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The NCCN

Anal Carcinoma

Clinical Practice Guidelines in Oncology™

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Overview

An estimated 5290 new cases (2100 men and 3190 women) of anal cancer (involving the anus, anal canal, or anorectum) will occur in the United States in 2009, accounting for approximately 1.9% of digestive system cancers,[1] and an estimated 710 deaths due to anal cancer. Although considered to be a rare type of cancer, the incidence rate of invasive anal carcinoma in the United States increased by approximately 1.6-fold for men and 1.5-fold for women from 1973–1979 to 1994–2000[2] (see Risk Factors, facing page).

This manuscript summarizes the NCCN Clinical Practice Guidelines in Oncology 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 are addressed

Anal Carcinoma Clinical Practice Guidelines in Oncology

Key Words

NCCN Clinical Practice Guidelines, anal neoplasms, neoplasm staging, surgery, biopsy (*JNCCN* 2010;8:106–120)

NCCN Categories of Evidence and 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.

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.

Please Note

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Anal Carcinoma Guidelines Panel

At the beginning of each NCCN guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Anal Carcinoma Guidelines Panel members can be found on page 120. (To view the most recent version of these guidelines and accompanying disclosures, visit the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, please visit NCCN.org.

in other NCCN guidelines (i.e., anal adenocarcinoma and anal melanoma are managed according to the NCCN Clinical Practice Guidelines in Oncology on Rectal Cancer and Melanoma, respectively). Except where noted, the recommendations in these guidelines are classified as category 2A, meaning that uniform NCCN consensus was present among the panel 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); history of receptive anal intercourse or sexually transmitted disease; history of cervical, vulvar, or vaginal cancer; immunosuppression after solid organ transplantation or HIV infection; and smoking.[3–5] Currently, the association between anal carcinoma and persistent infection with a high-risk form of HPV (e.g., HPV-16 or -18) is believed to be strongest.[4,6,7] For example, a study of tumor specimens from 60 pathology laboratories showed that HPV-16 was detected in 84% and 0% of anal and rectal cancer specimens, respectively.[4] In addition, results of a systematic review of peer-reviewed studies of anal cancer published up until July 2007, including detection of HPV DNA, showed the prevalence of HPV-16 and -18 to be 72% in patients with invasive anal cancer.[7]

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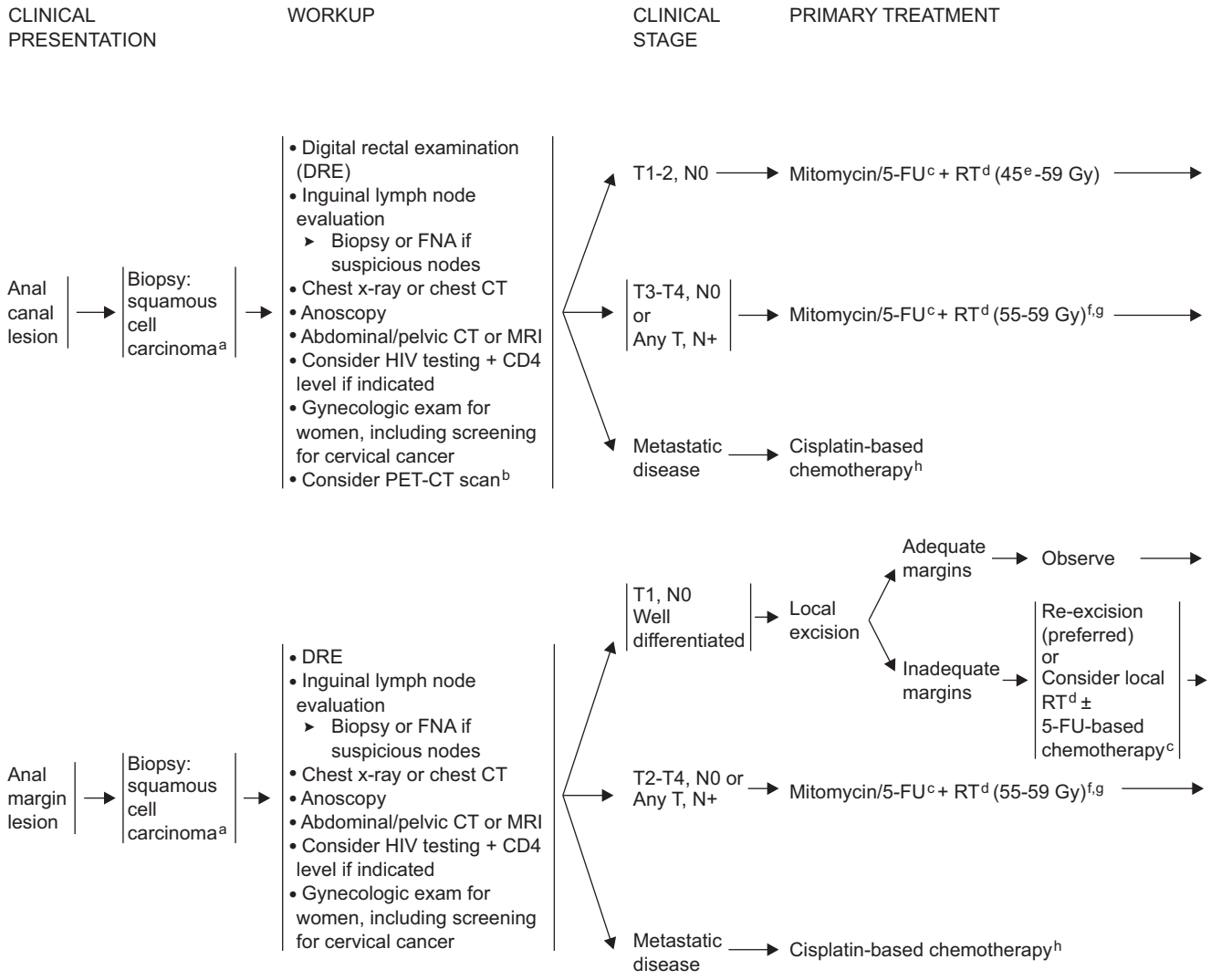

[a] For melanoma histology, see the NCCN Clinical Practice Guidelines in Oncology: Melanoma; for adenocarcinoma, see the NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer (to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org).

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

[c] See Principles of Chemotherapy (page 110). 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. 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.

[d] See Principles of Radiation Therapy (page 110).

[e] Reevaluate after 45 Gy; if persistent disease, dose should be increased to 55-59 Gy.

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

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

[h] Cisplatin/5-fluorouracil recommended for metastatic disease. If this regimen fails, no other regimens have shown to be effective. See Principles of Chemotherapy (page 110).

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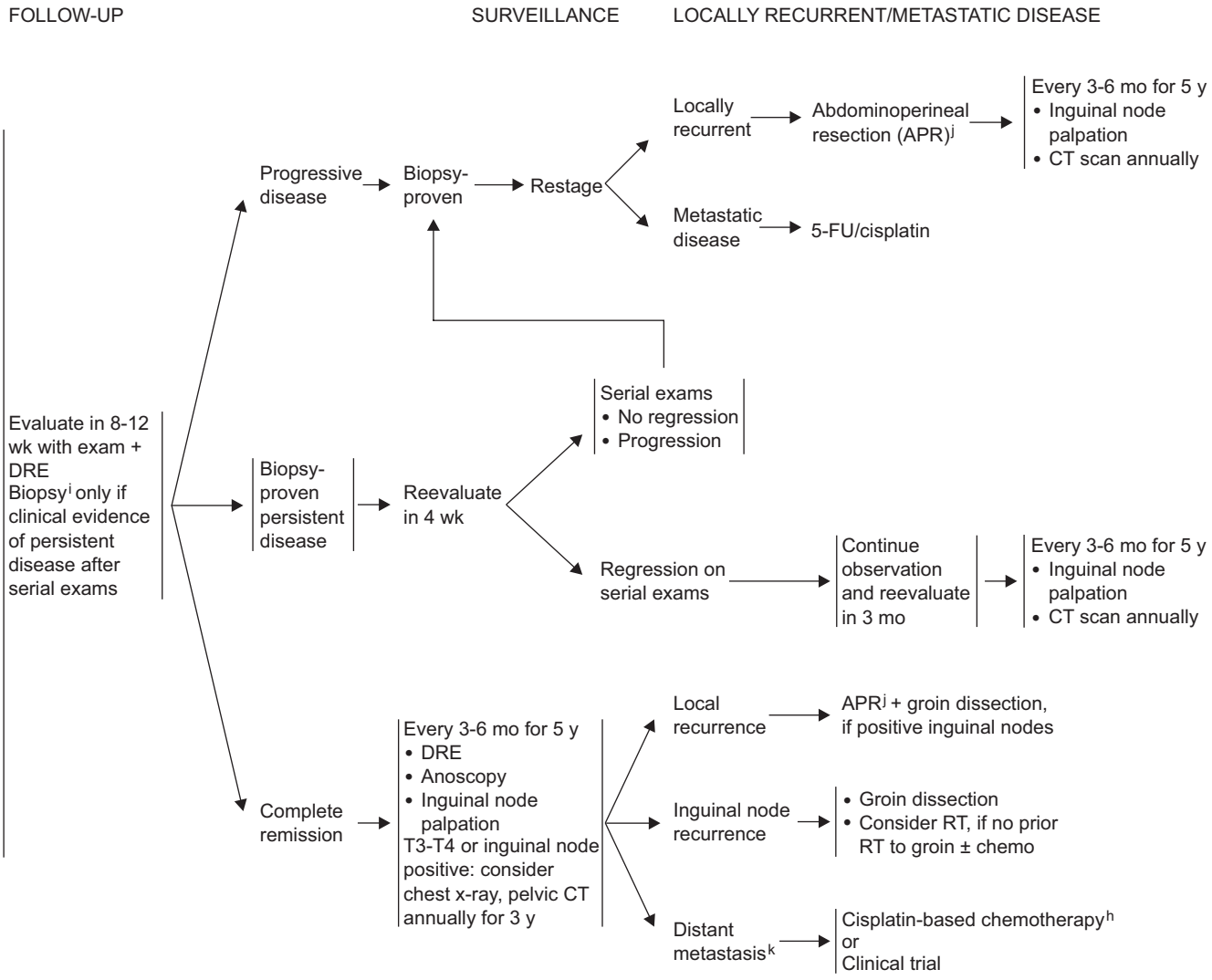

[h] Cisplatin/5-fluorouracil recommended for metastatic disease. If this regimen fails, no other regimens have shown to be effective. See Principles of Chemotherapy (page 110).
[i] If patient with an initially tethered tumor returns 6 wk postoperative RT with a mobile but suspicious mass, consider biopsy.
[j] Consider muscle flap reconstruction.
[k] There is no evidence supporting resection of metastatic disease.

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 wk 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 wk

PRINCIPLES OF RADIATION THERAPY[1]

- All patients should receive a minimum dose of 45 Gy in 25 fractions of 1.8 Gy over 5 weeks to the primary cancer with supervoltage radiation (photon energy of > 6 mV) using anteroposterior-posteroanterior (AP-PA) or multifield techniques.
- Initial radiation fields include the pelvis, anus, perineum, and inguinal nodes, with the superior field border at L5-S1 and the inferior border to include the anus with a minimum margin of 2.5 cm around the anus and tumor. The lateral border of AP fields includes the lateral inguinal nodes as determined from bony landmarks or imaging (CT), but lateral inguinal nodes are not routinely included in the PA fields to allow adequate sparing of the femoral heads.
- After a dose of 30.6 Gy in 17 fractions, the superior field extent is reduced to the bottom of the sacroiliac joints and an additional 14.4 Gy is given in 8 fractions (total dose of 45 Gy in 25 fractions/5 wk), with additional field reduction off node-negative inguinal nodes after 36 Gy.
- For patients treated with an AP-PA rather than 4-field technique, an anterior electron boost (matched to the PA exit field) is used to bring the lateral inguinal region to the minimum dose of 30.6 Gy.
- For patients with T3, T4, node-positive disease or patients with T2 residual disease after 45 Gy, the intent is usually to deliver an additional boost of 10 to 14 Gy in 2-Gy fractions (total dose of 55-59 Gy in 30-32 fractions over 5.5-6.5 wk).
- The target volume for boost field 2 is the original primary tumor volume/node plus a 2- to 2.5-cm margin. Treatment field options include a multifield photon approach (AP-PA plus paired laterals, PA + laterals, or other) or a direct perineal boost with electrons or photons with the patient in lithotomy position.
- Intensity modulated radiation therapy in addition to 3-dimensional conformal radiation therapy may be used in the treatment of patients with anal cancer.

[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;14:2527-2539.
[3] Faivre C, Rougier P, Ducreux M, et al. 5-fluorouracil and cisplatin combination chemotherapy for metastatic squamous-cell anal cancer. Bull Cancer 1999;86:861-865.

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Furthermore, suppression of the immune system using immunosuppressive drugs or from HIV infection is likely to facilitate persistence of HPV infection of the anal region.[8,9] 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 to 1995, increased to 78.2 during 2000 to 2003.[10] This result is likely to reflect 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.

Anatomy/Histology

The anal region comprises the anal canal and anal margin, thus dividing anal cancers into 2 categories. The anal canal is the more proximal portion of the anal region, and various definitions exist (e.g., functional/surgical, anatomic, and histologic anal canal) which are based on particular physical/anatomic landmarks or histologic characteristics. 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 long and its inferior border starts at the anal verge, the lowermost edge of the sphincter muscles that corresponds to the introitus of the anal orifice.[3,11,12] This definition is 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.[13,14] 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.[3,11] 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.[3,11] The most inferior aspect, located approximately at the anal verge, corresponds with 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.[11] The terms *anal margin* and *perianal skin* are frequently used synonomously.[11,15]

Pathology

Most primary cancers of the anal canal are of squamous cell histology.[11,13] 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.[16] Squamous cell cancers in the more proximal region of the anal canal are reported to be more likely 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.[14–18] This change was made because both cloacogenic (which is sometimes used interchangeably with the term basaloid) and transitional tumors are now considered to be non-keratinizing tumors; a report has shown that both keratinizing and non-keratinizing tumors have a similar natural history and prognosis;[15] a mixture of cell types frequently characterize histologic specimens of squamous cell carcinomas of the anal canal.[11,15–18]

The guidelines do not distinguish between squamous anal canal tumors based on cell type. Less common anal canal tumors include adenocarcinomas of the anal glands, small cell and undifferentiated cancers, and melanomas.[11] 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 (e.g., sweat glands) in anal margin tumors can distinguish them from anal canal tumors.[15] However, anal canal and anal margin squamous cell carcinoma are not always distinguishable because tumors can involve both areas.[15]

Lymph drainage of anal cancer tumors is dependent on the tumor location 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; and more proximal cancers drain to nodes of the inferior mesenteric system.[11] 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.[11]

Staging

The TNM staging system for anal canal cancer developed by the American Joint Committee on Cancer (AJCC) is detailed in the staging table[14] (available online, in these guidelines, at www.NCCN.org [ST-1]). Because current recommendations for primary treatment of anal canal cancer do not involve a surgical excision, most tumors are staged clinically, with an emphasis on the primary tumor size determined through direct examination and microscopic confirmation.[14] 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, opposite column). The AJCC TNM system used for staging anal margin cancer (Table 2; available online, in these guidelines, at www.NCCN.org [ST-2]) is the same one used to stage skin cancer because the cancers have a similar biology.[14]

Lymph node staging is based on location of involved nodes in the staging of anal canal cancer: N1 designates metastasis in 1 or more perirectal nodes; N2 represents metastasis in unilateral internal iliac nodes and/or inguinal nodes; 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, 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 primary tumor size and presence of lymph node metastases.[14] Approximately 60% to 70% of anal carcinoma tumors are initially staged as I or II.[19,20] The 5-year survival rates are reported to be approximately 80% and less than 50% for patients treated with chemoradiation (chemoRT) with tumors that are 2 cm or smaller or larger than 5 cm, respectively.[11] The following 5-year overall survival rates according to disease stage were determined in a recent analysis of 19,199 patients with anal canal cancer included in the National Cancer Data Base from 1985 through 2000: stage I, 69.5%; stage II, 59.0%; stage III, 40.6%; and stage IV, 18.7%.[21] Reports of the extent of nodal involvement associated with anal cancers at presentation have varied widely, with most values ranging between 10% and 40%.[11,15,19–23]

Although some reports have shown that the extent of nodal involvement correlates with the T stage of the tumor,[23] others have not supported this conclusion.[20] A surgical series of patients with anal cancer who underwent an abdominoperineal resection (APR) noted that pelvic nodal metastases were often smaller than 0.5 cm,[24] suggesting that routine radiologic evaluation with CT and PET may not be reliable in determining lymph nodal involvement. In a retrospective study of 270 patients with anal canal cancer treated with radiation therapy (RT) between 1980 and 1996, synchronous inguinal node metastasis was observed in 6.4% with tumors staged as T1 or T2, increasing to 16% in those with T3 or T4 tumors.[19] 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.

Management of Anal Carcinoma

Clinical Presentation/Evaluation

Most patients with anal carcinoma present with rectal bleeding. Approximately 30% of patients with anal carcinoma experience either pain or the sensation of a rectal mass.[3] The panel's recommendations for the clinical evaluation of patients with suspected anal canal cancer are the same as for those with suspected anal margin cancer, except for consideration of PET/CT scan, which is not included in the workup of anal margin cancers (see page 108). After biopsy confirmation of squamous cell carcinoma, the panel recommends a thorough examination/evaluation, including a careful digital rectal examination (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 the anal margin or anal canal cancer is performed using fine-needle aspiration (FNA) biopsy and/or excisional biopsy of nodes found to be enlarged through 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 or pelvic organs.

Because veins of the anal region are part of the venous network associated with systemic circulation,[11] chest radiograph or CT scan is performed to evaluate for pulmonary metastasis. PET/CT scanning has been reported to be useful in evaluating pelvic nodes, even in patients with anal canal cancer who have normal-sized lymph nodes on CT imaging,[25–27] although the panel does not consider PET/CT to be a replacement for a diagnostic CT. Furthermore, the panel noted that the routine use of PET/CT for staging or treatment planning has not been validated. HIV testing and measurement of CD4 level is recommended, because the risk for anal carcinoma has been reported in some studies to be higher in patients who are HIV-positive.[28] Gynecologic examination, including cervical cancer screening, is suggested for women because of the association of anal cancer and HPV.[4]

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 chemoRT alone as an alternative to an APR is the recommended primary treatment for patients with anal canal 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 et al.[29] 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 anal carcinoma may be possible to cure without surgery and permanent colostomy. Subsequent nonrandomized studies using similar regimens and varied doses of chemotherapy and radiation supported this conclusion.[30,31]

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.[32] Results from a phase III EORTC study 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.[33] 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; $P < .0001$), although no significant differences were observed in overall survival.[34]

Several 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,[35] patients treated with chemoRT with combination 5-FU and mitomycin had lower colostomy (9% vs. 22%; $P = .002$) and higher disease-free survival rates (73% vs. 51%; $P = .0003$) than those treated with chemoRT and 5-FU alone, indicating that mitomycin is an important component of chemoRT in the treatment of anal carcinoma. The survival rate at 4 years was the same between the 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- and mitomycin-containing chemoRT were comparable.[36] Use of 5-FU–based chemoRT combined with 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.[37] 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 end point, disease-free survival (54% vs. 60%; $P = .17$), or 5-year overall survival (70% vs. 75%; $P = .10$). However, the colostomy rate was significantly higher in the group receiving cisplatin (19% vs. 10%; $P = .02$).

Because the 2 treatment arms in RTOG 98-11 differed regarding the use of cisplatin or mitomycin in concurrent chemoRT, and the inclusion of neoadjuvant chemotherapy in the cisplatin-containing arm, attributing the increased rate of colostomy to the substitution of cisplatin for mitomycin or the use of induction chemotherapy is not currently possible.[38,39]

A secondary combined multivariate analysis of the 2 arms showed that pretreatment tumor size of less than 5 cm was predictive of an increased likelihood of colostomy.[40] A summary of ongoing clinical trials involving patients with anal cancer has been presented.[39]

Results from the phase III United Kingdom ACT II trial, the largest trial ever conducted in patients with anal cancer, were recently presented.[41] More than 900 patients with newly diagnosed anal cancer were randomly assigned to primary treatment with either 5-FU/mitomycin or 5-FU/cisplatin in concomitant chemoRT. A continuous course (i.e., no treatment gap) of radiation at 50.4 Gy was administered in both arms; patients in each arm were further randomized to undergo 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 either arm regarding the primary end points of either complete response rate for the chemoRT comparison or recurrence-free survival for the comparison of maintenance versus no maintenance therapy. In addition, a secondary end point of colostomy did not show differences based on the chemotherapeutic components of chemoRT. These results show that replacing mitomycin with cisplatin in chemoRT does not increase the rate of complete response nor does administration of maintenance therapy decrease the rate of disease recurrence after primary treatment with chemoRT in patients with anal cancer.

The optimal dose and schedule of RT for anal carcinoma 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.[11]

Several nonrandomized studies have evaluated the effects of RT dose and schedule. In one study of patients with early-stage (Tis or T1) anal canal cancer, most were effectively treated with RT doses of 40 to 50 Gy and 50 to 60 Gy for Tis and T1 lesions, respectively.[42] In another study, most patients had stage II or III anal canal cancer, and local control of disease was higher in those receiving RT doses of 50 Gy or greater.[43] In a third study of patients with T3, T4, or lymph node–positive tumors, RT doses of 54 Gy or more administered within 60 days were associated with increased local control.[44]

Evidence shows that treatment interruptions (i.e., gaps), either planned or required by treatment-related toxicity, can compromise the effectiveness of treatment.[27] The phase II RTOG 92-08 trial showed that planned 2-week treatment breaks in the delivery of chemoRT to patients with anal cancer were associated with increased locoregional failure rates and lower colostomy-free survival rates compared with results from previous trials in which lower RT doses were used without a mandated treatment break. Although the study was not powered for comparison, the number of patients involved was small and the differences not significant.[45] 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 (75% at 3 years).[41]

Although results of other studies have also supported the benefit of delivering chemoRT over shorter periods,[46,47] treatment breaks are frequently required (e.g., ≤ 50% of patients in clinical trials undergo treatment breaks) because related toxicities are common. For example, one third of patients undergoing primary chemoRT for anal carcinoma at RT doses of 30 Gy in 3 weeks were reported to develop acute anoproctitis and dermatitis, increasing to one half to two thirds of patients when RT doses of 54 to 60 Gy were administered in 6 to 7 weeks.[11] 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.[48] 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 RT for anal cancer compared with those who did not receive RT.[49]

An increasing body of literature suggests that toxicity can be reduced with advanced radiation delivery techniques.[27,50–53] Intensity-modulated radiation therapy (IMRT) uses detailed beam-shaping to target specific volumes and limit the exposure of normal tissue.[50,53] Multiple pilot studies have shown reduced toxicity while maintaining local control using IMRT. For example, a cross-study comparison of 53 patients with anal cancer in a multicenter study treated with concurrent 5-FU/mitomycin C chemotherapy and IMRT, and those observed in the 5-FU/mitomycin C arm of the randomized RTOG 98-11 study involv-

ing use of conventional 3-dimensional RT showed grade 3/4 dermatologic toxicity rates of 38%/0% and 43%/5%, respectively.[37,51] No decrease in treatment effectiveness or local control rate was observed with IMRT, although the small sample size and short follow-up limit the conclusions drawn. IMRT studies (e.g., RTOG 0529) are ongoing to further evaluate its benefit in the treatment of anal cancer. Its use requires expertise and careful application to avoid reduction in local control probability. The clinical target volumes for anal cancer used in RTOG -0529 have been described in detail[54] (http://atc.wustl.edu/protocols/rtog-closed/0529/ANAL_Ca_CTVs_5-21-07_Final.pdf).

Patients with HIV/AIDS have been reported to be at increased risk for anal carcinoma (see Risk Factors, page 107).[28,32] Although most studies evaluating outcomes of these patients treated with chemoRT for anal carcinoma are retrospective,[32] evidence indicates that those 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 those not infected with HIV.[55,56] 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 in receipt of treatment or 2-year survival rates were observed when the patients with HIV were compared with those who tested negative for HIV.[57]

This conclusion was supported by a study of 36 consecutive patients with anal cancer, including 19 immunocompetent and 17 immunodeficient (14 HIV-positive) patients, which showed no differences in the efficacy or toxicity of chemoRT.[58] Nevertheless, a recent cohort comparison of 40 HIV-positive 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 among those infected with HIV.[59] However, no differences in rates of complete response or 5-year overall survival were observed between the 2 groups.

Other factors to consider include compliance with HAART (although it is unclear whether increased compliance with HAART is associated with better outcomes after chemoRT for anal carcinoma[55,60]) and performance status.[32] Patients with active HIV/AIDS-related complications or a history of complications (e.g., malignancies, opportunistic infections) may not tolerate full-dose therapy and may require dosage adjustment.

Recommendations for the Primary Treatment of Anal Canal Cancer: The primary treatment option for anal canal cancer is chemoRT (5-FU/mitomycin plus RT; see pages 108 and 110). Recommendations regarding RT doses follow those used in the RTOG 98-11 trial (see page 110).[40] 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 (see page 110). Field reduction of the superior field border and node-negative inguinal nodes is recommended after delivery of 30.6 and 36 Gy, respectively. Patients with disease clinically staged as T3-T4, N0; T-any with nodal involvement; or T2 residual disease after 45 Gy should receive an additional boost of 9 to 14 Gy. The panel consensus is that IMRT may be used in place of 3-dimensional conformal RT in the treatment of anal carcinoma. Two cycles of 5-FU/mitomycin delivered during the first and fifth week of RT is recommended (see page 110). Cisplatin-based chemotherapy is recommended to treat metastatic disease (see Recommendations for the Treatment of Locally Recurrent/Metastatic Disease [Anal Canal/Margin Cancer], page 112).[61]

Recommendations for the Primary Treatment of Anal Margin Cancer: Anal margin lesions can be treated with either local excision or chemoRT depending on clinical stage. Primary treatment for patients with T1, N0 well-differentiated anal margin cancers involves local excision with adequate margins (see page 108). 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 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 (see pages 108 and 110). Cisplatin-based chemotherapy is recommended to treat metastatic disease (see Recommendations for the Treatment of Locally Recurrent/Metastatic Disease [Anal Canal/Margin Cancer], page 116).[61]

Follow-up and Surveillance After Primary Treatment

After primary treatment, the surveillance and follow-up treatment recommendations for anal margin

and anal canal cancer are the same. Patients are re-evaluated with DRE between 8 and 12 weeks after completion of primary treatment with chemoRT (see page 109). Biopsy is performed only if presence of disease is suspected after serial DRE. Disease can continue to regress for a period of months after completion of chemoRT; the likelihood of a false-positive result is high.[62,63]

Some indications for biopsy include new hard-edged ulcer, enlarging mass, or increasing pain. After re-evaluation, patients are classified according to whether they experience complete remission or progressive or persistent disease. In one study, persistent disease was defined as presence of biopsy-proven carcinoma within 6 months of completion of chemoRT.[64]

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 no 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 [Anal Canal/Margin Cancer], opposite column). Patients who continue to show evidence of disease regression should be re-evaluated clinically in 3 months (see page 109).

The panel recommends that patients classified as having a complete remission of disease undergo more intensive surveillance every 3 to 6 months for 5 years, including DRE, anoscopic evaluation, and inguinal node palpation. A chest radiograph and pelvic CT scan should be considered annually for 3 years for patients with locally advanced disease (i.e., T3/T4 tumor) or node-positive cancers.

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,[65] and radical salvage surgery with an APR has been preferred treatment for these patients.[64] Some disease characteristics associated with higher recurrence rates after chemoRT include higher T and N stage.[66] In several surgical series involving a minimum of 25 patients undergoing a salvage APR for anal carcinoma, 5-year survival rates of 39% to 64% were observed, although complication rates were reported to be high in some of these studies.[18,64,67–70] Factors associated with worse prognosis after salvage APR include an initial presentation of node-positive disease and RT doses less than 55 Gy used in the treatment of primary disease.[64] For patients undergoing an APR that was preceded by RT, closure of the perineal wound using rectum abdominus myocutaneous flap reconstruction has been shown to result in decreased perineal wound complications.[71]

Reports have shown the most common sites of metastasis outside of the pelvis to include the liver, lung, and extrapelvic lymph nodes.[72] Because anal carcinoma is a rare cancer and only 10% to 20% of patients with anal carcinoma present with metastatic disease,[72] limited data are available on this population of patients, although some evidence indicates that chemotherapy with a fluoropyrimidine-based regimen plus cisplatin has some benefit in patients with metastatic anal carcinoma.[61,72–74]

Recommendations for the Treatment of Progressive Disease (Anal Canal/Margin Cancer): Evidence of progression found on DRE should be followed by biopsy and restaging with CT and/or PET imaging. Patients with biopsy-proven progressive disease are candidates for an APR. Muscle flap reconstruction of the perineum should be considered because of extensive previous RT to the area (see page 109). These patients should be re-evaluated every 3 to 6 months for 5 years, including annual clinical evaluation of nodal metastasis (i.e., inguinal node palpation) and CT scan.

Recommendations for the Treatment of Locally Recurrent/Metastatic Disease (Anal Canal/Margin Cancer): Patients experiencing complete remission should be evaluated every 3 to 6 months for 5 years (see page 109 and Follow-up and Surveillance After Primary Treatment, page 115). Treatment recommendations for patients who develop a local recurrence include an APR, and 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 when 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 prior limited RT to the groin was given.

Treatment recommendations for patients who develop a distant metastasis should be individualized, and local treatment could be considered for patients experiencing symptoms. No evidence supports resection of metastatic disease. Treatment recommendations for patients with metastatic anal carcinoma include platinum-based chemotherapy (see page 110) or enrollment in a clinical trial. Currently, no other regimens have been shown to be effective in these patients after failure of 5-FU/cisplatin.

Summary

The 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 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 because salvage is possible.

Patients with biopsy-proven evidence of locoregional progressive disease after primary treatment should undergo an APR. After complete remission of disease, patients with a local recurrence should be treated with an APR with groin dissection if they have 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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