Anus

Protocol applies to all invasive carcinomas of the anal canal.

Protocol revision date: January 2004
Based on AJCC/UICC TNM, 6th edition

Procedures

- **Cytology** (No Accompanying Checklist)
- **Incisional Biopsy**
- **Excisional Biopsy**
- **Abdominoperineal Resection**

Authors
Carolyn C. Compton, MD, PhD
Department of Pathology, McGill University, Montreal, Quebec, Canada
R. R. Rickert, MD
Department of Pathology, St. Barnabas Medical Center, Livingston, New Jersey
For the Members of the Cancer Committee, College of American Pathologists

Surgical Pathology Cancer Case Summary (Checklist)

Protocol revision date: January 2004
Applies to invasive carcinomas only
Based on AJCC/UICC TNM, 6th edition

ANUS: Polypectomy

Patient name:
Surgical pathology number:

Note: Check 1 response unless otherwise indicated.

MACROSCOPIC

***Tumor Site**
* Specify, if known: _____
*___ Not specified

Polyp Size
Greatest dimension: ___ cm
*Additional dimensions: ___x___ cm
___Cannot be determined (see Comment)

***Polyp Configuration**
*___ Pedunculated, with stalk
*Stalk length: ___ mm
*___ Pedunculated, no stalk, narrow-based
*___ Sessile/broad-based
*___ Cannot be determined

MICROSCOPIC

Histologic Type
___ Squamous cell carcinoma
___ Adenocarcinoma
___ Mucinous adenocarcinoma
___ Small cell carcinoma
___ Undifferentiated carcinoma
___ Other (specify): _____
___ Carcinoma, type cannot be determined

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Histologic Grade (if applicable to tumor type)
___ Not applicable
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ G4: Undifferentiated

Extent of Invasion
___ Epithelium only (no invasion)
Invasion (deepest):
___ Cannot be determined
___ Into lamina propria
___ Into muscularis mucosae
___ Into submucosa

Polyp Resection Margin (check all that apply)
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
Distance of invasive carcinoma from margin: ___ mm
___ Carcinoma in situ absent at mucosal margin
___ Carcinoma in situ present at mucosal margin
___ Involved by invasive carcinoma
___ Not applicable (specify reason): _____

Venous/Lymphatic (Large/Small Vessel) Invasion (V/L)
___ Not applicable
___ Absent
___ Present
___ Indeterminate

***Additional Pathologic Findings (check all that apply)**
*___ None identified
*___ Active colitis
*___ Other (specify): _____

***Comment(s)**

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Surgical Pathology Cancer Case Summary (Checklist)

Protocol revision date: January 2004
Applies to invasive carcinomas only
Based on AJCC/UICC TNM, 6th edition

ANUS: Local Excision (Transanal Disk Excision)

Patient name:
Surgical pathology number:

Note: Check 1 response unless otherwise indicated.

MACROSCOPIC

Specimen Integrity
___ Intact
___ Fragmented
*Number of pieces in fragmented specimens: ___
___ Other (specify): _____

***Tumor Site**
*___ Unknown
* Specify, if known: _____

Tumor Size
Greatest dimension: ___ cm
*Additional dimensions: ___x___ cm
___ Cannot be determined (see Comment)

***Tumor Configuration**
*___ Polypoid
*___ Infiltrative
*___ Ulcerating
*___ Other (specify): _____

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

MICROSCOPIC

Histologic Type

___ Squamous cell carcinoma
___ Adenocarcinoma
___ Mucinous adenocarcinoma
___ Small cell carcinoma
___ Undifferentiated carcinoma
___ Paget disease
___ Other (specify): _____
___ Carcinoma, type cannot be determined

Histologic Grade

___ Not applicable
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ G4: Undifferentiated
___ Other (specify): _____

Pathologic Staging (pTNM)

Primary Tumor (pT)

___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ
___ pT1: Tumor 2 cm or less in greatest dimension
___ pT2: Tumor more than 2 cm but not more than 5 cm in greatest dimension
___ pT3: Tumor more than 5 cm in greatest dimension
___ pT4: Tumor of any size with invasion of adjacent organ(s); eg, vagina, urethra, bladder (involvement of sphincter muscles alone is not classified as T4).

Margins (check all that apply)

___ Cannot be assessed
___ Margins uninvolved by invasive carcinoma
    Distance of invasive carcinoma from closest margin: ___ mm
    Specify margin (if possible): _____
    ___ Carcinoma in situ absent at lateral mucosal margin
    ___ Carcinoma in situ present at lateral mucosal margin
___ Margin(s) involved by invasive carcinoma
___ Not applicable (specify reason): _____

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

***Venous/Lymphatic (Large/Small Vessel) Invasion (V/L)**
*___ Absent
*___ Present
*___ Indeterminate

***Perineural Invasion**
*___ Absent
*___ Present

***Additional Pathologic Findings (check all that apply)**
*___ None identified
*___ Crohn disease
*___ Condyloma accuminatum
*___ Dysplasia
*___ Associated rectal carcinoma (Paget disease)
*___ Other (specify): _____

***Comment(s)**

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Surgical Pathology Cancer Case Summary (Checklist)

Protocol revision date: January 2004
Applies to invasive carcinomas only
Based on AJCC/UICC TNM, 6th edition

ANUS: Resection

Patient name:
Surgical pathology number:

Note: Check 1 response unless otherwise indicated.

MACROSCOPIC

Specimen Type
___ Abdominoperineal resection
___ Other (specify): _____
___ Not specified

Tumor Site (check all that apply)
___ Anterior wall
___ Anal margin
___ Not specified

Tumor Size
Greatest dimension: ___ cm
*Additional dimensions: ___x___ cm
___ Cannot be determined (see Comment)

***Tumor Configuration:**
*___ Polypoid
*___ Infiltrative
*___ Ulcerating
*___ Other (specify): _____

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

MICROSCOPIC

Histologic Type

___ Squamous cell carcinoma
___ Adenocarcinoma
___ Mucinous adenocarcinoma
___ Small cell carcinoma
___ Undifferentiated carcinoma
___ Paget disease
___ Other (specify): _____
___ Carcinoma, type cannot be determined

Histologic Grade

___ Not applicable
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ G4: Undifferentiated

Pathologic Staging (pTNM)

Primary Tumor (pT)

___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ
___ pT1: Tumor 2 cm or less in greatest dimension
___ pT2: Tumor more than 2 cm but not more than 5 cm in greatest dimension
___ pT3: Tumor more than 5 cm in greatest dimension
___ pT4: Tumor of any size with invasion of adjacent organ(s); eg, vagina, urethra, bladder (involvement of sphincter muscles alone is not classified as T4).

Regional Lymph Nodes (pN)

___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Metastasis in perirectal lymph nodes
___ pN2: Metastasis in unilateral internal iliac and/or inguinal lymph node(s)
___ pN3: Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes

Specify: Number examined: ___
Number involved: ___

Distant Metastasis (pM)

___ pMX: Cannot be assessed
___ pM1: Distant metastasis
*Specify site(s), if known: _____

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Margins (check all that apply)

Proximal Margin
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
    ___ Carcinoma in situ absent at mucosal margin
    ___ Carcinoma in situ present at mucosal margin
___ Involved by invasive carcinoma

Distal Margin
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
    ___ Carcinoma in situ absent at mucosal margin
    ___ Carcinoma in situ present at mucosal margin
___ Involved by invasive carcinoma

Circumferential (Radial) Margin
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma

Distance of invasive carcinoma from closest margin: ___ mm
    Specify margin: _____

***Perineural Invasion**
*___ Absent
*___ Present

***Venous/Lymphatic (Large/Small Vessel) Invasion (V/L)**
*___ Absent
*___ Present
*___ Indeterminate

***Additional Pathologic Findings (check all that apply)**
*___ None identified
*___ Crohn disease
*___ Condyloma accuminatum
*___ Dysplasia
*___ Associated rectal carcinoma (Paget disease)
*___ Other (specify): _____

***Comment(s)**

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Background Documentation

Protocol revision date: January 2004

I. Cytologic Material

A. Clinical Information

1. Patient identification
   a. Name
   b. Identification number
   c. Age (birth date)
   d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
   a. Relevant history
      (1) sexually transmitted diseases (human immunodeficiency virus [HIV], herpes simplex virus [HSV], human papilloma virus [HPV])
      (2) genital neoplasms
      (3) immunosuppression
      (4) inflammatory bowel disease
   b. Relevant findings (eg, direct inspection, endoscopic and/or imaging studies)
   c. Clinical diagnosis
   d. Procedure (brushing, washing, other)
   e. Anatomic site(s) of specimen(s) (Note **A**)

B. Macroscopic Examination

1. Specimen
   a. Unfixed/fixed (specify fixative)
   b. Number of slides received, if applicable
   c. Quantity and appearance of fluid specimen, if applicable
   d. Other (eg, cytologic preparation from tissue)
   e. Results of intraprocedural consultation
2. Material submitted for microscopic evaluation
3. Special studies, specify (eg, cytochemistry, immunocytochemistry, DNA analysis [specify type], morphometry, cytogenetic analysis)

C. Microscopic Evaluation

1. Adequacy of specimen (if unsatisfactory for evaluation, specify reason)
2. Tumor, if present
   a. Histologic type, if possible (Note **B**)
   b. Other characteristics of neoplasm (eg, nuclear grade, necrosis) (Note **C**)
3. Additional pathologic findings, if present (specify)
4. Results/status of special studies (specify)
5. Comments
   a. Correlation with intraprocedural consultation, as appropriate
   b. Correlation with other specimens, as appropriate
   c. Correlation with clinical information, as appropriate

II. Biopsy (Incisional, Local Excision, or Other)

A. Clinical Information

1. Patient identification

   a. Name
   b. Identification number
   c. Age (birth date)
   d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
   a. Relevant history
      (1) sexually transmitted diseases (human immunodeficiency virus [HIV], herpes simplex virus [HSV], human papilloma virus [HPV])
      (2) genital neoplasms
      (3) immunosuppression
      (4) inflammatory bowel disease
   b. Relevant findings (eg, direct inspection, endoscopic and/or imaging studies)
   c. Clinical diagnosis
   d. Procedure (eg, endoscopic biopsy, local excision)
   e. Anatomic site(s) of specimen(s) (Note **A**)

B. Macroscopic Examination

1. Specimen
   a. Unfixed/fixed (specify fixative)
   b. Number of pieces
   c. Largest dimension of each piece
   d. Results of intraoperative consultation
2. Tumor, if discernible
   a. Largest dimension
   b. Configuration
3. Margins, relation to tumor in an excisional biopsy
4. Additional pathologic findings, if present
5. Tissue submitted for microscopic evaluation
   a. Incisional biopsy: submit entirely
   b. Excisional biopsy
      (1) tumor
      (2) margin(s) of excision, if identifiable
      (3) other lesions, if applicable
   c. Frozen section tissue fragment(s) (unless saved for special studies)
6. Special studies (specify) (eg, histochemistry, immunohistochemistry, DNA analysis [specify type], morphometry, cytogenetic analysis)

C. Microscopic Evaluation

1. Tumor
   a. Histologic type (Note **B**)
   b. Histologic grade (Note **C**)
   c. Extent of invasion, as appropriate
   d. Relationship of tumor to anal transitional zone or glandular mucosa or perianal skin, if possible
2. Margins (excisional biopsy)
   a. Lateral (distance to closest margin in millimeters)
   b. Deep (distance to closest approach of tumor in millimeters)
3. Additional pathologic findings, if present
   a. Condyloma

   b. Anal canal intraepithelial neoplasia
   c. Inflammatory processes
   d. Other(s)
4. Results/status of special studies (specify)
5. Comments
   a. Correlation with intraoperative consultation, as appropriate
   b. Correlation with other specimens, as appropriate
   c. Correlation with clinical information, as appropriate

III. Abdominoperineal Resection

A. Clinical Information

1. Patient identification
   a. Name
   b. Identification number
   c. Age (birth date)
   d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
   a. Relevant history
      (1) sexually transmitted diseases (human immunodeficiency virus [HIV], herpes simplex virus [HSV], human papilloma virus [HPV])
      (2) genital neoplasms
      (3) immunosuppression
      (4) inflammatory bowel disease
   b. Relevant findings (eg, endoscopic and/or imaging studies)
   c. Clinical diagnosis
   d. Procedure (eg, abdominoperineal resection)
   e. Anatomic site(s) of specimen(s) (Note **A**)

B. Macroscopic Examination

1. Specimen
   a. Organ(s)/tissue(s) received (specify)
   b. Unfixed/fixed (specify fixative)
   c. Number of pieces
   d. Dimensions
   e. Descriptive characteristics
   f. Orientation of specimen
   g. Results of intraoperative consultation
2. Tumor
   a. Location (Note **A**)
   b. Configuration (Note **D**)
   c. Size
   d. Descriptive characteristics (eg, color, consistency)
   e. Sinus or anorectal fistula, if present
   f. Distance from margins
      (1) proximal
      (2) distal
      (3) circumferential (lateral/radial soft tissue margin closest to deepest tumor penetration)

   g. Estimated depth of invasion
3. Additional pathologic findings, if present
4. Regional lymph nodes (Notes **E**)
5. Other organ(s) or structure(s)
6. Tissues submitted for microscopic evaluation
   a. Tumor, including
      (1) point of deepest penetration
      (2) interface with adjacent proximal glandular or transitional mucosa, if feasible
      (3) interface with distal anal squamous mucosa
   b. Margins
      (1) proximal
      (2) distal
      (3) circumferential (radial/lateral/deep soft tissue margin closest to deepest tumor penetration)
   c. All lymph nodes (Note **E**)
   d. Other lesions (eg, ulcers, polyps)
   e. Rectal and anal tissue uninvolved by tumor
   f. Other tissue(s)/organ(s)
   g. Frozen section tissue fragment(s) (unless saved for special studies)
7. Special studies (specify) (eg, histochemistry, immunohistochemistry, DNA analysis [specify type], morphometry, cytogenetic analysis) (Note **F**)

C. Microscopic Evaluation

1. Tumor
   a. Histologic type (Note **B**)
   b. Histologic grade (Note **C**)
   c. Extent of invasion (Note **G**)
   d. Relation of tumor to anal transitional or glandular mucosa or perianal skin, if possible
   e. Venous/lymphatic vessel invasion
2. Margins
   a. Proximal
   b. Distal
   c. Circumferential (radial/lateral/deep soft tissue margin closest to deepest tumor penetration)
3. Regional lymph nodes (Notes **E** and **G**)
   a. Number
   b. Number with metastases
4. Other organs or structures (Note **F**)
   a. Involvement by tumor, direct extension
   b. Metastatic involvement by tumor
5. Additional pathologic findings, if present
   a. Condyloma
   b. Anal canal intraepithelial neoplasia
   c. Polyps
   d. Fistula/sinus
   e. Inflammatory bowel disease
   f. Other(s)
6. Other tissues submitted (specify)

7. Results of special studies (specify) (Note **F**)
8. Comments
    a. Correlation with intraoperative consultation, as appropriate
    b. Correlation with other specimens, as appropriate
    c. Correlation with clinical information, as appropriate

Explanatory Notes

A. Location

Documentation of tumor location within the anal canal is important for purposes of stage assignment. Because the staging systems and the regional lymph nodes at risk of metastasis differ significantly for cancers of the anal canal, the rectum, and the perianal skin, it is essential to assure that the anatomic site of the tumor is the anal canal. For the pathologist, however, the documentation of location may be problematic. Currently, most anal canal carcinomas are managed successfully without surgery using combination chemotherapy and radiation therapy,[1] and resection specimens of anal tumors are seen only infrequently (primarily for small anal margin lesions or following failure of other treatment modalities). Although histological diagnosis is almost always performed on small biopsies, determination of the primary tumor location from biopsy specimens may be difficult or impossible. Therefore, documentation of anatomic site often requires clinical correlation.

A major problem complicating determination of anatomic site clinically or pathologically is the controversy over the anatomic definition of the anal canal itself. The surgical definition of the anal canal is the one most widely accepted for practical reasons and is the preferred definition of the American Joint Committee on Cancer (AJCC).[2] However, it is based on clinically identifiable landmarks that are difficult or impossible for the pathologist to locate. By this definition, the start of the anal canal is defined as the point where the rectum enters the puborectalis sling at the apex of the anal sphincter complex, a landmark that is palpable in vivo on digital exam as the anorectal ring. The termination of the anal canal is defined as the squamous mucocutaneous junction (ie, the junction of the distal squamous mucosa of the anal canal with the perianal hair-bearing skin).[2] Thus defined, the lining mucosa of the proximal anal canal includes a narrow zone (approximately 1 to 2 cm) of rectal-type glandular mucosa and transitional mucosa (if present) at the dentate line. In other words, this definition of the anal canal includes the anal transition zone (ATZ) and the dentate line, from which many of the most important and characteristic anal carcinomas develop. In the region of the dentate line, anal glands may be found subjacent to the mucosa extending across the internal sphincter.

B. Histologic Type

For consistency in reporting, the histologic classification proposed by the World Health Organization (WHO) is recommended.[3] However, this protocol does not preclude the use of other systems of classification or histologic types.

The great majority of carcinomas of the anus are squamous cell carcinomas. The previous edition of the WHO classification included 3 subtypes of squamous cell carcinoma (SCC): large cell keratinizing, large cell nonkeratinizing, and basaloid. However, because most SCCs of the anal canal show more than 1 subtype, the diagnostic reproducibility of these subtypes has been low. Furthermore, no significant prognostic differences between subtypes have been established. Therefore, the WHO now recommends that the generic diagnostic term “squamous cell carcinoma” be used for all squamous tumors of the anal canal. However, additional descriptive comment regarding specific histologic features, such as predominant cell size, basaloid features, degree of keratinization, or adjacent intraepithelial neoplasia, is encouraged. Prominent

basaloid features and small tumor cell size are related to infection with "high-risk" human papilloma virus.[3] SCC with a predominantly basaloid differentiation pattern was formerly known as cloacogenic carcinoma, but this term is now considered obsolete.

Two variants of SCC of the anal canal deserve note because they differ in prognosis from typical squamous tumors. One is verrucous carcinoma (also known as giant condyloma or Buschke-Lowenstein tumor), which resembles a condyloma macroscopically but is larger and fails to respond to conservative therapy. These lesions are regarded as biologic intermediates between condylomas and SCCs, with a better prognosis than SCC. However, nearly half of these lesions undergo malignant transformation. Another important variant is SCC with mucinous microcysts (well-formed cystic spaces containing Alcian blue- or PAS-stainable mucin). This entity has an unfavorable prognosis compared to SCC.

Finally, 2 rare types of anal canal carcinoma, anaplastic carcinoma and small cell carcinoma (high-grade neuroendocrine carcinoma), are tumors with aggressive biologic behavior and an unfavorable prognosis compared to typical SCC. Tumors of the more distal anal canal and especially anal margin (mucocutaneous junction) are generally purely squamous in type and show fewer basaloid or glandular features.

WHO Classification of Carcinoma of the Anal Canal[3]

Intraepithelial neoplasia
- Squamous or transitional epithelium
- Glandular
- Paget disease

Carcinoma
- Squamous cell carcinoma
- Adenocarcinoma
- Mucinous adenocarcinoma
- Small cell carcinoma[#]
- Undifferentiated carcinoma[#]
- Others

[#] By convention, these histologic types are assigned grade 4.

The term carcinoma, NOS (not otherwise specified) is not part of the WHO classification.

C. Histologic Grade

Histologic grades for anal canal squamous carcinoma are as follows.[2]

Grade X	Grade cannot be assessed
Grade 1	Well differentiated
Grade 2	Moderately differentiated
Grade 3	Poorly differentiated

If there are variations in the differentiation within the tumor, the highest (least favorable) grade is recorded as the overall grade.

Histologic grades for adenocarcinoma of the anal canal based on the proportion of gland formation by the tumor are suggested as follows.

Grade X Grade cannot be assessed
Grade 1 Well differentiated (greater than 95% of tumor composed of glands)
Grade 2 Moderately differentiated (50% to 95% of tumor composed of glands)
Grade 3 Poorly differentiated (49% or less of tumor composed of glands)

Small cell carcinomas and tumors with no differentiation or minimal differentiation that is discernible only in rare, tiny foci (undifferentiated carcinomas by WHO classification) are categorized as grade 4.

D. Configuration
Configurations include exophytic (fungating/polypoid), endophytic (ulcerative), and diffusely infiltrative, but overlap among these types is common. Complex configurations may be reported using more than 1 descriptor.

E. Regional Lymph Nodes
Regional lymph nodes (N) comprise the perirectal (anorectal, perirectal and lateral sacral), the internal iliac (hypogastric), and the inguinal (superficial and deep).[2] All other nodal groups represent sites of distant metastasis (M). The sites of regional node involvement correspond to the local lymphatic drainage, above to the rectal ampulla and below to the perineum. Tumors that arise in the anal canal usually spread initially to the anorectal and perirectal nodes, and those that arise at the anal margin spread to the superficial inguinal nodes.

F. Special Studies
Immunohistochemistry may be an especially helpful adjunct to the pathologic analysis of anal Paget disease. Immunohistochemical staining for cytokeratin (CK) 7 is a sensitive method for detection of Paget cells within involved anal and perianal epithelium. In addition, however, the specific immunophenotype of Paget cells has been shown to correlate with pathogenesis and may be important in patient management. Staining for CK20 has been shown to identify Paget disease that is likely to be associated with underlying rectal adenocarcinoma (presenting either synchronously or metachronously). In contrast, Paget cells that do not express CK20 but instead are positive for gross cystic disease fluid protein (GCDFP) are likely to represent primary cutaneous intraepithelial malignancy (with sweat gland differentiation).[3,4]

G. TNM and Stage Groupings
The TNM staging system for anal carcinoma of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended by the protocol and shown below.[2,5] The primary tumor is staged according to its size and local extension, as determined by clinical or pathologic examination. For most histologic types of anal canal cancer, the diameter of the tumor correlates with the depth of penetration. The staging system applies to all carcinomas arising in the anal canal, including carcinomas that arise within anorectal fistulas and anal glands, but excluding melanomas, carcinoid tumors, and sarcomas. Cancers that arise in the perianal skin are staged according to the classification for cancers of the skin (see Skin protocols).

By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically unfeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size invades adjacent organ(s), eg, vagina, urethra, bladder[#]

[#] Direct invasion of the rectal wall, perianal skin, subcutaneous tissue, or the sphincter muscle is not classified as T4.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis[#]
N1	Metastasis in perirectal lymph node(s)
N2	Metastasis in unilateral internal iliac and/or inguinal lymph node(s)
N3	Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes

[#] Regional Lymph Nodes (pN0): Isolated Tumor Cells

Isolated tumor cells (ITCs) are single cells or small clusters of cells not more than 0.2 mm in greatest dimension. Lymph nodes or distant sites with ITCs found by either histologic examination, immunohistochemistry, or nonmorphologic techniques (eg, flow cytometry, DNA analysis, polymerase chain reaction [PCR] amplification of a specific tumor marker) should be classified as N0 or M0, respectively. Specific denotation of the assigned N category is suggested as follows for cases in which ITCs are the only evidence of possible metastatic disease.[6,7]

pN0	No regional lymph node metastasis histologically, no examination for isolated tumor cells (ITCs)

pN0(i-)	No regional lymph node metastasis histologically, negative morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs
pN0(i+)	No regional lymph node metastasis histologically, positive morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs
pN0(mol-)	No regional lymph node metastasis histologically, negative nonmorphologic (molecular) findings for ITCs
pN0(mol+)	No regional lymph node metastasis histologically, positive nonmorphologic (molecular) findings for ITCs

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Groupings

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage IIIA	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T4	N0	M0
Stage IIIB	T4	N1	M0
	Any T	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

TNM Descriptors

For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y,” “r,” and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (ie, before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval, and is identified by the “r” prefix: rTNM.

The “a” prefix designates the stage determined at autopsy: aTNM.

Additional Descriptors

Residual Tumor (R)
Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

Vessel Invasion
By AJCC/UICC convention, vessel invasion (lymphatic or venous) does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category. In all other cases, lymphatic and venous invasion by tumor are coded separately as follows.

Lymphatic Vessel Invasion (L)
LX Lymphatic vessel invasion cannot be assessed
L0 No lymphatic vessel invasion
L1 Lymphatic vessel invasion

Venous Invasion (V)
VX Venous invasion cannot be assessed
V0 No venous invasion
V1 Microscopic venous invasion
V2 Macroscopic venous invasion

References

1. Ryan DP, Compton CC, Mayer RJ. Carcinoma of the anal canal. *N Engl J Med.* 2000;342:792-800.
2. Greene FL, Page DL, Fleming ID, et al, eds. *AJCC Cancer Staging Manual.* 6th ed. New York: Springer; 2002.
3. Fenger C, Frisch M, Marti MC, Parc R. Tumours of the anal canal. In: Hamilton SR, Aaltonen LA, eds. *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Digestive System.* Lyon: IARC Press; 2000:145-155.
4. Goldblum JR, Hart WR. Perianal Paget's disease: a histological and immunohistochemical study of 11 cases with and without associated rectal adenocarcinoma. *Am J Surg Pathol.* 1998;22:170-179.

5. Sobin LH, Wittekind C, eds. *UICC TNM Classification of Malignant Tumours.* 6th ed. New York: Wiley-Liss; 2002.
6. Wittekind C, Greene FL, Henson DE, Hutter RVP, Sobin LH, eds. *TNM Supplement. A Commentary on Uniform Use.* 3rd ed. New York: Wiley-Liss; 2003.
7. Singletary SE, Greene FL, Sobin LH. Classification of isolated tumor cells: clarification of the 6th edition of the American Joint Committee on Cancer Staging Manual. *Cancer*. 2003 Dec 15;90(12):2740-2741.

Bibliography

Beckmann AM, Acker R, Christiansen AE, Sherman KJ. Human papilloma virus infection in women with multicentric squamous cell neoplasia. *Am J Obstet Gynecol*. 1991: 165;1431-1437.

Boman B, Moertel CG, O'Connell MJ, et al. Carcinoma of the anal canal: a clinical and pathological study of 188 cases. *Cancer*. 1984;54:114-125.

Daling JR, Weiss NS, Hislop G, et al. Sexual practices, sexually transmitted diseases and the incidence of anal cancer. *N Engl J Med.* 1987;317:973-977

Daling JR, Sherman KJ, Hislop G, et al. Cigarette smoking and the risk of anogenital cancer. *Am J Epidemiol.* 1992;135:180-189.

Deans GT, McAleer JJA, Spence RAJ. Malignant anal tumors. *Br J Surg.* 1994;81:500-508.

Dixon AR, Pringle JH, Holmes JT, Watkin DFL. Cervical intraepithelial neoplasia and squamous cell carcinoma of the anus in sexually active women. *Postgrad Med J.* 1991;67:557-559.

Duggan, MA, Boras VF, Inoue M, McGregor SE. Human papilloma virus DNA in anal carcinomas: comparison of in situ and dot blot hybridization. *Am J Clin Pathol.* 1991;96:318-325.

Fenger C. Anal canal tumors and their precursors. *Pathol Annu*. 1988 Part 1;23:45-66.

Fenger C. Anal neoplasia and its precursors: facts and controversies. *Sem Diag Pathol*. 1991;8:190-201.

Fenger C. Histology of the anal canal. *Am J Surg Pathol*. 1988;12:41-55.

Higgins GD, Uzelin DM, Phillips GE, et al. Differing characteristics of human papilloma virus, RNA-positive and RNA-negative anal carcinomas. *Cancer.* 1991;68:561-567.

Hobbs CM, Lowry MA, Owen D, Sobin LH. Anal gland carcinoma. *Cancer*. 2001;92:2045-2049.

Lewin KJ, Riddell RH, Weinstein WM. The anal canal. In: Lewin KJ, Riddell RH, Weinstein WM, eds. *Gastrointestinal Pathology and Its Clinical Implications.* New York: Igaku-Shoin; 1992:1318-1359.

Mitchell EP. Carcinoma of the anal canal. *Semin Oncol.* 1988;15:146-153.

Noffsinger AE, Suzuk L, Hui Y. Differential sensitivities of E6 type-specific and L1 consensus primers in the detection of human papilloma virus in anal carcinoma. *Mod Pathol.* 1995;8:509-514.

Papillon J, Montbaron JT. Epidermoid carcinoma of the anal canal: a series of 276 cases. *Dis Colon Rectum.* 1987;30:324-333.

Rickert RR. Disorders of the anal region. In: Ming SC, Goldman H, eds. *Pathology of the Gastrointestinal Tract.* Philadelphia, Pa: Saunders; 1992:882-903.

Salmon RJ, Zafrani B, Labib A, et al. Prognosis of cloacogenic and squamous cancers of the anal canal. *Dis Colon Rectum.* 1986;29:336-340.

Shepherd NA, Scholefield JH, Love SB, England J, Northover JM. Prognostic factors in anal squamous carcinoma: a multivariate analysis of clinical, pathological and flow cytometric parameters in 235 cases. *Histopathology.* 1990;16:545-555.

Williams GR, Talbot IC. Anal carcinoma: a histologic review. *Histopathology*. 1994;25:507-516.

Wittekind C, Compton CC, Greene FL, Sobin LH. Residual tumor classification revisited. *Cancer*. 2002;94:2511-2516.

Wolber R, Dupuis B, Thiyagaratnam P, Owen D. Anal cloacogenic and squamous carcinomas. *Am J Surg Pathol.* 1990;14:176-182.

Zaki SR, Judd R, Coffield LM, et al. Human papilloma virus infection and anal carcinoma. *Am J Pathol.* 1992;140:1345-1355.