NCCN Guidelines® Insights

Anal Carcinoma, Version 2.2012

Featured Updates to the NCCN Guidelines

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Abstract

The workup and management of squamous cell anal carcinoma, which represents the most common histologic form of the disease, are addressed in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Anal Carcinoma. These NCCN Guidelines Insights provide a summary of major discussion points of the 2012 NCCN Anal Carcinoma Panel meeting. In summary, the panel made 4 significant changes to the 2012 NCCN Guidelines for Anal Carcinoma: 1) local radiation therapy was added as an option for the treatment of patients with metastatic disease; 2) multifield technique is now preferred over anteroposterior-posteroanterior (AP-PA) technique for radiation delivery and the AP-PA technique is no longer recommended as the standard of care; 3) PET/CT should now be considered for radiation therapy planning; and 4) a section on risk reduction was added to the discussion section. In addition, the panel discussed the use of PET/CT for the workup of anal canal cancer and decided to maintain the recommendation that it can be considered in this setting. They also discussed the use of PET/CT for the workup of anal margin cancer and for the assessment of treatment response. They reaffirmed their recommendation that PET/CT is not appropriate in these settings. (*JNCCN* 2012;10:449–454)

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Disclosures for the NCCN Anal Carcinoma Panel

Individual disclosures of potential conflicts of interest for the NCCN Anal Carcinoma Panel can be found online at NCCN.org.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.

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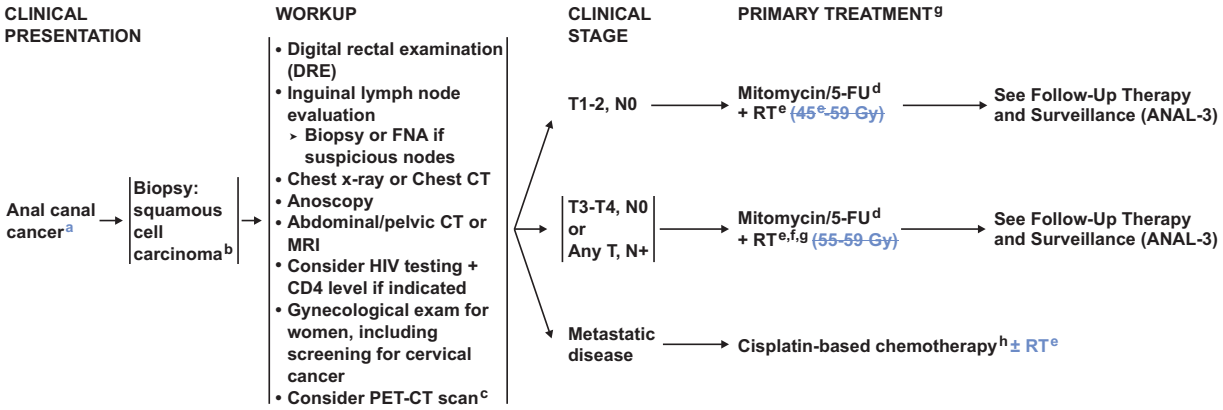

[a]The superior border of the functional anal canal, separating it from the rectum, has been defined as the palpable upper border of the anal sphincter and puborectalis muscles of the anorectal ring. It is approximately 3 to 5 cm in length, and its inferior border starts at the anal verge, the lowermost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

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

[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.

[e]~~Re-evaluate at 45 Gy, if persistent disease, consider increasing 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, may be treated with the same regimen as non-HIV patient. Patients with active HIV/AIDS-related complications or a history of complications (eg, malignancies, opportunistic infections) may not tolerate full-dose therapy or may not tolerate mitomycin and require dosage adjustment or treatment without mitomycin.

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

ANAL-1

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.

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

Overview

An estimated 6230 new cases (2250 in men and 3980 in 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 is also estimated that 780 deaths from 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 1973–1979, to 1994–2000.[2] Anal carcinoma has been associated with human papilloma virus (HPV) infection (anogenital warts); receptive anal intercourse or sexually transmitted disease; 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 (e.g., HPV-

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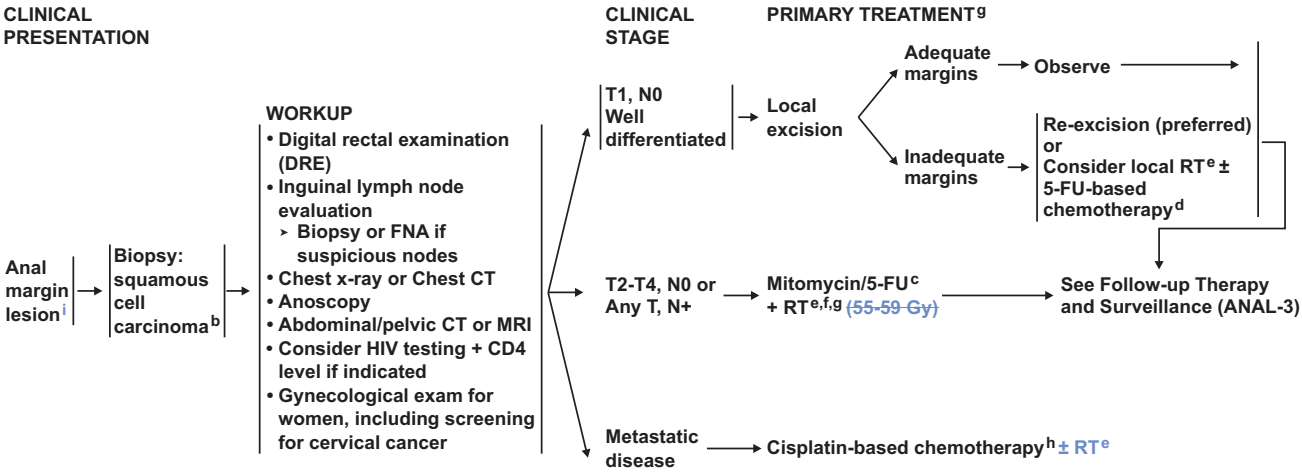

[b]For melanoma histology, see the NCCN Melanoma Guidelines, for adenocarcinoma, see the NCCN Rectal Cancer Guidelines.
[d]See Principles of Chemotherapy ANAL-A.
Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. JAMA 2008;299:1914. 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]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, may be treated with the same regimen as non-HIV patient. Patients with active HIV/AIDS-related complications or a history of complications (eg, malignancies, opportunistic infections) may not tolerate full-dose therapy or may not tolerate mitomycin and require dosage adjustment or treatment without mitomycin.
[h]Cisplatin/5-fluorouracil recommended for metastatic disease. If this regimen fails, no other regimens have shown to be effective. See Principles of Chemotherapy ANAL-A. Local control can be achieved with the use of RT.
[i]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.

ANAL-2

16/-18) is especially strong.[4,10,11] Results of a systematic review of 35 peer-reviewed studies that included detection of HPV DNA showed the prevalence of HPV-16/-18 to be 72% in patients with invasive anal cancer.[11] Suppression of the immune system through the use of immunosuppressive drugs or HIV infection is likely to facilitate persistence of HPV infection of the anal region.[12,13] 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 1992–1995, increased to 78.2 during 2000–2003.[14] 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 workup and management of squamous cell anal carcinoma, which represents the most common histologic form of the disease, are addressed in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Anal Carcinoma (the NCCN Guidelines are available online at www.NCCN.org). A summary of major discussion points of the 2012 NCCN Anal Carcinoma Panel meeting follows. In addition, a section on risk reduction that was added to the 2012 discussion of the Guidelines is included.

Risk Reduction

High-grade anal intraepithelial neoplasia (AIN) is a precursor to anal cancer,[15,16] and therefore treatment of high-grade AIN may prevent the development of anal cancer. AIN can be identified through cytology, HPV testing, digital rectal examination, high-resolution anoscopy, and/or biopsy.[17,18] However, routine screening for AIN, even in high-risk individuals, such as those who are HIV-positive or men who have sex with men, is controversial because of the lack of randomized controlled trials showing that these screening programs are efficacious at reducing anal cancer incidence and mortality.[19–21]

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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.**
- **PET-CT should be considered for treatment planning.**
- **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 ~~(computed tomography), but lateral inguinal nodes are not routinely included in the PA fields to allow adequate sparing of the femoral heads.~~ There should be attempts to reduce the dose to 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/5weeks), 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 36 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 9 to 14 Gy in 1.8 to 2 Gy fractions (total dose of 54-59 Gy in 30-32 fractions over 6.0-7.5 weeks).**
- **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 three dimensional conformal radiation therapy may be used in the treatment of patients with anal cancer.[2]**
- **Side effect management:**
  Female patients should be considered for vaginal dilators and instructed on the symptoms of vaginal stenosis.
  ~~All male patients should be evaluated for erectile dysfunction and considered for early treatment intervention if necessary.~~

[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. Copyright © (2008) American Medical Association. All rights reserved.

[2] Myerson RJ, Garofolo MC, Naqa IE, 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.

ANAL-B

A quadrivalent HPV vaccine is available and has been shown to be effective in women for preventing persistent cervical infection with HPV-6, -11, -16, or -18, and preventing high-grade cervical intraepithelial neoplasia related to these strains of the virus.[22–24] A recent substudy of a larger double-blind study assessed the efficacy of the vaccine for preventing AIN and anal cancer related to infection with HPV-6, -11, -16, or -18 in men who have sex with men.[25] 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. Although none of the participants in either arm developed anal cancer during the 3-year follow-up period, 5 cases of grade 2/3 vaccine strain–associated AIN in the vaccine arm and 24 cases in the placebo arm in the per-protocol population, giving an observed efficacy of 77.5% (95% CI, 39.6–93.3). Because high-grade AINs are known to have the ability to progress to anal cancer,[15,16] these results suggest that use of the quadrivalent HPV vaccine in men who have sex with men is likely to significantly reduce the risk of anal cancer in this population.

A bivalent HPV vaccine against HPV-16 and -18 is also available.[26] 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).[27] The effect of this vaccine on precancerous anal lesions has not yet been reported.

Local Radiation for Metastatic Disease

For the 2012 version of the NCCN Guidelines for Anal Carcinoma, the panel added local radiation therapy (RT) as an option for treatment of patients with metastatic disease (see ANAL-1 and ANAL-2). During the review of the 2011 NCCN Guidelines that preceded the 2012 panel meeting, a comment was made that many clinicians might consider adding RT for local control in the case of a symptomatic bulky primary and metastatic disease. Although none of the panelists

disagreed with the appropriateness of using local RT as palliation in these cases, they disagreed on when it is best given. Many panelists stated that they prefer to administer chemotherapy first, because many patients have rapid relief of symptoms as their primary tumor responds to the systemic treatment. They pointed out that chemotherapy-naïve patients, in particular, have very high response rates to chemotherapy. These panel members would reserve RT with additional chemotherapy for patients whose disease failed to respond to systemic therapy, sparing many patients the morbidities associated with RT. Other panelists commented that they see higher response rates to combined modality chemotherapy with radiation (chemoRT) than to chemotherapy alone. These panelists would therefore prefer to begin treatment of symptomatic patients with chemoRT to provide relief of extreme rectal discomfort as quickly as possible.

The panel listed the new recommendation as "cisplatin-based chemotherapy +/- RT" for treatment of metastatic disease. They added a statement to the footnote associated with this recommendation to stress that this RT is for the primary tumor, not the metastases. The panel also emphasized that RT, if given, is intended for palliation only and is best administered with 5-fluorouracil (5-FU)–based chemotherapy with a platinum agent.

Updates to Principles of Radiation

The panel made 2 significant updates to the Principles of Radiation section of the 2012 NCCN Guidelines for Anal Carcinoma (see ANAL-B).

Radiation Delivery Technique

During the review that preceded the panel meeting, a reviewer questioned the continued listing of the anteroposterior-posteroanterior (AP-PA) technique for radiation delivery. The panel agreed that this recommendation is outdated and that the AP-PA technique is no longer the standard of care. The original recommendation was based on the RTOG 98-11 trial, the protocol for which was written more than 10 years ago.[28] That trial also allowed for treatment using multifield techniques, and the panel unanimously agreed that multifield technique is preferred over the AP-PA technique.

PET/CT for Treatment Planning

The panel also discussed the use of PET/CT for RT planning, based on a reviewer's comment. Considerable controversy surrounded this issue. Importantly, the uptake of the radiolabeled sugar (18F-fluorodeoxyglucose) used in PET/CT scans is not specific for malignancy and can be taken up by normal tissue, for instance during inflammation, infection, or injury.[29] Some panelists expressed concern that a suspicious lymph node might appear on PET/CT that had not been palpated. They stated that these nodes cannot be assumed nor are likely to be clinically significant (containing metastatic disease), and that excisional biopsy may lead to a delay of treatment. Other panelists disagreed that a small excision would significantly delay chemoRT. Because the radiation oncologists on the panel pointed out that PET/CT can provide valuable information to aid in treatment plans, and because all panelists agreed that a core needle biopsy could be performed on suspicious nodes without delaying treatment initiation, the panel decided to add the statement that "PET/CT should be considered for treatment planning."

PET/CT for Assessment of Treatment Response

The panel discussed the use of PET/CT during 3 different stages in the management of anal carcinoma: workup, response assessment, and treatment planning. As discussed in the section on Updates to Principles of Radiation, the panel agreed that PET/CT should be considered for RT planning. In addition, the panel reaffirmed that PET/CT scans can be considered in the workup of anal canal cancer but are not appropriate for use during the workup of anal margin cancer.

The discussion about PET/CT use for the assessment of treatment response engendered some controversy. As with the use of PET/CT for treatment planning, some panelists are concerned about the risks associated with the identification of positive lymph nodes that had not been found on clinical examination. The panelists agreed that these nodes cannot be assumed to be clinically significant, and many panelists expressed concern that some patients may be inappropriately given salvage surgery for responding disease that is mistaken for progressive or persistent disease. Therefore, the panel decided not to recommend PET/CT for the assessment of treatment response.

Summary of the 2012 NCCN Guidelines for Anal Carcinoma Recommendations

The NCCN Anal Carcinoma 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 for 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, because salvage is possible. Patients with biopsy-proven evidence of locoregional progressive or recurrent disease after primary treatment should undergo an abdominoperineal resection. 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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