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Anal Carcinoma

V.1.2009

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NCCN Anal Carcinoma Panel Members

*Paul F. Engstrom, MD/Chair †
Fox Chase Cancer Center

Juan Pablo Arnoletti, MD ¶
University of Alabama at Birmingham
Comprehensive Cancer Center

*Al B. Benson, III, MD †
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Yi-Jen Chen, MD, PhD §
City of Hope

Michael A. Choti, MD ¶
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Harry S. Cooper, MD ≠
Fox Chase Cancer Center

Anne Covey, MD ϕ
Memorial Sloan-Kettering Cancer Center

Raza A. Dilawari, MD ¶
St. Jude Children's Research
Hospital/University of Tennessee Cancer
Institute

Dayna S. Early, MD ¤
Siteman Cancer Center at Barnes-Jewish
Hospital and Washington University
School of Medicine

Peter C. Enzinger, MD †
Dana-Farber/Brigham and Women's
Cancer Center

Marwan G. Fakih, MD †
Roswell Park Cancer Institute

James Fleshman, Jr., MD ¶
Siteman Cancer Center at Barnes-Jewish
Hospital and Washington University School
of Medicine

Charles Fuchs, MD †
Dana-Farber/Brigham and Women's Cancer
Center | Massachusetts General Hospital
Cancer Center

Jean L. Grem, MD †
UNMC Eppley Cancer Center at The
Nebraska Medical Center

Krystyna Kiel, MD §
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

James A. Knol, MD ¶
University of Michigan Comprehensive
Cancer Center

Lucille A. Leong, MD †
City of Hope Cancer Center

Edward Lin, MD †
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

Mary F. Mulcahy, MD ‡
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Sujata Rao, MD †
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

*David P. Ryan, MD ¤
Massachusetts General Hospital Cancer Center

Leonard Saltz, MD † ‡ Þ
Memorial Sloan-Kettering Cancer Center

David Shibata, MD ¶
H. Lee Moffitt Cancer Center and Research
Institute at the University of South Florida

John M. Skibber, MD ¶
The University of Texas M. D. Anderson Cancer
Center

Constantinos Sofocleous, MD, PhD ϕ
Memorial Sloan-Kettering Cancer Center

James Thomas, MD
Arthur G. James Cancer Hospital & Richard J.
Solove Research Institute at The Ohio State
University

Alan P. Venook, MD † ‡
UCSF Comprehensive Cancer Center

Christopher Willett, MD §
Duke Comprehensive Cancer Center

† Medical Oncology
§ Radiotherapy/Radiation oncology
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≠ Pathology
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Þ Internal medicine
¤ Gastroenterology
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*Writing Committee Member

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Clinical Trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

Summary of the Guidelines updates

Summary of changes in the 1.2009 version of the Anal Carcinoma Guidelines from the 2.2008 version include:

ANAL-1

- Footnote "b" was updated to reflect the published reference with the following text "In a randomized trial, the strategy of using neoadjuvant therapy with 5-FU + cisplatin followed by concurrent therapy with 5-FU + cisplatin + RT was not superior to 5-FU + mitomycin + RT.

ANAL-2

- Same change as noted above for footnote "b".

ANAL-3

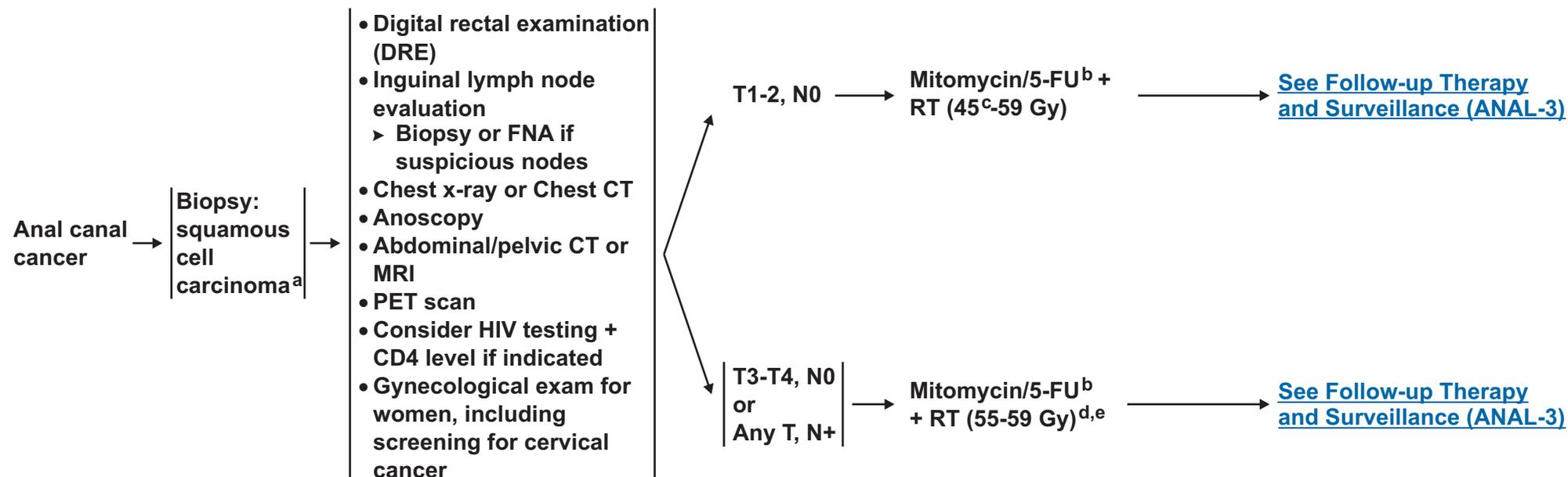- CT scan in follow-up was defined as "annually".

ANAL-A

- Principles of Chemotherapy is a new section to the Guidelines.

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Anal Canal Cancer

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CLINICAL PRESENTATION	WORKUP	CLINICAL STAGE	PRIMARY TREATMENT	
Anal canal cancer → **Biopsy: squamous cell carcinoma**[a] →	• **Digital rectal examination (DRE)** • **Inguinal lymph node evaluation** ➤ **Biopsy or FNA if suspicious nodes** • **Chest x-ray or Chest CT** • **Anoscopy** • **Abdominal/pelvic CT or MRI** • **PET scan** • **Consider HIV testing + CD4 level if indicated** • **Gynecological exam for women, including screening for cervical cancer**	**T1-2, N0**	**Mitomycin/5-FU[b] + RT (45[c]-59 Gy)**	**See Follow-up Therapy and Surveillance (ANAL-3)**
		T3-T4, N0 or Any T, N+	**Mitomycin/5-FU[b] + RT (55-59 Gy)[d,e]**	**See Follow-up Therapy and Surveillance (ANAL-3)**

[a] For melanoma histology, see the NCCN Melanoma Guidelines, for adenocarcinoma, see the NCCN Rectal Cancer Guidelines.

[b] See Principles of Chemotherapy ANAL-A.
  Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. In a randomized trial, the strategy of using neoadjuvant therapy with 5-FU + cisplatin followed by concurrent therapy with 5-FU + cisplatin + RT was not superior to 5-FU + mitomycin + RT.

[c] Re-evaluate at 45 Gy, if persistent disease, consider increasing to 55-59 Gy.

[d] Include bilateral inguinal/low pelvic nodal regions based upon estimated risk of inguinal involvement.

[e] Patients with anal cancer as the first manifestation of HIV/AIDS, may be treated with same regimen as non-HIV patient. Patients with active HIV/AIDS-related complications or a history of complications (eg, malignancies, opportunistic infections) may not tolerate full-dose therapy or may not tolerate mitomycin and require dosage adjustment or treatment without mitomycin.

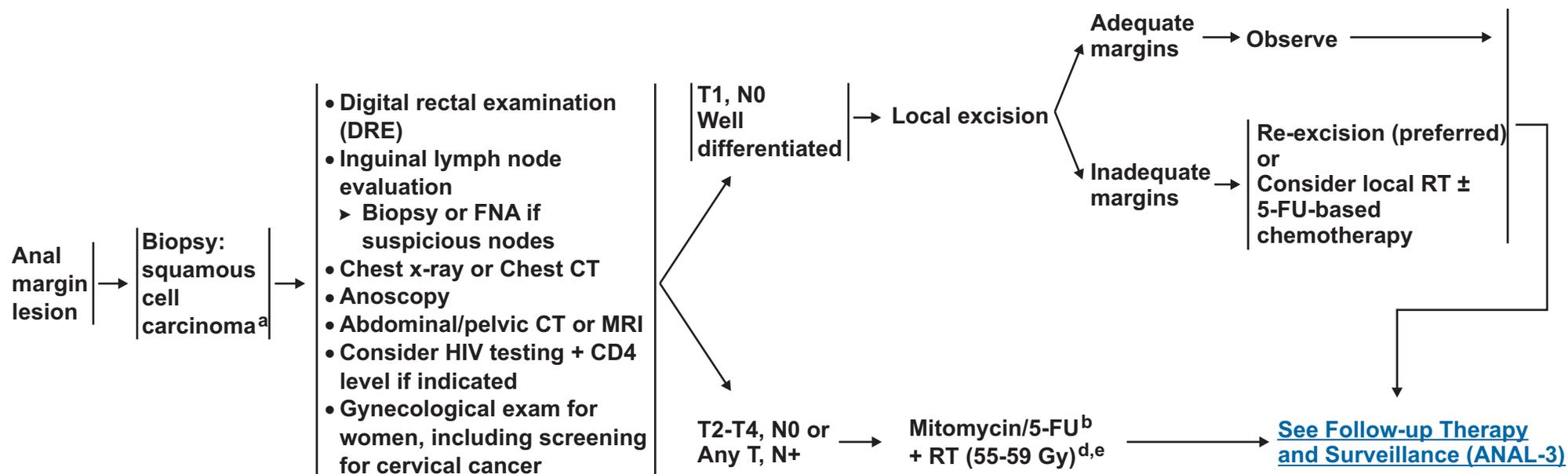Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Anal Margin Cancer

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**CLINICAL
PRESENTATION**

WORKUP

**CLINICAL
STAGE**

PRIMARY TREATMENT

Anal margin lesion → **Biopsy: squamous cell carcinoma[a]** →

- **Digital rectal examination (DRE)**
- **Inguinal lymph node evaluation**
  - ➤ **Biopsy or FNA if suspicious nodes**
- **Chest x-ray or Chest CT**
- **Anoscopy**
- **Abdominal/pelvic CT or MRI**
- **Consider HIV testing + CD4 level if indicated**
- **Gynecological exam for women, including screening for cervical cancer**

T1, N0 Well differentiated → **Local excision** →
- **Adequate margins** → **Observe** →
- **Inadequate margins** → **Re-excision (preferred) or Consider local RT ± 5-FU-based chemotherapy**

T2-T4, N0 or Any T, N+ → **Mitomycin/5-FU[b] + RT (55-59 Gy)[d,e]** → **See Follow-up Therapy and Surveillance (ANAL-3)**

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[a] For melanoma histology, see the NCCN Melanoma Guidelines, for adenocarcinoma, see the NCCN Rectal Cancer Guidelines.

[b] See Principles of Chemotherapy ANAL-A.

Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. JAMA 2008;299:1914. The strategy of using neoadjuvant therapy with 5-FU + cisplatin followed by concurrent therapy with 5-FU + cisplatin + RT was not superior to 5-FU + mitomycin + RT.

[d] Include bilateral inguinal/low pelvic nodal regions based upon estimated risk of inguinal involvement.

[e] Patients with anal cancer as the first manifestation of HIV/AIDS, may be treated with same regimen as non-HIV patient. Patients with active HIV/AIDS-related complications or a history of complications (eg, malignancies, opportunistic infections) may not tolerate full-dose therapy or may not tolerate mitomycin and require dosage adjustment or treatment without mitomycin.
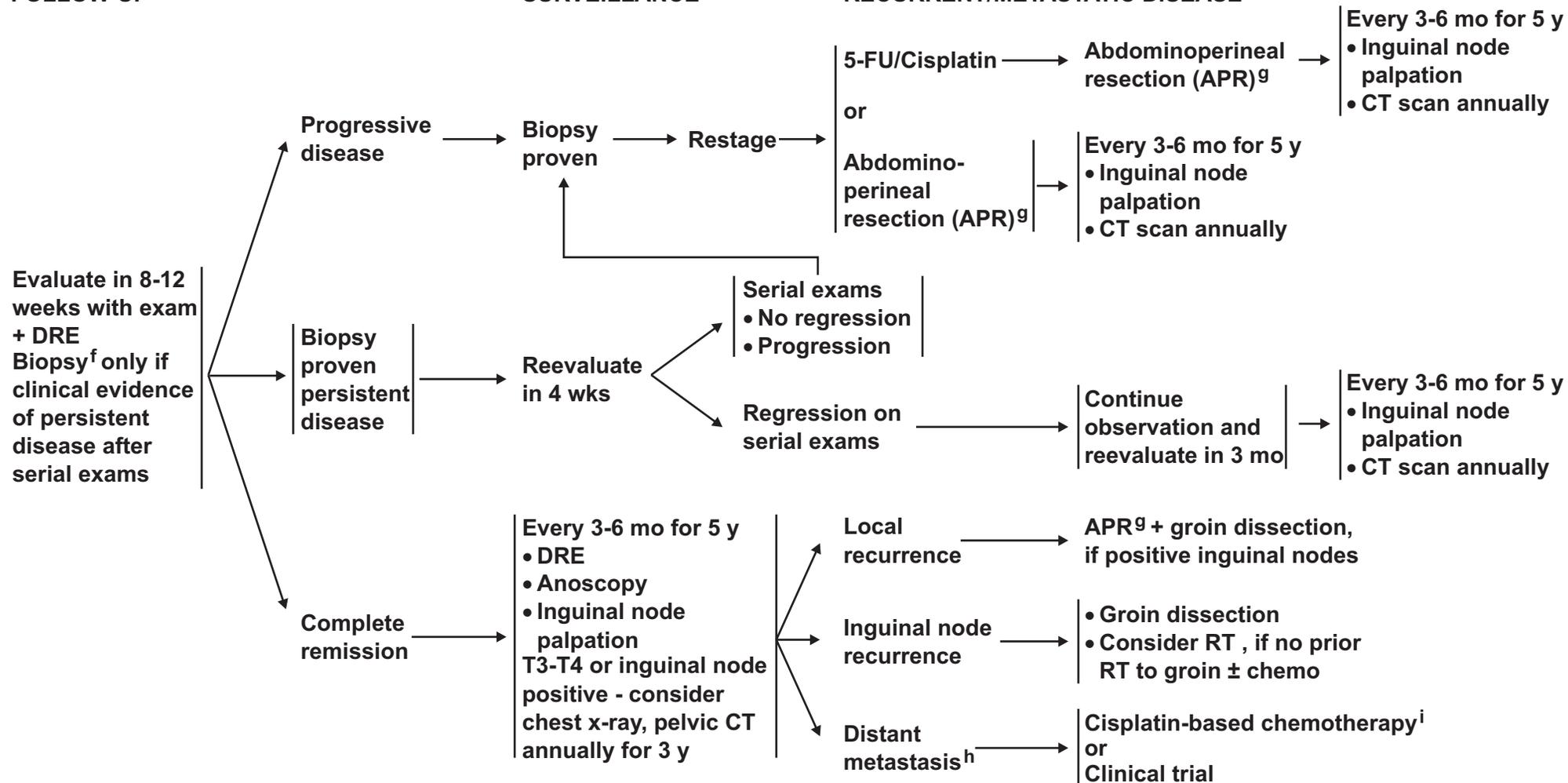

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FOLLOW-UP

SURVEILLANCE

RECURRENT/METASTATIC DISEASE

Evaluate in 8-12 weeks with exam + DRE
Biopsy[f] only if clinical evidence of persistent disease after serial exams

→ **Progressive disease** → **Biopsy proven** → **Restage** →

5-FU/Cisplatin → **Abdominoperineal resection (APR)**[g] →
Every 3-6 mo for 5 y
• Inguinal node palpation
• CT scan annually

or

Abdomino-perineal resection (APR)[g] →
Every 3-6 mo for 5 y
• Inguinal node palpation
• CT scan annually

→ **Biopsy proven persistent disease** → **Reevaluate in 4 wks** →

Serial exams
• No regression
• Progression

→ **Regression on serial exams** → **Continue observation and reevaluate in 3 mo** →
Every 3-6 mo for 5 y
• Inguinal node palpation
• CT scan annually

→ **Complete remission** →
Every 3-6 mo for 5 y
• DRE
• Anoscopy
• Inguinal node palpation
T3-T4 or inguinal node positive - consider chest x-ray, pelvic CT annually for 3 y

→ **Local recurrence** → APR[g] + groin dissection, if positive inguinal nodes

→ **Inguinal node recurrence** →
• Groin dissection
• Consider RT , if no prior RT to groin ± chemo

→ **Distant metastasis**[h] →
Cisplatin-based chemotherapy[i]
or
Clinical trial

---

[f] If patient with an initially tethered tumor returns 6 weeks postop RT with a mobile but suspicious mass, consider biopsy.

[g] Consider muscle flap reconstruction.

[h] There is no evidence supporting resection of metastatic disease.

[i] Cisplatin/5-fluorouracil recommended for metastatic disease. If this regimen fails, no other regimens have shown to be effective.
See Principles of Chemotherapy ANAL-A.

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PRINCIPLES OF CHEMOTHERAPY

Localized cancer

5-FU + Mitomycin + RT[1,2]
5-FU 1000 mg/m^2/d IV days 1-4 and 29-32
Mitomycin 10 mg/m^2 IV bolus days 1 and 29
Concurrent radiotherapy 1.8 Gy/d for 5 weeks to 45 Gy

Metastatic Cancer

5-FU + Cisplatin[3]
5-FU 1000 mg/m^2/d IV days 1-5
Cisplatin 100 mg/m^2 IV day 2
Repeat every 4 weeks

[1]Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. JAMA 2008;299:1914-1921.

[2]Flam M, John M, Pajak TF, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. J Clin Oncol 1996;14:2527

[3]Faivre C, Rougier P, Ducreux M, et al. 5-fluorouracil and cisplatin combination chemotherapy for metastatic squamous-cell anal cancer. Bull Cancer 1999;86:861-5.

Note: All recommendations are category 2A unless otherwise indicated.
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ANAL-A

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Anal Carcinoma

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Staging Anal Canal Cancer

Table 1

2002 American Joint Committee on Cancer (AJCC) Staging System for Anal Canal 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), e.g., vagina, urethra, bladder†

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

Distant Metastasis (M)
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Staging for Anal Margin Cancer, see ST-2

Stage Grouping

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

Histologic Grade (G)
GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

*Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the *AJCC Cancer Staging Manual, Sixth edition* (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed written permission of Springer-Verlag New York on behalf of the AJCC.

†Direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) is not classified as T4.

Staging Anal Margin Cancer

Table 2

2002 American Joint Committee on Cancer (AJCC) TNM Staging System for Skin 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 invades deep extradermal structures (i.e., cartilage, skeletal muscle, or bone)
Note: In the case of multiple simultaneous tumors, the tumor with the highest T category will be classified and the number of separate tumors will be indicated in parentheses, e.g., T2 (5).

Regional Lymph Nodes (N)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

Distant Metastasis (M)
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Stage Grouping

Stage	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

Histologic Grade (G)
GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

*Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the *AJCC Cancer Staging Manual, Sixth edition* (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed written permission of Springer-Verlag New York on behalf of the AJCC.

†**Anal margin tumors are biologically comparable to other skin tumors and therefore are classified by this schema.**

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 08/05/08

NCCN Categories of Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

An estimated 5,070 new cases (2,020 men and 3,050 women) of anal cancer (involving the anus, anal canal, or the anorectum) will occur in the United States in 2008, accounting for approximately 1.9% of digestive system cancers.[1] It has been estimated that 680 deaths due to anal cancer will occur in the U.S. in 2008. Although considered to be a rare type of cancer, the incidence rate of invasive anal carcinoma in the U.S. increased by approximately 1.6-fold for men and 1.5-fold for women from the period of 1973-1979 to 1994-2000[2] (see section entitled Risk Factors, below).

This manuscript summarizes the NCCN clinical practice guidelines for managing squamous cell anal carcinoma which represents the most common histologic form of the disease. Other types of cancers occurring in the anal region, such as adenocarcinoma or melanoma,

are addressed in other NCCN guidelines (ie, anal adenocarcinoma and anal melanoma are managed according to the NCCN Rectal Cancer Guidelines and the NCCN Melanoma Guidelines, respectively). The recommendations in these guidelines are classified as category 2A except where noted, meaning that there is uniform NCCN consensus, based on lower-level evidence that the recommendation is appropriate. The panel unanimously endorses patient participation in a clinical trial over standard or accepted therapy.

Risk Factors

Anal carcinoma has been associated with human papilloma virus (HPV) infection (anal-genital warts); a history of receptive anal intercourse or sexually transmitted disease; a history of cervical, vulvar, or vaginal cancer; immunosuppression after solid organ transplantation or human immunodeficiency virus (HIV) infection, and smoking.[3,4, 5] Currently, it is believed that the association between anal carcinoma and persistent infection with a high-risk form of HPV (eg, HPV-16) is strongest. For example, results of a study of tumor specimens from 60 pathology laboratories showed that HPV-16 was detected in 84% and 0% of the anal and rectal cancer specimens, respectively.[4] Furthermore, suppression of the immune system by the use of immunosuppressive drugs or HIV infection is likely to facilitate persistence of HPV infection of the anal region.[6,7]

Anatomy/Histology

The anal region is comprised of the anal canal and the anal margin, dividing anal cancers into 2 categories. The anal canal is the more proximal portion of the anal region. Various definitions of the anal canal exist (eg, functional/surgical anal canal; anatomic anal canal; and histological anal canal) which are based on particular physical/anatomic landmarks or histological characteristics of the anal canal. The functional anal canal is defined by the sphincter muscles. The superior border of the functional anal canal, separating it from the rectum, has

been defined as the palpable upper border of the anal sphincter and puborectalis muscles of the anorectal ring. It is approximately 3 to 4 cm in length and its inferior border starts at the anal verge, the lowermost edge of the sphincter muscles which corresponds to the introitus of the anal orifice.[3,8,9] This definition is a primarily used in the radical surgical treatment of anal cancer. In describing anal cancers, more useful definitions include histologic characteristics of the mucosal lining of the anal region. [10,11] The mucosa of the anal canal is predominantly formed by squamous epithelium, in contrast to the mucosa of the rectum which is lined with glandular epithelium.[3,8] The most superior aspect of anal canal is a 1 to 2 cm zone between the anal and rectal epithelium which has rectal, urothelial, and squamous histologic characteristics.[3,8] The most inferior aspect of the anal canal, approximately at the anal verge, corresponds to the area where the mucosa lined with modified squamous epithelium transitions to an epidermis-lined anal margin. The anal margin starts at the anal verge, and includes the perianal skin over a 5 cm radius around the anal verge.[8] The terms anal margin and perianal skin are frequently used synonomously.[8, 12]

Pathology

Most primary cancers of the anal canal are of squamous cell histology.[8,10] The second edition of the World Health Organization (WHO) classification system of anal carcinoma designated all squamous cell carcinoma variants of the anal canal as cloacogenic and identified subtypes as large cell keratinizing, large cell non-keratinizing (transitional), or basaloid.[13] It has been reported that squamous cell cancers in the more proximal region of the anal canal are more likely to be non-keratinizing and less differentiated.[3] However, the terms cloacogenic, transitional, keratinizing and basaloid have been removed from the current WHO classification system of anal canal carcinoma, and all subtypes have been included under a single generic heading of squamous cell carcinoma.[11,12,14, 15] Reasons for this change include the following: both cloacogenic (which is sometimes used interchangeably

with the term basaloid) and transitional tumors are now considered to be non-keratinizing tumors; it has been reported that both keratinizing and nonkeratinizing tumors have similar a natural history and prognosis[12]; and a mixture of cell types frequently characterize histologic specimens of squamous cell carcinomas of the anal canal. [8,12-15] No distinction between squamous anal canal tumors on the basis of cell type has been made in the guidelines. Other less common anal canal tumors include adenocarcinomas of the anal glands, small cell and undifferentiated cancers, and melanomas.[8] Squamous cell carcinomas of the anal margin are more likely than anal canal tumors to be well-differentiated and keratinizing,[3] but they are not characterized in the guidelines according to cell type. The presence of skin appendages (eg, sweat glands) in anal margin tumors can distinguish them from anal canal tumors.[12] However, it is not always possible to distinguish between anal canal and anal margin squamous cell carcinoma since tumors can involve both areas.[12]

Lymph drainage of anal cancer tumors is dependent on the location of the tumor in the anal region: cancers in the perianal skin and the region of the anal canal distal to the dentate line drain mainly to the superficial inguinal nodes; lymph drainage at and proximal to the dentate line is directed toward the perirectal nodes and to some of the nodes of the internal iliac system; more proximal cancers drain to nodes of the inferior mesenteric system.[8] Therefore, distal anal cancers present with a higher incidence of inguinal node metastasis, although the lymphatic drainage systems throughout the anal canal are not isolated from each other.[8]

Staging

The TNM staging system for anal canal cancer developed by the American Joint Committee on Cancer (AJCC) is detailed in Table 1[11] Since current recommendations for the primary treatment of anal canal cancer do not involve a surgical excision, most tumors are staged

clinically with an emphasis on the size of the primary tumor as determined by direct examination and microscopic confirmation.[11] An incisional tumor biopsy is required. Rectal ultrasound to determine depth of tumor invasion is not used in the staging of anal cancer (see Clinical Presentation/Evaluation, below). The AJCC TNM system used for anal margin cancer (Table 2) is the same system used to stage skin cancer since the 2 types of cancers have a similar biology.[11]

Lymph node staging is based on location of involved nodes in the staging of anal canal cancer: N1 designates metastasis in one or more perirectal nodes; N2 represents metastasis in unilateral internal iliac nodes and/or inguinal node(s); and N3 designates metastasis in perirectal and inguinal nodes and/or bilateral internal iliac and/or inguinal nodes. For anal margin cancer, N0 and N1 simply represent the absence or presence of regional nodal metastasis. However, because initial therapy of anal cancer does not typically involve surgery, the true lymph node status may not be determined accurately. Biopsy of inguinal nodes is recommended if tumor metastasis to these nodes is suspected.

The prognosis of anal carcinoma is related to the size of the primary tumor and the presence of lymph node metastases.[11] Approximately 60% to 70% of anal carcinoma tumors are initially staged as I or II.[16, 17] Overall, the 5-year survival rate for patients with tumors that are no more than 2 cm in diameter that are treated with chemoRT is approximately 80%, whereas the 5-year survival rate for patients 5 cm or more is less than 50%.[8] Reports of the extent of nodal involvement associated with anal cancers at presentation have varied widely, with most values ranging between 10% and 40%.[8,12,16-19] Although there have been reports that the extent of nodal involvement is correlated with the T-stage of the tumor,[19] other studies have not supported this conclusion.[17] In a surgical series of patients with anal cancer who underwent an abdominoperineal resection (APR), it was noted that

pelvic nodal metastases were often under 0.5 cm,.[20]suggesting that routine radiological evaluation with CT and PET scan may not be reliable in the determination of lymph nodal involvement. In a retrospective study of 270 patients treated for anal canal cancer with RT between 1980 and 1996, synchronous inguinal node metastasis was observed in 6.4% of patients with tumors staged as T1 or T2, and increased to 16% in patients with T3 or T4 tumors.[16] In patients with N2-3 disease, survival was related to T-stage rather than nodal involvement with respective 5-year survival rates of 72.7% and 39.9% for patients with T1-T2 and T3-T4 tumors; however, the numbers of patients involved in this analysis were small.

Management of Anal Carcinoma

Clinical Presentation/Evaluation

Most patients with anal carcinoma present with rectal bleeding. Approximately 30% of patients with anal carcinoma have either pain or the sensation of a rectal mass.[3] The recommendations of the NCCN Anal Carcinoma Guidelines panel for the clinical evaluation of patients with suspected anal canal or anal margin cancer are the same, with the exception of PET scan which is not included in the workup of anal margin cancers. Following confirmation of squamous cell carcinoma by biopsy, the panel recommends a thorough examination/evaluation, including a careful DRE, palpation of the inguinal lymph nodes, and an anoscopic examination with biopsy of suspicious lesions. Assessment of T stage is primarily performed through clinical examination. Assessment of inguinal lymph node involvement for either anal margin or anal canal cancer is performed by fine-needle aspiration (FNA) biopsy and/or excisional biopsy of nodes found to be enlarged by either clinical or radiological examination. Evaluation of pelvic lymph nodes with computed tomography (CT) or magnetic resonance imaging (MRI) of the pelvis is also recommended. These methods can also provide information on whether tumor involves other abdominal/pelvic organs. Since veins of the anal region are part of the venous network

associated with systemic circulation,[8] chest x-ray or chest CT scan is performed to evaluate for pulmonary metastasis. Positron emission tomography (PET)/CT scanning has been reported to be useful in the evaluation of pelvic nodes, even in patients with anal canal cancer who have normal-sized lymph nodes on CT imaging.[21,22] HIV testing and measurement of CD4 level is suggested as the risk of anal carcinoma has been reported in some studies to be higher in HIV-positive patients.[23] Gynecological exam, including cervical cancer screening, is suggested for female patients due to the association of anal cancer and HPV.[4] HPV testing does not contribute to the management of anal cancer.

Primary Treatment of Anal Carcinoma

In the past, patients with invasive anal carcinoma were routinely treated with an APR; however, local recurrence rates were high, 5-year survival was only 40% to 70%, and the morbidity with a permanent colostomy was considerable.[3] Currently, concurrent chemoradiation (chemoRT) alone, as an alternative to an APR, is the recommended primary treatment for patients with anal canal cancer, or anal margin cancer characterized as T2-T4, N0 or node positive. Well differentiated anal margin lesions characterized as T1,N0 can be treated with margin-negative local excision alone.

In 1974, Nigro and coworkers observed complete tumor regression in some patients with anal carcinoma treated with preoperative 5-fluorouracil- (5-FU-) based concurrent chemoRT including either mitomycin or porfiromycin, suggesting that it might be possible to cure anal carcinoma without surgery and permanent colostomy.[24] Subsequent nonrandomized studies using similar regimens and varied doses of chemotherapy and radiation provided support for this conclusion.[25, 26] Results of randomized trials evaluating the efficacy and safety of administering chemotherapy with RT support the use of combined modality therapy in the treatment of anal cancer.[27] Results

from a phase III study from the European Organization for Research and Treatment of Cancer (EORTC) comparing use of chemoRT (5-FU plus mitomycin) and RT alone in the treatment of anal carcinoma showed that patients in the chemoRT arm had a higher rate of locoregional control and a longer colostomy-free interval.[28] The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) randomized trial confirmed that chemoRT with 5-FU and mitomycin was more effective in controlling local disease than RT alone (relative risk=0.54, 95% CI, 0.42-0.69; $P<0.0001$), although no significant differences in overall survival were observed.[29]

A number of studies have addressed the efficacy and safety of specific chemoRT regimens (involving chemotherapy regimens containing both 1 and 2 agents) used in the treatment of anal carcinoma. In a phase III Intergroup study,[30] patients receiving chemoRT with the combination of 5-FU and mitomycin had a lower colostomy rate (9% versus 22%; $P = 0.002$) and a higher disease-free survival (73% vs 51%; $P = 0.0003$) compared with patients receiving chemoRT with 5-FU alone, indicating that mitomycin is an important component of chemoRT in the treatment of anal carcinoma. Survival rate at 4 years was the same for the two groups reflecting the ability to salvage recurrent patients with an APR. Cisplatin as a substitute for mitomycin was evaluated in several phase II trials and results suggested that cisplatin-containing and mitomycin-containing chemoRT were comparable.[31] Use of 5-FU-based chemoRT combined with either mitomycin or cisplatin in the treatment of patients with anal carcinoma has been investigated in the randomized Intergroup Radiation Therapy Oncology Group (RTOG) 98-11 trial.[32] In this study, 644 patients were randomly assigned to receive either neoadjuvant 5-FU plus cisplatin for 2 cycles followed by concurrent chemoRT with 5-FU and cisplatin, or concurrent chemoRT with 5-FU and mitomycin. No significant differences were observed in the primary endpoint, disease-free survival (DFS) (54% vs. 60%; $P=0.17$), or in 5-year overall survival (70% vs. 75%; $P=0.10$). However, the colostomy

rate was significantly higher in the group receiving cisplatin compared to the mitomycin-containing arm (19% vs.10%; P=0.02).

The optimal dose and schedule of RT for anal carcinoma also continues to be explored, in addition to the schedule of chemotherapy relative to RT. Most studies have delivered 5-FU as a protracted 96 to 120 hour infusion during the first and fifth weeks of RT, and bolus injection of mitomycin is typically given on the first or second day of the 5-FU infusion.[8] The effects of RT dose and RT schedule have been evaluated in a number of nonrandomized studies. In one study of patients with early-stage (T1 or Tis) anal canal cancer, most patients were effectively treated with RT doses of 40-50 Gy for Tis lesions and 50-60 Gy for T1 lesions.[33] In another study in which the majority of patients had stage II/III anal canal cancer, local control of disease was higher in the group of patients receiving RT doses ≥50 Gy.[34] In a third study, patients with T3, T4 or lymph node-positive tumors, RT doses of ≥ 54 Gy administered within 60 days were associated with increased local control.[35] In the phase II RTOG 92-08 trial, planned 2 week treatment breaks in the delivery of chemoRT to patients with anal cancer were associated with increased local regional failure rates and colostomy-free survival rates when compared with delivery of the same regimen of chemoRT without a treatment break, although the number of patients involved in this study was small and the differences were not significant.[36] Although results of other studies have also supported the benefit of delivery of chemoRT over shorter time periods,[37] treatment breaks in the delivery of chemoRT are frequently required (eg. up to 50% of patients in clinical trials undergo treatment breaks) since chemoRT-related toxicities are common. For example, it has been reported that one-third of patients receiving primary chemoRT for anal carcinoma at RT doses of 30 Gy in 3 weeks develop acute anoproctitis and dermatitis, increasing to one-half to two-thirds of patients when RT doses of 54-60 Gy are administered in 6 to 7 weeks.[8] Of note, results of a phase II randomized trial of patients with locally advanced anal

carcinoma sponsored by the EORTC showed that an estimated 3-year rate of local control of 88% could be attained with reasonable toxicity when a chemoRT regimen including a 2-week treatment gap was used.[38] Some of the reported late side effects of chemoRT include urgency and increased frequency of defecation, chronic perineal dermatitis, dyspareunia, and impotence. In some cases, severe late RT complications, such as anal ulcers, stenosis, and necrosis, may necessitate surgery involving colostomy.[39] In addition, results from a retrospective cohort study of data from the Surveillance, Epidemiology, and End Results (SEER) registry showed the risk of subsequent pelvic fracture to be 3-fold higher in older women undergoing radiation therapy for anal cancer compared with older women with anal cancer who did not receive radiation therapy.[40]

There is an increasing body of literature suggesting that toxicity can be reduced with advanced radiation delivery techniques.[41-44] Multiple pilot studies have demonstrated reduced toxicity while maintaining local control using intensity modulated radiation therapy (IMRT). IMRT studies are now ongoing to confirm its benefit in treatment of anal cancer. Its use requires expertise and careful application to avoid reduction in local control probability.

As discussed above (see Risk Factors), patients with HIV/AIDS have been reported to be at increased risk of anal carcinoma.[23,27] Although most studies evaluating outcomes of patients with HIV/AIDS treated with chemoRT for anal carcinoma are retrospective,[27] there is evidence to indicate that patients with anal carcinoma as the first manifestation of HIV/AIDS (especially those with a CD4 count of ≥200/mm3) may be treated with the same regimen as non-HIV patients.[45] Furthermore, in a recent retrospective cohort study of 1184 veterans (15% of whom tested positive for HIV) diagnosed with squamous cell carcinoma of the anus between 1998 and 2004 no differences with respect to receipt of treatment or 2-year survival rates were observed when the group of

patients infected with HIV was compared with the group of patients testing negative for HIV.[46] Other factors to consider include compliance with highly active antiretroviral therapy (HAART) (although it is unclear whether increased compliance with HAART is associated with better outcomes following chemoRT for anal carcinoma[45,47]) and performance status.[27] Patients with active HIV/AIDS-related complications or a history of complications (eg, malignancies, opportunistic infections) may not tolerate full-dose therapy and may require dosage adjustment.

Recommendations for the Primary Treatment of Anal Canal Cancer
Anal canal cancer is treated with chemoRT (5-FU/mitomycin plus RT) as the primary treatment option. Recommended RT doses are 36-40 Gy to potential areas of microscopic disease, such as the inguinal and high pelvic nodes, and 45-59 Gy to gross disease for patients with disease clinically staged as T1-2,N0, and 55-59 Gy for those with disease staged as T3-T4, N0 or T any with nodal involvement. Two cycles of 5-FU/mitomycin to be delivered during the first and fifth week of RT are recommended.

Recommendations for the Primary Treatment of Anal Margin Cancer
Anal margin lesions can be treated with either local excision or chemoRT depending on the clinical stage. Primary treatment for patients with T1N0 well differentiated anal margin cancers is by local excision with adequate margins. If the margins are not adequate, re-excision is the preferred treatment option. Local RT with or without 5-FU-based chemotherapy can be considered as an alternative treatment option when surgical margins are inadequate. T2 to T4 and node-positive anal margin cancers should are treated with mitomycin/5-FU plus RT (with doses and scheduling as described for anal canal cancers). Inclusion of bilateral inguinal/low pelvic nodal regions in the RT field should be considered for more advanced cancers.

Follow-up and Surveillance Following Primary Treatment
Following primary treatment, the surveillance and follow-up treatment recommendations for anal margin and anal canal cancer are the same. Patients are re-evaluated by DRE between 8 and 12 weeks after completion of primary treatment with chemoRT. A biopsy is performed only if presence of disease is suspected after serial DRE Disease can continue to regress for a period of months following completion of chemoRT, and the likelihood of a false positive result is high.[48,49] Some of the indications for biopsy include new hard-edged ulcer, enlarging mass, or increasing pain. Following re-evaluation, patients are classified according to whether they have a complete remission of disease, progressive disease, or persistent disease. In one study, persistent disease was defined as presence of biopsy-proven carcinoma within 6 months of completion of chemoRT.[50] Although a clinical assessment of progressive disease requires histologic confirmation, patients can be classified as having a complete remission without biopsy verification, if clinical evidence of disease is absent. Patients with biopsy results of persistent disease but without evidence of progression may be managed with close follow-up (in 4 weeks) to see if further regression occurs. If no regression of disease is observed on serial examination or if progression of disease occurs, further intensive treatment is indicated (see Recommendations for the Treatment of Progressive Disease). Patients who continue to show evidence of disease regression should be re-evaluated clinically in 3 months. The panel recommends that patients classified as having a complete remission of disease should undergo more intensive surveillance every 3-6 months for 5 years, including DRE, anoscopic evaluation, inguinal node palpation. A chest x-ray and a pelvic CT scan should be considered annually for 3 years for patients with locally advanced disease (ie, T3/T4 tumor) or node-positive cancers. The usefulness of post-treatment PET scan in the surveillance of patients with anal canal cancer is supported by the study of Schwartz et al.[51] which showed a partial local metabolic response to chemoRT at 0.9-5.4

months after therapy completion to be strongly predictive of decreased PFS and cause-specific survival.

Treatment of Progressive/Recurrent/Metastatic Anal Carcinoma

Despite the effectiveness of chemoRT in the primary treatment of anal carcinoma, rates of locoregional failure of up to 40% have been reported,[52] and radical salvage surgery with an APR has been the treatment of choice for these patients.[50] Some of the disease characteristics that have been associated with higher recurrence rates following chemoRT include higher T stage and higher N stage.[53] In several surgical series involving a minimum of 25 patients undergoing a salvage APR for anal carcinoma, 5-year survival rates of 39%-64% were observed, although complication rates were reported to be high in some of these studies.[15, 50, 54-56,57] Factors associated with worse prognosis following salvage APR include an initial presentation of node-positive disease and RT doses < 55 Gy used in the treatment of primary disease.[50]. It has been shown that for patients undergoing an APR which had been preceded by RT, closure of the perineal wound using rectum abduminus myocutaneous flap reconstruction resulted in decreased perineal wound complications.[58]

It has been reported that the most common sites of metastasis outside of the pelvis include the liver, lung, and extrapelvic lymph nodes.[59] Since anal carcinoma is a rare cancer and only 10%-20% of patients with anal carcinoma present with metastatic disease,[59] only limited data are available on this population of patients, although there is some evidence to indicate that chemotherapy with a fluoropyrimidine-based regimen plus cisplatin has some benefit in patients with metastatic anal carcinoma.[59-61]

Recommendations for the Treatment of Progressive Disease (Anal Canal/Margin Cancer)

Evidence of progression found on DRE should be followed by biopsy as well as restaging with CT and/or PET imaging. Patients with biopsy-proven progressive disease are candidates for an APR or additional chemotherapy with 5-FU/cisplatin followed by an APR. Muscle flap reconstruction of the perineum should be considered because of the extensive previous RT to the area. These patients should be re-evaluated every 3-6 months for 5 years, including clinical evaluation of nodal metastasis (ie, inguinal node palpation) and CT scan.

Recommendations for the Treatment of Locally Recurrent/Metastatic Disease (Anal Canal/Margin Cancer)

Patients who are in complete remission should be evaluated every 3-6 months for 5 years. Treatment recommendations for patients who develop a local recurrence include an APR; muscle flap reconstruction of the perineum should be considered. Inguinal node dissection is reserved for recurrence in that area, and can be performed without an APR in cases where recurrence is limited to the inguinal nodes. Patients who develop inguinal node metastasis who do not undergo an APR can be considered for RT to the groin with or without chemotherapy if limited prior RT to the groin was given. Treatment recommendations for patients who develop a distant metastasis should be individualized, and local treatment, as described above, could be considered for the locally-symptomatic patient. There is no evidence supporting resection of metastatic disease. Treatment recommendations for patients with metastatic anal carcinoma include platinum-based chemotherapy or enrollment in a clinical trial. Currently, no other regimens have been shown to be effective in these patients following failure of cisplatin/5-FU.

Summary

The NCCN Anal Carcinoma Guidelines panel believes that a multidisciplinary approach, including physicians from gastroenterology, medical oncology, surgical oncology, radiation oncology, and radiology is necessary for treating patients with anal carcinoma. Recommendations for the primary treatment of anal margin cancer and

anal canal cancer are very similar and include 5-FU/mitomycin-based RT, although small, well differentiated anal margin lesions can be treated with margin-negative local excision alone. Follow-up clinical evaluations are recommended for all patients with anal carcinoma since salvage is possible. Patients with biopsy-proven evidence of locoregional progressive disease following primary treatment should receive either chemotherapy with 5-FU/cisplatin followed by an APR or surgery alone. Following complete remission of disease, patients with a local recurrence should be treated with an APR with a groin dissection if there is clinical evidence of inguinal nodal metastasis, and patients with a regional recurrence in the inguinal nodes can be treated with an inguinal node dissection, with consideration of RT with or without chemotherapy, if limited prior RT to the groin was given. Patients with evidence of extrapelvic metastatic disease should be treated with cisplatin-based chemotherapy or enrolled in a clinical trial. The panel endorses the concept that treating patients in a clinical trial has priority over standard or accepted therapy.

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