Protocol for the Examination of Resection Specimens From Patients With Carcinoma of the Anus

Version: 5.0.0.0
Protocol Posting Date: June 2022
CAP Laboratory Accreditation Program Protocol Required Use Date: March 2023

The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection</td>
<td>Abdominoperineal resection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
<td>Invasive carcinomas including small cell and large cell (poorly differentiated) neuroendocrine carcinoma</td>
</tr>
</tbody>
</table>

This protocol is NOT required for accreditation purposes for the following:

<table>
<thead>
<tr>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excisional biopsy (polypectomy)</td>
</tr>
<tr>
<td>Local excision (transanal disk incision)</td>
</tr>
<tr>
<td>Primary resection specimen with no residual cancer (eg, following neoadjuvant therapy)</td>
</tr>
<tr>
<td>Cytologic specimens</td>
</tr>
</tbody>
</table>

The following tumor types should NOT be reported using this protocol:

<table>
<thead>
<tr>
<th>Tumor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols)</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor (GIST) (consider the GIST protocol)</td>
</tr>
<tr>
<td>Non-GIST sarcoma (consider the Soft Tissue protocol)</td>
</tr>
<tr>
<td>Rectal Adenocarcinoma</td>
</tr>
</tbody>
</table>

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.
* Denotes primary author.
Accreditation Requirements
This protocol can be utilized for a variety of procedures and tumor types for clinical care purposes. For accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format.

- **Core data elements** are required in reports to adequately describe appropriate malignancies. For accreditation purposes, essential data elements must be reported in all instances, even if the response is “not applicable” or “cannot be determined.”
- **Conditional data elements** are only required to be reported if applicable as delineated in the protocol. For instance, the total number of lymph nodes examined must be reported, but only if nodes are present in the specimen.
- **Optional data elements** are identified with “+” and although not required for CAP accreditation purposes, may be considered for reporting as determined by local practice standards.

The use of this protocol is not required for recurrent tumors or for metastatic tumors that are resected at a different time than the primary tumor. Use of this protocol is also not required for pathology reviews performed at a second institution (ie, secondary consultation, second opinion, or review of outside case at second institution).

Synoptic Reporting
All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired Data element: Response format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including “Cannot be determined” if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
  - Anatomic site or specimen, laterality, and procedure
  - Pathologic Stage Classification (pTNM) elements
  - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location

Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report ie, all required elements must be in the synoptic portion of the report in the format defined above.
CAP
Approved

Summary of Changes
v 5.0.0.0
  • AJCC 9th Version Updates
Reporting Template

Protocol Posting Date: June 2022
Select a single response unless otherwise indicated.

CASE SUMMARY: (ANUS: Abdominoperineal Resection)
Standard(s): AJCC-UICC 9

SPECIMEN (Note A)

Procedure#
# For excisional biopsy or transanal disc excision, use the anus protocol for excision specimens
___ Abdominoperineal resection
___ Other (specify): ______________________
___ Not specified

TUMOR

Tumor Site (Note B)
___ Anal canal: ______________________
___ Perianal region: ____________________
___ Anus, not otherwise specified: __________
___ Other (specify): ____________________
___ Not known: _______________________

Histologic Type (Note C)
___ Squamous cell carcinoma
___ Basaloid squamous cell carcinoma
___ Basal cell carcinoma
___ Verrucous squamous cell carcinoma
___ Adenocarcinoma
___ Adenocarcinoma of the anal glands
___ Neuroendocrine carcinoma
___ Large cell neuroendocrine carcinoma
___ Small cell neuroendocrine carcinoma
___ Mixed adenoneuroendocrine carcinoma (MANEC)
___ Undifferentiated carcinoma
___ Other histologic type not listed (specify): ______________________
___ Carcinoma, type cannot be determined: ______________________
+Histologic Type Comment: ______________________

Histologic Grade (Note D)
___ G1, well differentiated
___ G2, moderately differentiated
___ G3, poorly differentiated
___ G4, undifferentiated
___ Other (specify): ______________________
___ GX, cannot be assessed: _________________
___ Not applicable: _________________

Tumor Size
___ Greatest dimension in Centimeters (cm): _________________ cm
   +Additional Dimension in Centimeters (cm): ____ x ____ cm
___ Cannot be determined (explain): _________________

Tumor Extent (select all that apply)
___ Carcinoma in situ
___ Invades lamina propria
___ Invades muscularis mucosae
___ Invades submucosa
___ Invades into but not through sphincter muscle
___ Invades into but not through muscularis propria of rectum
___ Invades through sphincter muscle into perianal or perirectal soft tissue without involvement of adjacent structures
___ Directly invades adjacent structure(s) (specify): _________________
___ Invades perianal skin
___ Cannot be determined: _________________
___ No evidence of primary tumor

Treatment Effect (Note E)
___ No known presurgical therapy
___ Present, with no viable cancer cells (complete response, score 0)
___ Present, with single cells or rare small groups of cancer cells (near complete response, score 1)
___ Present, with residual cancer showing evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response, score 2)
___ Present (not otherwise specified)
___ Absent, with extensive residual cancer and no evident tumor regression (poor or no response, score 3)
___ Cannot be determined: _________________

+Lymphovascular Invasion
___ Not identified
___ Present
___ Cannot be determined: _________________

+Perineural Invasion
___ Not identified
___ Present
___ Cannot be determined: _________________

+Tumor Comment: _________________
MARGINS

Margin Status for Invasive Carcinoma
___ All margins negative for invasive carcinoma
+Closest Margin(s) to Invasive Carcinoma (select all that apply)
   ___ Proximal: _________________
   ___ Distal: _________________
   ___ Circumferential (radial): _________________
   ___ Other (specify): _________________
   ___ Cannot be determined: _________________
+Distance from Invasive Carcinoma to Closest Margin
   Specify in Centimeters (cm)
   ___ Exact distance in cm: _________________ cm
   ___ Greater than 1 cm
   Specify in Millimeters (mm)
   ___ Exact distance in mm: _________________ mm
   ___ Greater than 10 mm
   Other
   ___ Other (specify): _________________
   ___ Cannot be determined: _________________
   ___ Not applicable: _________________
___ Invasive carcinoma present at margin
Margin(s) Involved by Invasive Carcinoma (select all that apply)
___ Proximal: _________________
___ Distal: _________________
___ Circumferential (radial): _________________
___ Other (specify): _________________
___ Cannot be determined (explain): _________________
___ Other (specify): _________________
___ Cannot be determined (explain): _________________
___ Not applicable

Margin Status for High-Grade Intraepithelial Neoplasia
___ All margins negative for high-grade intraepithelial neoplasia
___ High-grade intraepithelial neoplasia present at margin
Margin(s) Involved by High-Grade Intraepithelial Neoplasia (select all that apply)
___ Proximal: _________________
___ Distal: _________________
___ Other (specify): _________________
___ Cannot be determined (explain): _________________
___ Other (specify): _________________
___ Cannot be determined (explain): _________________
___ Not applicable

+Margin Comment: _________________
REGIONAL LYMPH NODES

Regional Lymph Node Status
___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present
___ All regional lymph nodes negative for tumor
___ Tumor present in regional lymph node(s)

Number of External Iliac Nodes with Tumor
___ Exact number (specify): _________________
___ At least (specify): _________________
___ Other (specify): _________________
___ Cannot be determined (explain): _________________

Number of All Other Regional Nodes with Tumor
___ Exact number (specify): _________________
___ At least (specify): _________________
___ Other (specify): _________________
___ Cannot be determined (explain): _________________

Other Regional Nodal Site(s) with Tumor (select all that apply)
___ Not applicable
___ Right inguinal: _________________
___ Left inguinal: _________________
___ Superior rectal: _________________
___ Obturator: _________________
___ Mesorectal: _________________
___ Right internal iliac: _________________
___ Left internal iliac: _________________
___ Other (specify): _________________
___ Cannot be determined: _________________
___ Other (specify): _________________
___ Cannot be determined (explain): _________________

Number of External Iliac Nodes Examined
___ Exact number (specify): _________________
___ At least (specify): _________________
___ Other (specify): _________________
___ Cannot be determined (explain): _________________

Number of All Other Regional Nodes Examined
___ Exact number (specify): _________________
___ At least (specify): _________________
___ Other (specify): _________________
___ Cannot be determined (explain): _________________

Other Regional Nodal Site(s) Examined, if applicable (select all that apply)
___ Not applicable (no other regional nodes examined)
___ Right inguinal: _________________
___ Left inguinal: _________________
___ Superior rectal: _________________
___ Obturator: _________________
Mesorectal: _________________
Right internal iliac: _________________
Left internal iliac: _________________
Other (specify): _________________
Cannot be determined: _________________

Regional Lymph Node Comment: _________________

DISTANT METASTASIS

Distant Site(s) Involved, if applicable (select all that apply)
Not applicable
Non-regional lymph node(s): _________________
Liver: _________________
Other (specify): _________________
Cannot be determined: _________________

PATHOLOGIC STAGE CLASSIFICATION (pTNM, AJCC 9th Version) (Note F)
Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician’s responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

TNM Descriptors (select all that apply)
Not applicable: _________________
m (multiple)
r (recurrent)
y (post-treatment)

pT Category
pT not assigned (cannot be determined based on available pathological information)
pT0: No evidence of primary tumor
pT1: Tumor less than or equal to 2 cm in greatest dimension
pT2: Tumor greater than 2 cm but less than or equal to 5 cm in greatest dimension
pT3: Tumor greater than 5 cm in greatest dimension
pT4: Tumor of any size invading adjacent organ(s), such as the vagina, urethra, or bladder

pN Category
pN not assigned (no nodes submitted or found)
pN not assigned (cannot be determined based on available pathological information)
pN0: No tumor involvement of regional lymph node(s)
pN1: Tumor involvement of regional lymph node(s)
pN1a: Tumor involvement of inguinal, mesorectal, superior rectal, internal iliac or obturator lymph node(s)
pN1b: Tumor involvement of external iliac lymph node(s)
pN1c: Tumor involvement of N1b (external iliac) with any N1a node(s)
pN1 (subcategory cannot be determined)
pM Category (required only if confirmed pathologically)
___ Not applicable - pM cannot be determined from the submitted specimen(s)
___ pM1: Distant metastasis

ADDITIONAL FINDINGS (Note G)

+Additional Findings (select all that apply)
___ None identified
___ Crohn disease
___ Condyloma acuminatum
___ Anal fistula
___ Dysplasia
___ Associated rectal carcinoma (Paget disease)
___ Other (specify): ___________________

SPECIAL STUDIES

+Ancillary Studies (specify) (Note H): ___________________

COMMENTS

Comment(s): ___________________
Explanatory Notes

A. Specimen Integrity and Handling
For specimens from local excision procedures, all relevant margins, including the deep resection margin, should be inked. Evaluation of margins and invasion is facilitated if the specimen is pinned before fixation in formalin.

B. Location
Documentation of tumor location within the anal canal is important for purposes of stage assignment. The regional lymph nodes at risk of metastasis are different for cancers of the anal canal, the rectum, and the perianal skin. Currently, most anal canal carcinomas are managed successfully without surgery, using combination chemotherapy and radiation therapy, and resection specimens of anal tumors are seen only infrequently (primarily for small anal margin lesions or after 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.

The anal canal begins where the rectum enters the puborectalis sling at the apex of the anal sphincter complex (palpable as the anorectal ring on digital rectal examination and approximately 1 cm to 2 cm proximal to the dentate line) and ends with the squamous mucosa blending with the perianal skin (Figure 1), which coincides roughly with the palpable intersphincteric groove or the outermost boundary of the internal sphincter muscle, easily visualized on endoanal ultrasound. The anus encompasses true mucosa of three different histologic types: glandular, transitional, and squamous (proximal to distal, respectively). The most proximal aspect of the anal canal is lined by colorectal mucosa in which squamous metaplasia may occur. When involved by metaplasia, this zone also may be referred to as the transformation zone. Immediately proximal to the macroscopically visible dentate line, a narrow zone of multilayered transitional mucosa is variably present. In the region of the dentate line, anal glands are subjacent to the mucosa, often penetrating through the internal sphincter into the intersphincteric plane. The distal zone of the anal canal extends from the dentate line to the mucocutaneous junction with the perianal skin and is lined by a nonkeratinizing squamous epithelium devoid of epidermal appendages (hair follicles, apocrine glands, and sweat glands).
Figure 1. Anatomy of the anal canal. From Greene et al.3 Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Atlas (2006) published by Springer Science and Business Media LLC, www.springerlink.com. This protocol applies to tumors involving the anal canal and perianal region (Figure 2). Tumors arising in the anal canal (including all three types of mucosa) that cannot be entirely visualized by gentle traction placed on the buttocks are considered as anal cancers, while tumors arising in the skin at or distal to the squamous mucocutaneous junction, can be entirely visualized with gentle traction placed on the buttocks, and are within 5cm of the anus are considered perianal cancers. For tumors that are localized to the perineal region and not obviously arising from anus or vulva, should be classified as “favor perianal” or “favor vulvar” based on clinical assessment. This protocol does not apply to tumors that are >5 cm from the anus.

Figure 2. Anal cancer (A–C), perianal cancer (D), and skin cancer (E) as visualized with gentle traction placed on the buttocks. From Amin et al.2 Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual (2016) published by Springer Science and Business Media LLC, www.springerlink.com.

References

C. Histologic Type
For consistency in reporting, the histologic classification proposed by the World Health Organization (WHO) is recommended.1 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.2 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 consistently been established, although the basaloid
subtype of squamous cell carcinoma may be associated with a higher risk of distant metastasis. Therefore, the WHO now recommends that the generic diagnostic term “squamous cell carcinoma” be used for all squamous malignancies 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 papillomavirus. SCC with a predominantly basaloid differentiation pattern was formerly known as cloacogenic carcinoma, but this term is now considered obsolete. Basaloid squamous cell carcinoma also needs to be differentiated from basal cell carcinoma, which is rare in this location, often arise in the perianal skin, and is a less aggressive neoplasm.

Two variants of SCC of the anal canal deserve note because they differ in prognosis from typical squamous tumors. One is verrucous carcinoma, which is an exophytic hyperkeratotic verrucous growth that is rarely associated with HPV when strict diagnostic criteria are applied. Endophytic growth is seen as bulbous rete pegs that grow in a pushing fashion into the underlying stroma, but infiltrative type invasion is absent. While controversial, verrucous carcinoma is now considered different from giant condyloma or Buschke-Lowenstein tumor. Giant condyloma or Buschke-Lowenstein tumor resembles condyloma acuminata, but is larger, with more florid excrescences, and is associated with HPV 6 and 11. Immunohistochemical staining for p16 does not help to differentiate it from verrucous carcinoma as both display negative or focal staining. 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 with that of SCC.

Finally, two rare types of anal canal carcinoma, anaplastic/undifferentiated carcinoma and small cell carcinoma (high-grade neuroendocrine carcinoma), are aggressive tumors with an unfavorable prognosis compared with typical SCC. Tumors of the distal anal canal and perianal region are generally purely squamous in type and are less likely to show basaloid or glandular features.

Adenocarcinoma of the anal canal includes many different sub-types of which colorectal-type and anal gland type are the two major sub-types. Other types include IBD-associated or fistula-associated adenocarcinomas and adnexal salivary gland type neoplasms. Differentiation between different types may not always be possible. Adenocarcinoma similar to colorectal adenocarcinoma may arise in the columnar-mucosa of the anal canal and are managed similar to rectal adenocarcinoma. Data regarding these primary anal adenocarcinomas are sparse, but these are currently staged as per this protocol (AJCC, 9th version). However, colorectal-type adenocarcinomas extending from the rectum into the anal canal should be staged using the colorectal adenocarcinoma scheme.

Poorly differentiated neuroendocrine carcinomas are typically classified as small or large cell type similar to other sites. Neuroendocrine carcinomas that do not meet the criteria for small cell type are by default regarded as large cell type. This distinction is not always possible and such neoplasms can be classified as poorly differentiated neuroendocrine carcinomas, not otherwise specified. Poorly differentiated squamous carcinoma or adenocarcinomas may also show variable amount of endocrine differentiation, typically identified on immunohistochemical evaluation of markers for endocrine differentiation; these are referred to as carcinoma with neuroendocrine differentiation. Their differentiation from poorly differentiated neuroendocrine carcinomas can be challenging, if not impossible, especially on small biopsies.
References
7. Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the forthcoming AJCC Version 9 Anus Cancer Staging System. Copyright 2022 American College of Surgeons.

D. Histologic Grade
Histologic grades for anal canal squamous carcinoma are as follows:

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 (less than 50% of tumor composed of glands)

Tumors with no squamous, glandular or neuroendocrine differentiation (undifferentiated carcinomas by WHO classification) are categorized as grade 4. These grading schemes are not applicable to poorly differentiated neuroendocrine carcinomas.

E. Treatment Effect
Response of tumor to previous chemotherapy or radiation therapy should be reported. Although grading systems for tumor response have not been established, 3-category systems generally provide good interobserver reproducibility. The following system is suggested:
Modified Ryan Scheme for Tumor Regression Score

<table>
<thead>
<tr>
<th>Description</th>
<th>Tumor Regression Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No viable cancer cells (complete response)</td>
<td>0</td>
</tr>
<tr>
<td>Single cells or rare small groups of cancer cells (near complete response)</td>
<td>1</td>
</tr>
<tr>
<td>Residual cancer with evident tumor regression, but more than single cells or</td>
<td>2</td>
</tr>
<tr>
<td>rare small groups of cancer cells (partial response)</td>
<td></td>
</tr>
<tr>
<td>Extensive residual cancer with no evident tumor regression (poor or no</td>
<td>3</td>
</tr>
<tr>
<td>response)</td>
<td></td>
</tr>
</tbody>
</table>

References


F. TNM and Anatomic Stage/Prognostic 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. The primary tumor is staged according to its size and local extension, as determined by clinical or pathologic examination. 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, well-differentiated/low-grade neuroendocrine tumors (carcinoid tumors), and sarcomas.

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 infeasible) 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.

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 after 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 before 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.

**T Category Considerations**

T categories for anal canal cancer are illustrated in Figures 3 through 6

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**Figure 3.** T1 is defined as tumor 2 cm or less in greatest dimension. From Greene et al. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, [www.springerlink.com](http://www.springerlink.com).
Figure 4. T2 is defined as tumor measuring more than 2 cm but 5 cm or less in greatest dimension. From Greene et al. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Atlas (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

Figure 5. T3 is defined as tumor measuring more than 5 cm in greatest dimension. From Greene et al. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Atlas (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

Figure 6. T4 is defined as tumor of any size invading adjacent organs such as vagina (illustrated), urethra, or bladder. From Greene et al. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Atlas (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

N Category Considerations
Regional lymph nodes (N) (Figure 7) include mesorectal, inguinal (superficial and deep), superior rectal (hemorrhoidal), external iliac and internal iliac (hypogastric). 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 mesorectal nodes, and those that arise at the anal margin spread to the superficial inguinal nodes.
Figure 7. Regional lymph nodes of the anal canal. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois.1

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.

References
1. Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the forthcoming AJCC Version 9 Anus Cancer Staging System. Copyright 2022 American College of Surgeons.

G. Additional Findings
Predisposing conditions to anal canal carcinoma that may be found in the pathologic specimen include condyloma acuminatum associated with human papilloma virus infection.1 Squamous intraepithelial neoplasia is recognized as a precursor lesion for squamous cell carcinoma of the anal canal,2 and its presence should be reported. Both adenocarcinomas and squamous cell carcinomas have been reported in the setting of chronic anorectal fistulae arising in long-standing Crohn disease,3 although the association of benign inflammatory lesions and anal cancer remains controversial.4,5

References
**H. Ancillary Studies**

Immunohistochemistry may be helpful in establishing tumor type for poorly differentiated carcinomas; squamous cell carcinomas of the anal canal express cytokeratin (CK) 7, CK5/6, p53, \(^1\), and p63\(^2\) but are negative for CK20. In contrast, anal gland carcinomas are mucin positive and express CK7 and/or CK20 but are negative for CDX2, CK5/6 and p63.\(^1\)\(^2\)\(^3\)

Immunohistochemical studies may also aid in distinguishing primary anal Paget disease from secondary Paget disease of the perianal area, which is associated with colorectal and anal canal carcinoma. CK7 expression is a sensitive method for detection of both primary and secondary Paget cells within involved anal and perianal squamous epithelium. In addition, however, the specific immunophenotype of Paget cells has been shown to correlate with pathogenesis and may be important in patient management. Demonstration of CK20 expression has been shown to identify Paget disease that is likely to be associated with underlying rectal adenocarcinoma (either synchronous or metachronous). In contrast, Paget cells that do not express CK20 but instead are positive for gross cystic disease fluid protein (GCDFP), a marker for apocrine differentiation, are likely to represent primary cutaneous intraepithelial malignancy.\(^4\)\(^5\)\(^6\)

**References**