National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Anal Carcinoma

Version 1.2014

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Clinical Trials: 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

NCCN Guidelines Version 1.2014 Updates Anal Carcinoma

Summary of changes in the 1.2014 version of the Guidelines for Anal Carcinoma from the 2.2013 version include:

ANAL-1

- **Workup: Consider PET-CT scan clarified with the addition of "for T3-T4, N0 or Any T, N+."**

ANAL-2

- **Consider PET-CT scan for T2-T4, N0 or Any T, N+ added to workup.**

ANAL-3

- **Persistent disease; serial exams: "no regression" removed.**
- **Persistent disease; regression on serial exams; continue observation and re-evaluate in 3 mo: "if progression" added with an arrow to "biopsy".**
- **Complete remission: T3-T4 or inguinal node positive: "consider" removed from chest/abdominal/pelvic imaging.**

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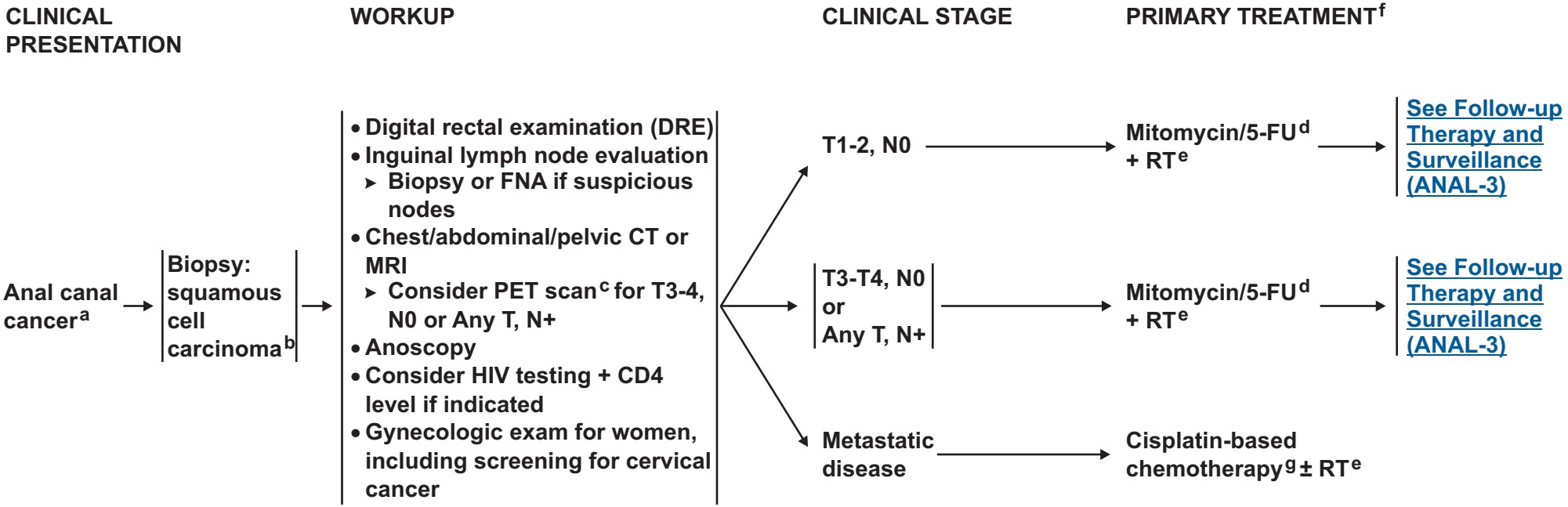

[a] The superior border of the functional anal canal, separating it from the rectum, has been defined as the palpable upper border of the anal sphincter and puborectalis muscles of the anorectal ring. It is approximately 3 to 5 cm in length, and its inferior border starts at the anal verge, the lowermost edge of the sphincter muscles, corresponding to the introitus of the anal orifice.

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

[c] PET-CT scan does not replace a diagnostic CT. The routine use of a PET-CT scan for staging or treatment planning has not been validated.

[d] 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. 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.

[e] See Principles of Radiation Therapy (ANAL-B).

[f] Patients with anal cancer as the first manifestation of HIV may be treated with the same regimen as non-HIV patients. 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.

[g] Cisplatin/5-FU is recommended for metastatic disease. If this regimen fails, no other regimens have been shown to be effective. See Principles of Chemotherapy (ANAL-A). Local control can be achieved with the use of RT.

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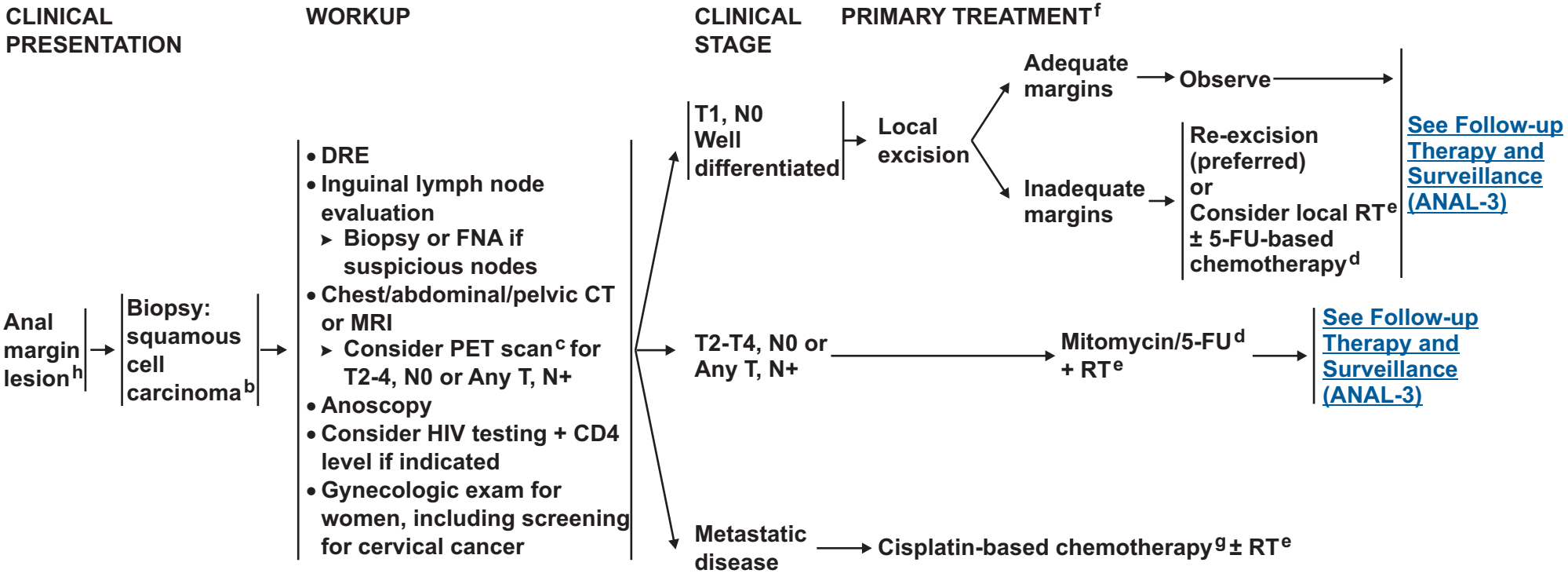

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[h] The anal margin starts at the anal verge and includes the perianal skin over a 5- to 6-cm radius from the squamous mucocutaneous junction.

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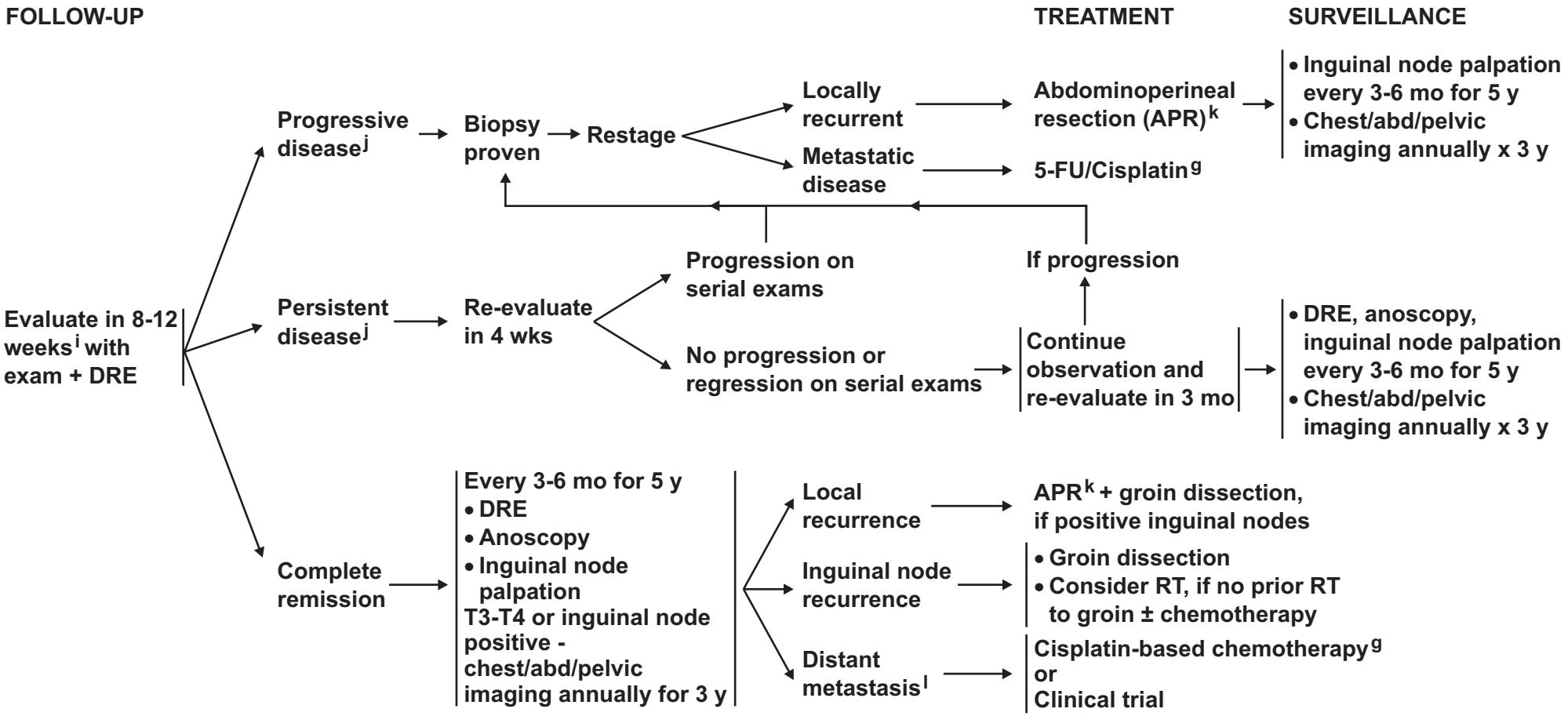

[g] Cisplatin/5-FU is recommended for metastatic disease. If this regimen fails, no other regimens have been shown to be effective. See Principles of Chemotherapy ANAL-A. Local control can be achieved with the use of RT.

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

[j] Based on the results of the ACT-II study, it may be appropriate to follow patients who have not achieved a complete clinical response with persistent anal cancer up to 6 months following completion of radiation therapy and chemotherapy as long as there is no evidence of progressive disease during this period of follow up. Persistent disease may continue to regress even at 26 weeks post-treatment. Gynne-Jones R, James R, Meadows H, et al. Optimum time to assess complete clinical response following chemoradiation using mitomycin or cisplatin, with or without maintenance cisplatin and 5-fluorouracil in squamous cell carcinoma of the anus: Results of Act II. J Clin Oncol 30, 2012 (suppl:abst 4004).

[k] Consider muscle flap reconstruction.

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

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PRINCIPLES OF CHEMOTHERAPY

Localized cancer

5-FU + Mitomycin + RT[1]
Continuous infusion 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 (See ANAL-B)

Metastatic cancer

5-FU + Cisplatin[2]
Continuous infusion 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] 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.

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PRINCIPLES OF RADIATION THERAPY[1]

- **Multifield techniques with supervoltage radiation (photon energy of > 6 mV) should be used to deliver a minimum dose of 45 Gy in 1.8 Gy-fractions (25 fractions over 5 weeks) to the primary cancer.**
- **PET-CT should be considered for treatment planning.**
- **The inguinal nodes and the pelvis, anus, and perineum should be included in the initial radiation fields. The superior field border should be at L5-S1, and the inferior border should include the anus with a minimum 2.5 cm-margin around the anus and tumor. The lateral border should include the lateral inguinal nodes (as determined from imaging or bony landmarks). There should be attempts to reduce the dose to the femoral heads.**
- **After 17 fractions (30.6 Gy), an additional 14.4 Gy should be given in 8 fractions with the superior field reduced to the bottom of the sacroiliac joints. Additional field reduction off inguinal nodes should occur after 36 Gy for node-negative lesions. This protocol brings the total dose to 45 Gy in 25 fractions over 5 weeks.**
- **For patients treated using an AP-PA technique, rather than the recommended multifield technique, the dose to the lateral inguinal region should be brought to the minimum dose of 36 Gy using an anterior electron boost matched to the PA exit field.**
- **For T2 lesions with residual disease after 45 Gy, T3/4 lesions, or N1 lesions, an additional boost of 9-14 Gy in 1.8-2 Gy fractions to the original primary tumor volume and involved nodes plus a 2-2.5 cm margin is usually delivered. This boost brings the total dose to 54-59 Gy in 30-32 fractions over 6-7.5 weeks. A direct perineal boost using photons or electrons with the patient in lithotomy position or a multifield photon approach (AP-PA plus paired laterals, PA + laterals, or other) can be used.**
- **The consensus of the panel is that IMRT may be used in place of 3-D conformal RT in the treatment of anal carcinoma.[2] IMRT requires expertise and careful target design to avoid reduction in local control by so-called "marginal-miss."[3] The clinical target volumes for anal cancer used in the RTOG-0529 trial have been described in detail.[2]**
  Also see http://atc.wustl.edu/protocols/rtog-closed/0529/ANAL_Ca_CTVs_5-21-07_Final.pdf for more details of the contouring atlas defined by RTOG.
- **Side effect management:**
  Female patients should be considered for vaginal dilators and instructed on the symptoms of vaginal stenosis.
  Male patients should be counseled on infertility risks and given information regarding sperm banking.
  Female patients should be counseled on infertility risks and given information regarding oocyte, egg or ovarian tissue banking prior to treatment.

[1] Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal. JAMA 2008;299:1914-1921.
[2] Myerson RJ, Garofalo MC, El Naqa I, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring atlas. Int J Radiat Oncol Biol Phys 2009;74:824-830.
[3] Pepek JM, Willett CG, Czito BG. Radiation therapy advances for treatment of anal cancer. J Natl Compr Canc Netw 2010;8:123-129.

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NCCN Guidelines Version 1.2014 Staging
Anal Carcinoma

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Table 1. DEFINITIONS OF TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (Bowen's disease, high-grade squamous intraepithelial lesion (HSIL), anal intraepithelial neoplasia II–III (AIN II–III)
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*

* Note: Direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) 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

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Table 2. ANATOMIC STAGE/PROGNOSTIC GROUPS

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

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 12/11/12

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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Overview

An estimated 6230 new cases (2250 men and 3980 women) of anal cancer involving the anus, anal canal, or anorectum will occur in the United States in 2012, accounting for approximately 2.2% of digestive system cancers.[1] It has been estimated that 780 deaths due to anal cancer will occur in the United States in 2012. Although considered to be a rare type of cancer, the incidence rate of invasive anal carcinoma in the United States increased by approximately 1.9-fold for men and 1.5-fold for women from the period of 1973 through1979 to 1994 through 2000 (see *Risk Factors*, below).[2]

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; anal adenocarcinoma and anal melanoma are managed according to the NCCN Guidelines for Rectal Cancer and the NCCN Guidelines for Melanoma, 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 HIV infection; hematologic malignancies; certain autoimmune disorders; and smoking.[3-9]

The association between anal carcinoma and persistent infection with a high-risk form of HPV (eg, HPV-16; HPV-18) is especially strong.[4,10,11] For example, a study of tumor specimens from more than 60 pathology laboratories in Denmark and Sweden showed that high-risk HPV DNA was detected in 84% of anal cancer specimens, with HPV-16 detected in 73% of them. In contrast, high-risk HPV was not detected in any of the rectal cancer specimens analyzed.[4] In addition, results of a systematic review of 35 peer-reviewed studies of anal cancer that included detection of HPV DNA published up until July 2007 showed the prevalence of HPV-16/18 to be 72% in patients with invasive anal cancer.[11] A recent report from the Centers for Disease Control and Prevention estimates that 86% to 97% of cancers of the anus are attributable to HPV infection.[12]

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.[13,14] In the HIV-infected population, the standardized incidence rate of anal carcinoma per 100,000 person-years in the United States, estimated to be 19.0 in 1992 through1995, increased to 78.2 during 2000 through 2003.[15] This result likely reflects both the survival benefits of highly active antiretroviral therapy (HAART) and the lack of an impact of HAART on the progression of anal cancer precursors. The incidence rate has recently been reported to be 131 per 100,000 person-years in HIV-infected men who have sex with men in North America. [16]

Risk Reduction

High-grade anal intraepithelial neoplasia (AIN) can be a precursor to anal cancer,[17,18] and treatment of high-grade AIN may prevent the development of anal cancer. AIN can be identified by cytology, HPV testing, digital rectal examination (DRE), high-resolution anoscopy,

and/or biopsy.[19,20] Estimates from a recent systematic review and meta-analysis of studies in men who have sex with men, however, suggest that the progression rates of AIN to cancer might be quite low, although prospective data are lacking.[21] In addition, the spontaneous regression rate of high-grade AIN is not known. Routine screening for AIN in high-risk individuals such as HIV-positive patients or men who have sex with men is controversial because randomized controlled trials showing that such screening programs are efficacious at reducing anal cancer incidence and mortality are lacking but the potential benefits are quite large.[22-27]

Guidelines for the treatment of AIN have been developed by several groups, including the American Society of Colon and Rectal Surgeons.[26,28,29]

HPV Immunization

A quadrivalent HPV vaccine is available and has been shown to be effective in women in preventing persistent cervical infection with HPV-6, 11, 16, or 18 as well as in preventing high-grade cervical intraepithelial neoplasia related to these strains of the virus.[30-32] The vaccine has also been shown to be efficacious in young men at preventing genital lesions associated with HPV-6, 11, 16, or 18 infection.[33] A recent substudy of a larger double-blind study assessed the efficacy of the vaccine for the prevention of AIN and anal cancer related to infection with HPV-6, 11, 16, or 18 in men who have sex with men.[34] In this study, 602 healthy men who have sex with men aged 16 to 26 years were randomized to receive the vaccine or a placebo. While none of the participants in either arm developed anal cancer during the 3-year follow-up period, there were 5 cases of grade 2/3 AIN associated with one of the vaccine strains in the vaccine arm and 24 such cases in the placebo arm in the per-protocol population, giving an observed efficacy of 77.5% (95% CI 39.6–93.3). Since high-grade AIN are known to have the ability to progress to anal cancer,[17,18] these results suggest that use of the quadrivalent HPV vaccine in men who have sex with men may reduce the risk of anal cancer in this population. The Advisory Committee on Immunization Practices recommends routine use of this quadrivalent vaccine in boys and girls aged 11 and 12 years and in females aged 13 to 26 years and males aged 13 to 21 years who have not been previously vaccinated.[35,36] The American Academy of Pediatrics concurs with this recommendation and also recommends that men who have sex with men up to age 26 should be immunized.[37]

A bivalent HPV vaccine against HPV-16 and 18 is also available.[35] In a randomized, double-blind, controlled trial of women in Costa Rica, the vaccine was 83.6% effective against initial anal HPV 16/18 infection (95% CI 66.7–92.8).[38] It has also been shown to be effective at preventing high-grade cervical intraepithelial neoplasias in young women.[39] The effect on precancerous anal lesions has not yet been reported.

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 (ie, functional/surgical; anatomic; histologic) that are based on particular physical/anatomic landmarks or histologic characteristics. Histologically, the mucosal lining of the anal canal is predominantly formed by squamous epithelium, in contrast to the mucosa of the rectum, which is lined with glandular epithelium.[6,40] The anal margin, on the other hand, is lined with skin.[41] By the histologic definition, the most superior aspect of the anal canal is a 1- to 2-cm zone between the anal and rectal epithelium, which has rectal, urothelial, and squamous histologic characteristics.[6,40] 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 anatomic anal canal begins at the dentate line and extends to the anal verge.[41] Functionally, the 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 5 cm in length, and its inferior border starts at the anal verge, the lowermost edge of the sphincter muscles, corresponding to the introitus of the anal orifice.[6,40,42] The functional definition of the anal canal is primarily used in the radical surgical treatment of anal cancer and is used in these guidelines to differentiate between treatment options.

The anal margin starts at the anal verge and includes the perianal skin over a 5- to 6-cm radius from the squamous mucocutaneous junction.[40,43] It is covered by epidermis, not mucosa.[6] Tumors can involve both the anal canal and the anal margin.

Pathology

Most primary cancers of the anal canal are of squamous cell histology.[40,44] The second edition of the 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.[45] 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.[6] However, the terms cloacogenic, transitional, keratinizing, and basaloid were removed from the third and fourth editions of the WHO classification system of anal canal carcinoma,[46,47] and all subtypes have been included under a single generic heading of squamous cell carcinoma.[43,46] 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 non-keratinizing tumors have a similar natural history and prognosis[46]; and a mixture of cell types frequently characterize histologic specimens of squamous cell carcinomas of the anal canal.[40,46,48] No distinction between squamous anal canal tumors on the basis of cell type has been made in these guidelines. Other less common anal canal tumors, not addressed in these guidelines, include adenocarcinomas in the rectal mucosa or the anal glands, small cell (anaplastic) carcinoma, undifferentiated cancers, and melanomas.[40]

Squamous cell carcinomas of the anal margin are more likely than those of the anal canal to be well-differentiated and keratinizing large-cell types,[49] but they are not characterized in the guidelines according to cell type. The presence of skin appendages (eg, hair follicles, sweat glands) in anal margin tumors can distinguish them from anal canal tumors. However, it is not always possible to distinguish between anal canal and anal margin squamous cell carcinoma since tumors can involve both areas.

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 anorectal, perirectal, and paravertebral nodes and to some of the nodes of the internal iliac system; more proximal cancers drain to perirectal nodes and to nodes of the inferior mesenteric system.[40,43] Therefore, distal anal cancers present with a higher incidence of inguinal node metastasis; since the lymphatic drainage systems throughout the anal canal are not isolated from each other,

however, inguinal node metastases can occur in proximal anal cancer as well.[40]

The College of American Pathologists publishes a protocol for the pathologic examination and reporting of anal tumors. The most recent update was made in June 2012.[50]

Staging

The TNM staging system for anal canal cancer developed by the AJCC is detailed in the guidelines.[43] 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.[43] A 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).

In the past, these guidelines have used the AJCC TNM skin cancer system for the staging of anal margin cancer since the 2 types of cancers have a similar biology. However, the latest addition of the AJCC Cancer Staging Manual made substantial changes to the cutaneous squamous cell carcinoma stagings,[43] making them much less appropriate for the staging of cancers of the anal margin. Furthermore, many anal margin cancers have involvement of the anal canal or have high-grade, pre-cancerous lesions in the anal canal. It is important to look for such anal canal involvement, particularly if conservative management (simple excision) is being contemplated. Many patients, particularly HIV-positive ones, could be significantly undertreated. For these reasons, these guidelines use the anal canal staging system for tumors of both the anal canal and the anal margin.

The prognosis of anal carcinoma is related to the size of the primary tumor and the presence of lymph node metastases.[6] According to the SEER database,[51] between 1999 and 2006, 50% of anal carcinomas were localized at initial diagnosis; these patients had an 80% 5-year survival rate. Approximately 29% of patients had anal carcinoma that had already spread to regional lymph nodes at diagnosis; these patients had a 60% 5-year survival rate. The 12% of patients presenting with distant metastasis demonstrated a 30.5% 5-year survival rate.[51] In a retrospective study of 270 patients treated for anal canal cancer with radiation therapy (RT) between 1980 and 1996, synchronous inguinal node metastasis was observed in 6.4% of patients with tumors staged as T1 or T2, and in 16% of patients with T3 or T4 tumors.[52] 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 number of patients involved in this analysis was small.[52]

Lymph node staging in anal canal cancer is based on location of involved nodes: N1 designates metastasis in 1 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.[43] However, initial therapy of anal cancer does not typically involve surgery, and the true lymph node status may not be determined accurately by clinical and radiologic evaluation. Fine needle aspiration (FNA) biopsy of inguinal nodes is recommended if tumor metastasis to these nodes is suspected. In a 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,[53] suggesting that routine radiologic evaluation with CT and PET scan may not be reliable in the determination of lymph nodal involvement.

Prognostic Factors

Multivariate analysis of data from the RTOG 98-11 trial showed that male sex and positive lymph nodes were independent prognostic factors for disease-free survival (DFS) in patients with anal cancer treated with 5-FU and radiation and either mitomycin or cisplatin.[54] Male sex, positive nodes, and tumor size greater than 5 cm were independently prognostic for worse overall survival. A secondary analysis of this trial found that tumor diameter could also be prognostic for colostomy rate and time to colostomy.[55] These results are consistent with earlier analyses from the EORTC 22861 trial, which found male sex, lymph node involvement, and skin ulceration to be prognostic for worse survival and local control.[56] Similarly, recent multivariate analyses of data from the ACT I trial also showed that positive lymph nodes and male sex are prognostic indicators for higher local regional failure, anal cancer death, and lower overall survival.[57]

Management of Anal Carcinoma

Clinical Presentation/Evaluation

Approximately 45% of patients with anal carcinoma present with rectal bleeding, while approximately 30% have either pain or the sensation of a rectal mass.[6] Following confirmation of squamous cell carcinoma by biopsy, the recommendations of the NCCN Anal Carcinoma Guidelines Panel for the clinical evaluation of patients with anal canal or anal margin cancer are the same, with the exception of consideration of PET/CT scan for tumors of the anal canal. 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[58-62]; however the panel does not consider PET/CT to be a replacement for a diagnostic CT. Furthermore, the panel noted that the routine use of a PET/CT scan for staging has not been validated.

The panel recommends a thorough examination/evaluation, including a careful DRE, an anoscopic examination, and palpation of the inguinal lymph nodes, with FNA and/or excisional biopsy of nodes found to be enlarged by either clinical or radiologic examination. Evaluation of pelvic lymph nodes with CT or MRI of the pelvis is also recommended. These methods can also provide information on whether the tumor involves other abdominal/pelvic organs; however, assessment of T stage is primarily performed through clinical examination. A CT scan of the abdomen is also recommended to assess possible disease dissemination. Since veins of the anal region are part of the venous network associated with systemic circulation,[40] chest CT scan is performed to evaluate for pulmonary metastasis. HIV testing and measurement of CD4 level is suggested, because the risk of anal carcinoma has been reported to be higher in HIV-positive patients.[8] Gynecologic exam, including cervical cancer screening, is suggested for female patients due to the association of anal cancer and HPV.[4]

Primary Treatment of Non-Metastatic 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.[6] In 1974, Nigro and coworkers observed complete tumor regression in some patients with anal carcinoma treated with preoperative 5-FU-based concurrent chemotherapy and radiation (chemoRT) including either mitomycin or porfiromycin, suggesting that it might be possible to cure anal carcinoma without surgery and permanent colostomy.[63] Subsequent nonrandomized studies using similar regimens and varied doses of chemotherapy and radiation provided support for this conclusion.[64,65] 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.[9] Summaries of clinical trials involving patients with anal cancer have been presented,[66,67] and several key trials are discussed below.

Chemotherapy

A phase III study from the European Organization for Research and Treatment of Cancer (EORTC) compared the use of chemoRT (5-FU plus mitomycin) to RT alone in the treatment of anal carcinoma. Results from this trial showed that patients in the chemoRT arm had an 18% higher rate of locoregional control at 5 years and a 32% longer colostomy-free interval.[56] The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) randomized ACT I 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* < .0001), although no significant differences in overall survival were observed at 3 years.[68] A recently published follow-up on these patients demonstrates that a clear benefit of chemoRT remains after 13 years, including a benefit in overall survival.[69] The median survival was 5.4 years in the RT arm and 7.6 years in the chemoRT arm. There was also a reduction in the risk of dying from anal cancer (HR, 0.67; 95% CI, 0.51–0.88, P=.004).

A few studies have addressed the efficacy and safety of specific chemotherapeutic agents in the chemoRT regimens used in the treatment of anal carcinoma.[54,70,71] In a phase III Intergroup study, patients receiving chemoRT with the combination of 5-FU and mitomycin had a lower colostomy rate (9% vs. 22%; *P* = .002) and a higher 4-year DFS (73% vs. 51%; *P* = .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.[71] The overall survival rate at 4 years was the same for the 2 groups, however, reflecting the ability to salvage recurrent patients with additional chemoradiation or an APR.

Cisplatin as a substitute for 5-FU was evaluated in a phase II trial, and results suggest that cisplatin-containing and 5-FU-containing chemoRT may be comparable for treatment of locally advanced anal cancer.[70]

The efficacy of replacing mitomycin with cisplatin has also been assessed. The phase III UK ACT II trial compared cisplatin with mitomycin and also looked at the effect of additional maintenance chemotherapy following chemoRT. Results from ACT II, the largest trial ever conducted in patients with anal cancer, were presented in 2009.[72] In this study, over 900 patients with newly diagnosed anal cancer were randomly assigned to primary treatment with either 5-FU/mitomycin or 5-FU/cisplatin with radiotherapy. A continuous course (ie, no treatment gap) of radiation of 50.4 Gy was administered in both arms, and patients in each arm were further randomized to receive 2 cycles of maintenance therapy with 5-FU and cisplatin or no maintenance therapy. At a median follow-up of 3 years, no differences were observed in the primary endpoint of complete response rate in either arm for the chemoRT comparison or in the primary endpoint of recurrence-free survival for the comparison of maintenance therapy versus no maintenance therapy. In addition, a secondary endpoint, colostomy, did not show differences based on the chemotherapeutic components of chemoRT.[72] These results demonstrate that replacement of mitomycin with cisplatin in chemoRT does not affect the rate of complete response, nor does administration of maintenance therapy decrease the rate of disease recurrence following primary treatment with chemoRT in patients with anal cancer. Longer follow-up of this trial is needed.

Cisplatin as a substitute for mitomycin in the treatment of patients with non-metastatic anal carcinoma was also evaluated in the randomized

phase III Intergroup RTOG 98-11 trial. The role of induction chemotherapy was also assessed. In this study, 682 patients were randomly assigned to receive either: 1) induction 5-FU plus cisplatin for 2 cycles followed by concurrent chemoRT with 5-FU and cisplatin; or 2) concurrent chemoRT with 5-FU and mitomycin.[54,73] A significant difference was observed in the primary endpoint, 5-year DFS, in favor of the mitomycin group (57.8% vs. 67.8%; *P* = .006).[73] Five-year overall survival was also significantly better in the mitomycin arm (70.7% vs. 78.3%; *P* = .026).[73] In addition, 5-year colostomy-free survival showed a trend towards statistical significance (65.0% vs. 71.9%; *P* = .05), again in favor of the mitomycin group. Since the 2 treatment arms in the RTOG 98-11 trial differed with respect to use of either cisplatin or mitomycin in concurrent chemoRT as well as inclusion of induction chemotherapy in the cisplatin-containing arm of the trial, it is difficult to attribute the differences to the substitution of cisplatin for mitomycin or to the use of induction chemotherapy.[66,74] However, since ACT II demonstrated that the two chemoRT regimens are equivalent, some have suggested that results from RTOG 98-11 suggest that induction chemotherapy is probably detrimental.[75]

Results from ACCORD 03 also suggest that there is no benefit of a course of chemotherapy given prior to chemoradiation.[76] In this study, patients with locally advanced anal cancer were randomized to receive induction therapy with 5-FU/cisplatin or no induction therapy followed by chemoRT (they were further randomized to receive an additional radiation boost or not). No differences were seen between tumor complete response, tumor partial response, 3-year colostomy-free survival, local control, event-free survival, or 3-year overall survival. Final analysis of the ACCORD 03 trial was recently published.[77] After a median follow-up of 50 months, no advantage to induction chemotherapy (or to the additional radiation boost) was observed, consistent with earlier results.

A recent retrospective analysis, however, suggests that induction chemotherapy preceding chemoradiation may be beneficial for the subset of patients with T4 anal cancer.[78] The 5-year colostomy-free survival rate was significantly better in T4 patients who received induction 5-FU/cisplatin compared to those who did not (100% vs. 38 ± 16.4%, *P* = .0006).

Cetuximab is an epidermal growth factor receptor (EGFR) inhibitor, whose anti-tumor activity is dependent on the presence of wild-type *KRAS*.[79] Because *KRAS* mutations appear to be very rare in anal cancer,[80,81] the use of an EGFR inhibitor such as cetuximab may be a promising avenue of investigation. Results of the phase II ECOG 3205 and AIDS Malignancy Consortium 045 trials were recently reported.[82] These trials evaluated the safety and efficacy of cetuximab with cisplatin/5-FU and radiation in immunocompetent (E3205) and HIV-positive (AMC045) patients with anal squamous cell carcinoma. Although additional recruitment and follow-up are required to assess the primary endpoints of a reduction in 3-year local-regional failure rates, preliminary results from these trials are encouraging with acceptable toxicity and 2-year PFS rates of 92% (95% CI, 81%–100%) and 80% (95% CI, 61%–90%) in the immunocompetent and HIV-positive populations, respectively.[82]

In addition, a trial assessing the safety and efficacy of capecitabine/oxaliplatin with radiation in the treatment of localized anal cancer has been completed, but final results have not yet been reported (clinicaltrials.gov NCT00093379). Preliminary results from this trial seem promising.[83]

Radiation Therapy

The optimal dose and schedule of RT for anal carcinoma also continues to be explored, and has 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 to 50 Gy for Tis lesions and 50 to 60 Gy for T1 lesions.[84] In another study, in which the majority of patients had stage II/III anal canal cancer, local control of disease was higher in patients who received RT doses greater than 50 Gy than in those who received lower doses (86.5% vs. 34%, P = .012).[85] In a third study of patients with T3, T4, or lymph node-positive tumors, RT doses of ≥ 54 Gy administered with limited treatment breaks (less than 60 days) were associated with increased local control.[86] The effect of further escalation of radiation dose was assessed in the ACCORD-03 trial, with the primary endpoint of colostomy-free survival at 3 years.[76] No benefit was seen with the higher dose of radiation. These results are supported by much earlier results from the RTOG 92-08 trial[87] and suggest that doses of >59 Gy provide no additional benefit to patients with anal cancer.

There is evidence that treatment interruptions, either planned or required by treatment-related toxicity, can compromise the effectiveness of treatment.[61] In the phase II RTOG 92-08 trial, a planned 2-week treatment break in the delivery of chemoRT to patients with anal cancer was associated with increased local regional failure rates and lower colostomy-free survival rates when compared to patients who only had treatment breaks for severe skin toxicity,[88] although the trial was not designed for that particular comparison. In addition, the absence of a planned treatment break in the ACT II trial was considered to be at least partially responsible for the high relapse-free survival rates observed in that study (75% at 3 years).[72] Although results of these and other studies have supported the benefit of delivery of chemoRT over shorter time periods,[89-91] treatment breaks in the delivery of chemoRT are required in up to 80% of patients since chemoRT-related toxicities are common.[91] 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 perineal dermatitis, increasing to one-half to two-thirds of patients when RT doses of 54 to 60 Gy are administered in 6 to 7 weeks.[40]

Some of the reported late side effects of chemoRT include increased frequency and urgency of defecation, chronic perineal dermatitis, dyspareunia, and impotence.[92,93] In some cases, severe late RT complications, such as anal ulcers, stenosis, and necrosis, may necessitate surgery involving colostomy.[93] In addition, results from a retrospective cohort study of data from the SEER registry showed the risk of subsequent pelvic fracture to be 3-fold higher in older women undergoing RT for anal cancer compared with older women with anal cancer who did not receive RT.[94]

There is an increasing body of literature suggesting that toxicity can be reduced with advanced radiation delivery techniques.[61,95-100] Intensity-modulated radiation therapy (IMRT) utilizes detailed beam shaping to target specific volumes and limit the exposure of normal tissue.[100] Multiple pilot studies have demonstrated reduced toxicity while maintaining local control using IMRT. For example, in a cross-study comparison of a multicenter study of 53 patients with anal cancer treated with concurrent 5-FU/mitomycin chemotherapy and IMRT compared to patients in the 5-FU/mitomycin arm of the randomized RTOG 98-11 study, which used conventional 3-D RT, the rates of grade 3/4 dermatologic toxicity were 38%/0% for IMRT-treated patients compared to 43%/5% for those undergoing conventional RT.[54,100] No decrease in treatment effectiveness or local control rates was observed with use of IMRT, although the small sample size and short duration of

follow-up limit the conclusions drawn from such a comparison. In one retrospective comparison between IMRT and conventional radiotherapy, IMRT was less toxic and showed better efficacy in 3-year overall survival, locoregional control, and progression-free survival.[101] In a larger retrospective comparison, no significant differences in local recurrence-free survival, distant metastasis-free survival, colostomy-free survival, and overall survival at 2 years were seen between patients receiving IMRT and those receiving 3-D conformal radiotherapy, despite the fact that the IMRT group had a higher average N stage.[102]

The only prospective study assessing IMRT for anal cancer is the phase II dose-painted IMRT study, RTOG 0529. This trial did not meet its primary endpoint of reducing grade 2+ combined acute genitourinary and gastrointestinal adverse events by 15% compared to the chemoRT/5-FU/mitomycin arm from RTOG 98-11, which used conventional radiation.[103] Of 52 evaluable patients, the grade 2+ combined acute adverse event rate was 77%; the rate in RTOG 98-11 was also 77%. However, significant reductions were seen in grade 2+ hematologic events (73% vs. 85%; $P = .032$), grade 3+ gastrointestinal events (21% vs. 36%; $P = .008$), and grade 3+ dermatologic events (23% vs. 49%; $P < .0001$). Clinical outcomes will be reported in the future and are of great interest because of the risk of underdosing (marginal miss) associated with highly conformal RT.[103]

Recommendations regarding RT doses follow the multifield technique used in the RTOG 98-11 trial.[54] PET/CT should be considered for treatment planning.[104] All patients should receive a minimum RT dose of 45 Gy to the primary cancer. The recommended initial RT dose is 30.6 Gy to the pelvis, anus, perineum, and inguinal nodes; there should be attempts to reduce the dose to the femoral heads. Field reduction off the superior field border and node-negative inguinal nodes is recommended after delivery of 30.6 Gy and 36 Gy, respectively. For patients treated with an anteroposterior-posteroanterior (AP-PA) rather than multifield technique, the dose to the lateral inguinal region should be brought to the minimum dose of 36 Gy using an anterior electron boost matched to the PA exit field. Patients with disease clinically staged as node-positive or T3-T4 or with T2 residual disease after 45 Gy should receive an additional boost of 9-14 Gy. The consensus of the panel is that IMRT may be used in place of 3-D conformal RT in the treatment of anal carcinoma.[105] IMRT requires expertise and careful target design to avoid reduction in local control by marginal miss.[61] The clinical target volumes for anal cancer used in the RTOG 0529 trial have been described in detail.[105] Also see http://atc.wustl.edu/protocols/rtog-closed/0529/ANAL_Ca_CTVs_5-21-07_Final.pdf and http://www.rtog.org/CoreLab/ContouringAtlases/Anorectal.aspx for more details of the contouring atlas defined by RTOG.

Treatment of Anal Cancer in Patients with HIV/AIDS

As discussed above (see *Risk Factors*), patients with HIV/AIDS have been reported to be at increased risk for anal carcinoma.[8,9] Although most studies evaluating outcomes of patients with HIV/AIDS treated with chemoRT for anal carcinoma are retrospective,[9] 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/mm^3) may be treated with the same regimen as non-HIV patients.[106,107] Furthermore, in a recent retrospective cohort study of 1184 veterans diagnosed with squamous cell carcinoma of the anus between 1998 and 2004 (15% of whom tested positive for HIV), 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.[108] This conclusion was supported by a study of 36 consecutive patients with anal cancer including 19 immunocompetent and 17 immunodeficient (14 HIV-positive) patients

who showed no differences in the efficacy or toxicity of chemoRT.[109] In contrast, a recent cohort comparison of 40 HIV-positive patients with 81 HIV-negative patients with anal canal cancer found local relapse rates to be 4 times higher in the HIV-positive group (62% vs. 13%) at 3 years and found significantly higher rates of severe acute skin toxicity for patients infected with HIV.[110] However, no differences in rates of complete response or 5-year overall survival were observed between the groups in that study. It is unclear whether increased compliance with HAART is associated with better outcomes following chemoRT for anal carcinoma.[9,111] 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

Currently, concurrent chemoRT is the recommended primary treatment for patients with nonmetastatic anal canal cancer. Mitomycin and 5-FU are administered concurrently with radiation.[54] 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.[40]

RT is associated with significant side effects. Patients should be counseled on infertility risks and given information regarding sperm, oocyte, egg, or ovarian tissue banking prior to treatment. In addition, female patients should be considered for vaginal dilators and should be instructed on the symptoms of vaginal stenosis.

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 T1, N0 well-differentiated anal margin cancers is by local excision with adequate margins. The American Society of Colon and Rectal Surgeons defines an adequate margin as 1 cm.[29] If the margins are not adequate, re-excision is the preferred treatment option. Local RT with or without continuous infusion 5-FU-based chemotherapy can be considered as an alternative treatment option when surgical margins are inadequate. For all other stages of anal margin cancer, the treatment options are the same as for anal canal cancer (see above).[112]

Treatment of Metastatic Anal Cancer

It has been reported that the most common sites of anal cancer metastasis outside of the pelvis are the liver, lung, and extrapelvic lymph nodes.[113] Since anal carcinoma is a rare cancer and only 10% to 20% of patients with anal carcinoma present with extrapelvic metastatic disease,[113] only limited data are available on this population of patients. Despite this fact, there is some evidence to indicate that chemotherapy with a fluoropyrimidine-based regimen plus cisplatin has some benefit in patients with metastatic anal carcinoma.[112-115] There is no evidence supporting resection of metastatic disease.

Treatment recommendations for patients with a distant metastasis should be individualized, but metastatic disease is usually treated with cisplatin-based chemotherapy.[112] Enrollment in a clinical trial is another option. Palliative RT (best administered with 5-FU–based chemotherapy with a platinum agent) can also be given to patients with metastatic disease for local control in the case of a symptomatic bulky primary.[104] If cisplatin-based chemotherapy fails, no other regimens have been shown to be effective.

Follow-up and Surveillance Following Primary Treatment

Following primary treatment of non-metastatic anal cancer, 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 chemoRT. Following re-evaluation, patients are classified according to whether they have a complete remission of disease, persistent disease, or progressive disease. Patients with persistent disease but without evidence of progression may be managed with close follow-up (in 4 weeks) to see if further regression occurs.

The National Cancer Research Institute's ACT II study compared different chemoRT regimens and found no difference in overall survival or progression-free survival.[116] Interestingly, 29% of patients in this trial who did not show a complete response at 11 weeks had achieved a complete response by 26 weeks. Based on these results, the panel believes it may be appropriate to follow patients who have not achieved a complete clinical response with persistent anal cancer for up to 6 months after completion of radiation and chemotherapy, as long as there is no evidence of progressive disease during this period of follow-up. Persistent disease may continue to regress even at 26 weeks post-treatment, and salvage APR can thereby be avoided in some patients. If no regression of disease is observed by 6 months or if disease progression occurs, further intensive treatment is indicated (see *Treatment of Locally Progressive or Recurrent Anal Carcinoma*, below).

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. The panel recommends that these patients should undergo evaluation every 3 to 6 months for 5 years, including DRE, anoscopic evaluation, and inguinal node palpation. Annual chest, abdominal, and pelvic imaging is recommended for 3 years for patients with slow disease regression and should also be considered for 3 years for patients who initially had locally advanced disease (ie, T3/T4 tumor) or node-positive cancers.

Treatment of Locally Progressive or Recurrent Anal Carcinoma

Despite the effectiveness of chemoRT in the primary treatment of anal carcinoma, rates of locoregional failure of 10% to 30% have been reported.[117,118] Some of the disease characteristics that have been associated with higher recurrence rates following chemoRT include higher T stage and higher N stage (also see the section on *Prognostic Factors*, above).[119] 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 locally progressive disease are candidates for radical salvage surgery with an APR and colostomy.[118]

A recent multicenter retrospective cohort study looked at the cause-specific colostomy rates in 235 patients with anal cancer who were treated with radiotherapy or chemoradiation from 1995 to 2003.[120] The 5-year cumulative incidence rates for tumor-specific and therapy-specific colostomy were 26% (95% CI, 21–32) and 8% (95% CI, 5–12), respectively. Larger tumor size (>6 cm) was a risk factor for tumor-specific colostomy, while local excision prior to radiotherapy was a risk factor for therapy-specific colostomy. However, it should be noted that these patients were treated with older chemotherapy and RT regimens, which could account for these high colostomy rates.[121]

In studies involving a minimum of 25 patients undergoing a salvage APR for anal carcinoma, 5-year survival rates of 39% to 64% were observed.[117,118,122-124] Complication rates were reported to be high in some of these studies. 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.[118]

It has been shown that for patients undergoing an APR that was preceded by RT, closure of the perineal wound using rectus abdominis

myocutaneous flap reconstruction resulted in decreased perineal wound complications.[125] Muscle flap reconstruction of the perineum should therefore be considered because of the extensive previous RT to the area.

A recent retrospective analysis of the medical records of 14 patients who received intraoperative radiotherapy (IORT) during salvage APR revealed that IORT is unlikely to improve local control or to give a survival benefit.[126] This technique is not recommended during salvage surgery in patients with recurrent anal cancer.

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 no prior RT to the groin was given.

Follow-up and Surveillance Following Salvage Treatment

Following salvage APR, patients should undergo re-evaluation every 3 to 6 months for 5 years, including clinical evaluation of nodal metastasis (ie, inguinal node palpation). In addition, it is recommended that these patients undergo annual imaging of the chest, abdomen, and pelvis for 3 years.

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 continuous infusion 5-FU/mitomycin-based RT in most cases. The exception is small, well-differentiated anal margin lesions, which 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 undergo an APR. 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 no 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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