the Distiller review as background information (316 articles), the current AJCC Cancer Staging Manual (7th edition) and other standard resources.

Initial scope and key questions for WG3:

WG 3 Scope/Overall Purpose:

- To provide definitions in current usage by lower anogenital body sites (in conjunction with WG 1).
- To include definitions of minimally invasive cancers (e.g. micro-invasive, minimally invasive, early invasive, and superficially invasive) and carcinoma in general integrated with clinical utility.
- To review data across sites to recommend specific terminology for minimally invasive cancers, especially where minimal invasion is not well defined (i.e., anus).
- To provide best pathways to communicate to clinicians in a clear and relevant fashion.
- To focus on clinical input – how the histopathologic diagnosis is reconciled with current clinical management.
- To make recommendations for new unified terminology if appropriate

Scope questions to be addressed (WG 3 Charge):

1. What is the current state of clinical management based on the morphologic diagnosis? (*In conjunction with by WG 1*)
2. What are the areas of potential overlap in histopathologic terminology (cytology, dermatopathology, GYN pathology)? (*In conjunction with WG1*)

3. What are the possibilities of integrating cytology, histology, molecular and clinical terminology? (molecular in conjunction with WG4)
4. Based on the possibilities, what would be the recommendation to clarify the histopathologic terminology?
5. Based on the recommendations, what are the criteria that define the histopathologic criteria?
6. Based on the criteria, what are the differences that affect clinical management that the clinicians need to know?

Background (by body site):

Cervix: Essentially 100% of squamous cell carcinomas of the cervix are attributable to HPV (Parkin & Bray Vaccine 2006). There are abundant data on early invasive squamous carcinoma (SCC) of the cervix that can safely be treated conservatively. Historically, a variety of terms, including "microinvasive carcinoma" have been used to label this group. Criteria for defining these various groups have changed over the years. Currently both SGO and FIGO staging are employed; although SGO staging definitions are more commonly used in the United States. FIGO defines Stage IA1 as an invasive carcinoma diagnosed only by microscopy with stromal invasion 3.0 mm or less in depth and 7.0 mm or less of horizontal spread and may be amenable to conservative surgical management (i.e. cone biopsy with negative margins). These microscopic measurements are well-defined and portend a cure via local excision in approximately 99%. Larger cervical cancers are staged clinically; although, early stage cancer is, by definition, defined on pathological examination of a biopsy specimen.

Vagina: Vaginal cancers are rare. Approximately 40-60% of squamous cell carcinomas of the vagina are attributable to HPV (Parkin & Bray Vaccine 2006). In addition, vaginal squamous carcinomas are, in general, not amenable to local resection. FIGO uses clinical staging for cancer of the vagina. All available data prior to first definitive treatment should be used, including the results of biopsy of FNA of regional lymph nodes. The primary role of pathologic staging of vaginal cancer is from examination of the resected specimen, including pelvic and retroperitoneal lymph nodes. The current AJCC definition of a T1 (FIGO Stage 1) tumor is a tumor confined to the vagina. T1 tumors are not further subdivided.

Vulva: Approximately 40-50% of squamous cell carcinomas of the vulva are attributable to HPV (Parkin & Bray Vaccine 2006); staging for SCC of the vulva is the same regardless of the etiology. The AJCC definition of a T1A (FIGO 1A) vulvar squamous carcinoma is a lesion 2 cm or less size, confined to the vulva or perineum and with stromal invasion of 1 mm or less. The depth of invasion is

defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

Penis: Cancers of the penis are rare in the United States. Approximately 40% of squamous cell carcinomas of the penis are attributable to HPV (Parkin & Bray Vaccine 2006). The AJCC definition of a T1a penile squamous carcinoma is a tumor that invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated (i.e., grade 3-4). If lymphovascular invasion is identified or the tumor is poorly differentiated the lesion is classified as T1b; both are independent predictors of inguinal lymph node involvement in patients with squamous cell carcinoma of the penis and should prompt more aggressive care.

Scrotum: Squamous cell carcinoma of the scrotum is now very rare; although some are HPV-related, historically its development was linked to occupational exposure in chimney sweeps [Refid 2476]. The current AJCC staging system for scrotal cancer is as per cutaneous squamous cell carcinoma. There are no subdivisions of T1 skin cancers, defined as 2 cm or less with fewer than two high-risk features (> 2 mm thickness, Clark level \geq IV, perineural invasion, poorly differentiated or undifferentiated).

Anal canal: Approximately 90-93% of squamous cell carcinomas of the anal canal are attributable to HPV (Parkin & Bray Vaccine 2006). There is a paucity of information regarding minimally invasive cancer of the anal canal. The current AJCC definition of a T1 anal tumor is a tumor 2 cm or less in greatest dimension. T1 tumors are not subdivided further. For the anal canal, the tumor size amenable to conservative surgical therapy is largely unknown and combined modality therapy (radiation and chemotherapy) is the current standard of care for anal cancer. As more early invasive anal cancers are diagnosed (due to increased awareness and screening in some centers), identifying minimally invasive cancers that are potentially amenable to conservative surgical therapy is imperative.

Perianus: Specific statistics regarding the proportion of squamous cell carcinoma of the perianus that are attributable to HPV are unknown; presumably, it is similar to other contiguous cutaneous genital sites, such as the vulva in women. Per current AJCC staging, perianal cancers are staged as per cutaneous squamous cell carcinoma. There are no subdivisions of T1 skin cancers, defined as 2 cm or less with fewer than two high-risk features (> 2 mm thickness, Clark level \geq IV, perineural invasion, poorly differentiated or undifferentiated).

Recommendations (by body site):

Overall recommendation: The purpose of these recommendations is to clarify terminology for HPV-related invasive squamous carcinomas of the lower anogenital tract that potentially can be managed conservatively through minimal or local surgery only. We recommend using the same term for minimally invasive SCC across all mucocutaneous sites of the lower anogenital tract, although the specific measurements that convey prognostic risk may vary by anatomic location.

Recommendation #1: The term ***“superficially invasive squamous cell carcinoma (SISCCA)”*** is recommended for minimally invasive squamous cell carcinoma of the lower anogenital tract that has been completely excised and is potentially amenable to conservative surgical therapy.

Recommendation #2: For cases of invasive squamous carcinoma with positive biopsy/resection margins, the pathology report should state whether:

- The examined invasive tumor exceeds the dimensions for a SISCCA (defined below) OR
- The examined invasive tumor component is less than or equal to the dimensions for a SISCCA (defined below), and conclude that the tumor is ***“At least a superficially invasive squamous carcinoma.”***

Recommendation #3: In cases of SISCCA, the following parameter should be included in the pathology report:

- The presence or absence of lymphovascular invasion (LVI).
- The presence, number, and size of independent multifocal carcinomas (after excluding the possibility of a single carcinoma).

Cervix: The term “superficially invasive squamous cell carcinoma” is recommended for an invasive cervical squamous carcinoma which has been completely excised and would be amenable to conservative treatment.

Definition of cervix SISCCA:

SISCCA of the cervix is an invasive squamous carcinoma 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.**

Vagina: Due to the rarity of primary SCC of the vagina, there are insufficient data to define early invasive squamous carcinoma in the vagina. **No recommendation is offered** for early invasive squamous carcinoma of the vagina.

Vulva: The term “superficially invasive squamous cell carcinoma” (SISCCA) is recommended for an invasive vulvar squamous carcinoma which has been completely excised and would be amenable to conservative treatment.

Definition of vulvar SISCCA:

No change in the current definition of T1a vulvar cancer is recommended.

- Current AJCC definition of T1a vulvar carcinoma.
- Tumor 2 cm or less size, confined to the vulva or perineum AND
- Stromal invasion of 1 mm or less.
- *Note: The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.*

Penis: The term “Superficially invasive squamous cell carcinoma (SISCCA) is recommended for an invasive penile squamous carcinoma which has been completely excised and would be amenable to conservative treatment.

Definition of penile SISCCA:

No change in the current definition of T1a penile cancer is recommended.

- Current AJCC definition of T1a penile carcinoma.
- Tumor that invades only the subepithelial connective tissue, AND
- No lymphovascular invasion AND
- Is not poorly differentiated (i.e., grade 3-4).

Scrotum: Due to the rarity of primary SCC of the scrotum, there is insufficient evidence to make a recommendation regarding the current AJCC staging of early scrotal cancers. **No recommendation is offered** for early invasive squamous carcinoma of the scrotum.

Anal canal: Based on expert opinion, the term “superficially invasive squamous cell carcinoma (SISCCA)” is recommended for an invasive an anal canal squamous carcinoma which has been completely excised and would be potentially amenable to conservative treatment.

Definition of anal canal SISCCA:

SISCCA of the anal canal is an invasive squamous carcinoma that:

- **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.**

Perianus: Based on expert opinion, the term “superficially invasive squamous cell carcinoma (SISCCA)” is recommended for an invasive perianal squamous carcinoma which has been completely excised and would be potentially amenable to conservative treatment.

Definition of perianal SISCCA:

SISCCA of the perianus is an invasive squamous carcinoma that:

- **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.**

Explanatory notes:

Resection margin status is best determined from a single intact marker/painted fragment of tissue. Depth is measured from the basement membrane at the presumptive site of origin of invasion. Horizontal spread is the greater of either the extent of involvement on a single slide or the sum of the involved thicknesses of the tissue sections in the paraffin blocks.

For potentially incompletely excised tumors, it is important to clearly communicate via the pathology report whether the squamous carcinoma has the potential of being managed conservatively as a SISCCA (reported as “*at least a superficially invasive squamous carcinoma*” or whether the tumor is larger than a SISCCA and is no longer (potentially) amenable to conservative treatment (reported as “*invasive squamous carcinoma*”).

The significance of LVI remains uncertain for SISCCA of the cervix and little data is available for other anogenital sites, with the exception of T1 penile carcinoma. However, continued reporting of this parameter will assure prospective data accumulation. Similarly, the presence, number, and size of independent multifocal carcinomas (after excluding the possibility of a single carcinoma) should also be included in the pathology report.

Assessments of histologic grade (with the exception of T1 penile carcinoma, according to current AJCC staging guidelines) and confluent invasion are neither reproducible nor of prognostic significance, so they are not included in the pathologic reporting suggestions for SISCCA. Before concluding that

multifocal carcinoma is present, it is important to exclude the possibility of a single carcinoma that appears discontinuous but exceed the maximum horizontal spread measurements. Leveled sections may be needed to fully examine such carcinoma.

Cervix: Within the FIGO System, any lesion which is visible without the use of colposcopy is Stage IB (or greater). Lymphovascular invasion is not a criterion in this definition. The entire invasive lesion must be available for histologic examination, i.e. the resection margins must be negative for invasive carcinoma. Usually LEEP, cone, or diagnostic excisional specimens are required to assess these features. Occasionally, a diagnosis may be rendered using the composite findings from a colposcopic biopsy and subsequent LEEP, cone, or diagnostic excisional specimen.

Anal canal: Since no definition for a T1a anal canal cancer currently exists, based on expert opinion, the recommended definition is similar to SISCCA of the cervix. This will allow for meaningful prospective data to be collected. If conservative management of a SISCCA of the anal canal is considered, the patient should be evaluated by an expert experienced in high-resolution anoscopy and management of anal canal cancer.

Perianus: Since no definition for a T1a anal canal cancer currently exists, based on expert opinion, the recommended definition is similar to SISCCA of the cervix. This will allow for meaningful prospective data to be collected.

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