Anal Carcinoma, Version 2.2023

Al B. Benson III, MD[1,*]; Alan P. Venook, MD[2,*]; Mahmoud M. Al-Hawary, MD[3]; Nilofer Azad, MD[4]; Yi-Jen Chen, MD, PhD[5]; Kristen K. Ciombor, MD[6]; Stacey Cohen, MD[7,*]; Harry S. Cooper, MD[8]; Dustin Deming, MD[9,*]; Ignacio Garrido-Laguna, MD, PhD[10]; Jean L. Grem, MD[11]; J. Randolph Hecht, MD[12]; Sarah Hoffe, MD[13]; Joleen Hubbard, MD[14]; Steven Hunt, MD[15]; Hisham Hussan, MD[16]; William Jeck, MD[17]; Kimberly L. Johung, MD, PhD[18]; Nora Joseph, MD[3]; Natalie Kirilcuk, MD[19]; Smitha Krishnamurthi, MD[20]; Jennifer Maratt, MD[21]; Wells A. Messersmith, MD[22]; Jeffrey Meyerhardt, MD, MPH[23]; Eric D. Miller, MD, PhD[24,*]; Mary F. Mulcahy, MD[1]; Steven Nurkin, MD, MS[25]; Michael J. Overman, MD[26,*]; Aparna Parikh, MD[27]; Hitendra Patel, MD[28]; Katrina Pedersen, MD, MS[15,*]; Leonard Saltz, MD[29]; Charles Schneider, MD[30]; David Shibata, MD[31,*]; John M. Skibber, MD[26]; Constantinos T. Sofocleous, MD, PhD[29]; Eden Stotsky-Himelfarb, BSN, RN[4]; Anna Tavakkoli, MD, MSc[32]; Christopher G. Willett, MD[17]; Grant Williams, MD, MSPH[33,*]; Frankie Algieri[34]; Lisa Gurski, PhD[34]; and Katie Stehman, PA-C, MMS[34]

ABSTRACT

This discussion summarizes the NCCN Clinical Practice Guidelines for managing squamous cell anal carcinoma, which represents the most common histologic form of the disease. A multidisciplinary approach including physicians from gastroenterology, medical oncology, surgical oncology, radiation oncology, and radiology is necessary. Primary treatment of perianal cancer and anal canal cancer are similar and include chemoradiation in most cases. Follow-up clinical evaluations are recommended for all patients with anal carcinoma because additional curative-intent treatment is possible. Biopsy-proven evidence of locally recurrent or persistent disease after primary treatment may require surgical treatment. Systemic therapy is generally recommended for extrapelvic metastatic disease. Recent updates to the NCCN Guidelines for Anal Carcinoma include staging classification updates based on the 9th edition of the AJCC Staging System and updates to the systemic therapy recommendations based on new data that better define optimal treatment of patients with metastatic anal carcinoma.

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[1]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [2]UCSF Helen Diller Family Comprehensive Cancer Center; [3]University of Michigan Rogel Cancer Center; [4]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [5]City of Hope National Medical Center; [6]Vanderbilt-Ingram Cancer Center; [7]Fred Hutchinson Cancer Center; [8]Fox Chase Cancer Center; [9]University of Wisconsin Carbone Cancer Center; [10]Huntsman Cancer Institute at the University of Utah; [11]Fred & Pamela Buffett Cancer Center; [12]UCLA Jonsson Comprehensive Cancer Center; [13]Moffitt Cancer Center; [14]Mayo Clinic Cancer Center; [15]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [16]UC Davis Comprehensive Cancer Center; [17]Duke Cancer Institute; [18]Yale Cancer Center/Smilow Cancer Hospital; [19]Stanford Cancer Institute; [20]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; [21]Indiana University Melvin and Bren Simon Comprehensive Cancer Center; [22]University of Colorado Cancer Center; [23]Dana-Farber Brigham and Women's Cancer Center; [24]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [25]Roswell Park Comprehensive Cancer Center; [26]The University of Texas MD Anderson Cancer Center; [27]Massachusetts General Hospital Cancer Center; [28]UC San Diego Moores Cancer Center; [29]Memorial Sloan Kettering Cancer Center; [30]Abramson Cancer Center at the University of Pennsylvania; [31]The University of Tennessee Health Science Center; [32]UT Southwestern Simmons Comprehensive Cancer Center; [33]O'Neal Comprehensive Cancer Center at UAB; and [34]National Comprehensive Cancer Network

*Discussion Writing Committee Member.

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 of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

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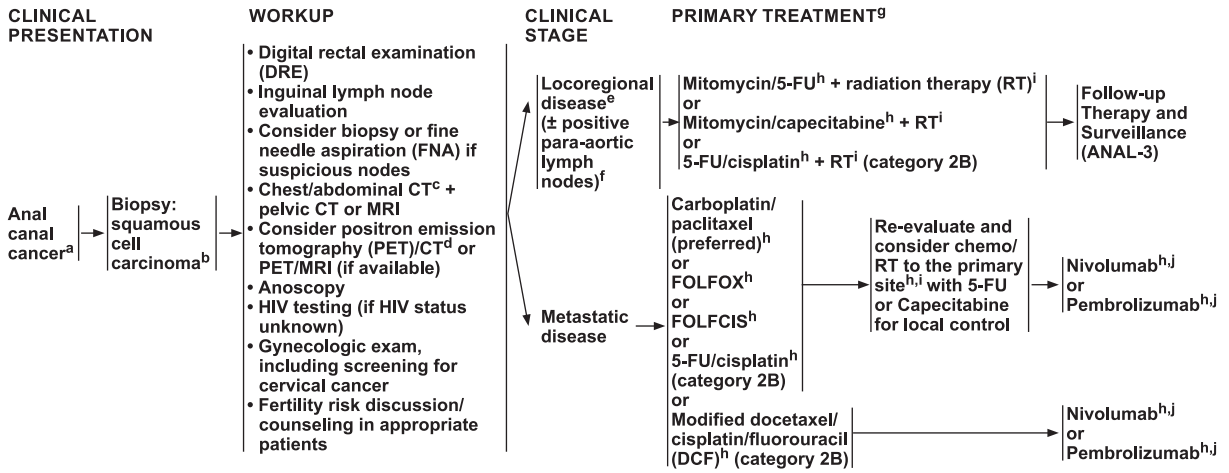
The complete NCCN Guidelines for Anal Carcinoma are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

Disclosures for the NCCN Anal Carcinoma Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Anal Carcinoma Panel members can be found on page 677. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.



[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: Cutaneous†; for adenocarcinoma, see the NCCN Guidelines for Rectal Cancer†.
[c] CT should be with IV and oral contrast. Pelvic MRI with contrast. If intravenous iodinated contrast material is contraindicated due to significant contrast allergy or renal failure, then MRI examination of the abdomen and pelvis with IV gadolinium-based contrast agent (GBCA) can be obtained in select patients (see American College of Radiology contrast manual: https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf). Intravenous contrast is not required for the chest CT.
[d] PET/CT scan does not replace a diagnostic CT. PET/CT performed skull base to mid-thigh.
[e] Principles of Surgery (ANAL-A*).
[f] Para-aortic nodes that can be included in a radiation field.
[g] Modifications to cancer treatment should not be made solely based on HIV status. See NCCN Guidelines for Cancer in People with HIV†.
[h] Principles of Systemic Therapy (ANAL-B).
[i] Principles of Radiation Therapy (ANAL-C*).
[j] NCCN Guidelines for the Management of Immunotherapy-Related Toxicities†.

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ANAL-1

Overview

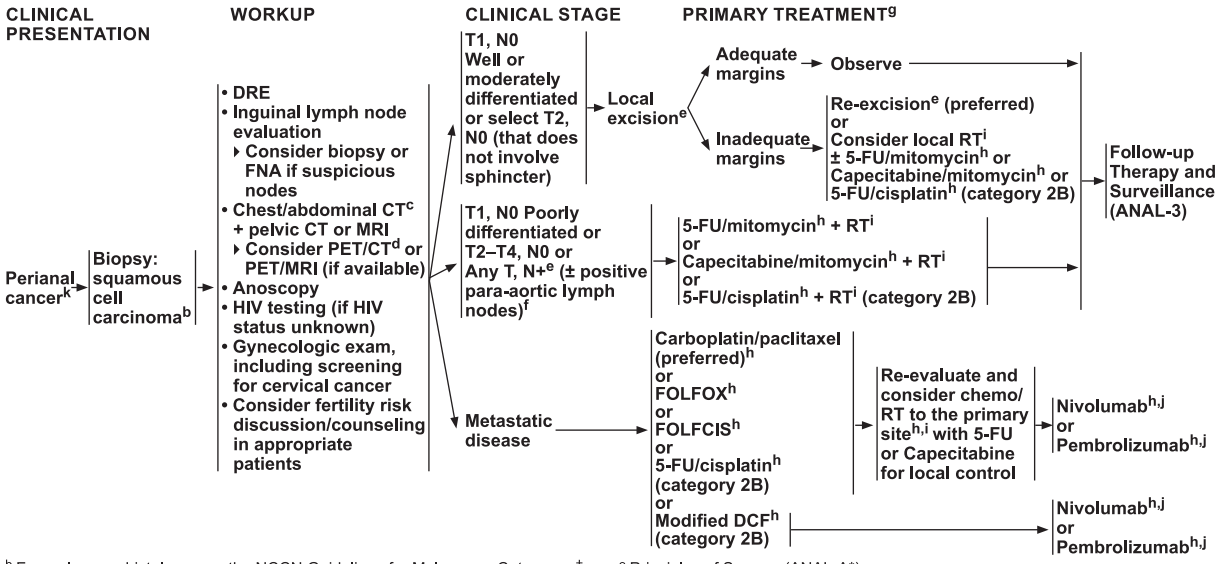
An estimated 9,760 new cases (3,180 male and 6,580 female) of anal cancer involving the anus, anal canal, or anorectum will occur in the United States in 2023, accounting for approximately 2.8% of digestive system cancers.[1] Experts project that 1,870 deaths due to anal cancer will occur in the United States in 2023.[1] Although considered to be a rare cancer, the incidence rate of invasive anal carcinoma in the United States increased by approximately 1.9-fold for males and 1.5-fold for females between the periods of 1973–1979 to 1994–2000 and has continued to increase since that time.[2–4] According to an analysis of SEER data, the incidence of anal squamous carcinoma increased at a rate of 2.9% per year from 1992 to 2001.[5] Supporting this, an analysis of the US Cancer Statistics dataset reported an annual increase of 2.7% between 2001 and 2015, with the greatest increases in age groups ≥50 years,[6] while the National Program of Cancer Registries and SEER programs showed similar trends from 2001 to 2016, with an annual percent change of 2.1 (95% CI, 1.7–2.5) overall, and 2.8 (95% CI, 2.5–3.1) in those ≥50 years of age.[7] Increases in incidence of anal cancer during that time frame were especially noted for women ≥50 years. Anal cancer mortality rates (2001–2016) also rose, with an average increase of 3.1% per year.[6]

This discussion summarizes the NCCN Clinical Practice Guidelines for managing squamous cell anal carcinoma, which represents the most common histologic form of the disease. Other groups have also published guidelines for the management of anal squamous cell carcinoma.[8–10] Other types of cancers occurring in the anal region 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.

Risk Factors

Anal carcinoma is associated with human papillomavirus (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.[11–19]

The association between anal carcinoma and persistent infection with a high-risk form of HPV (eg, HPV-16; HPV-18) is especially strong.[12,20,21] 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,



[b] For melanoma histology, see the NCCN Guidelines for Melanoma: Cutaneous†; for adenocarcinoma, see the NCCN Guidelines for Rectal Cancer†.
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[h] Principles of Systemic Therapy (ANAL-B).
[i] Principles of Radiation Therapy (ANAL-C*).
[j] NCCN Guidelines for the Management of Immunotherapy-Related Toxicities†.
[k] The perianal region starts at the anal verge and includes the perianal skin over a 5-cm radius from the squamous mucocutaneous junction.

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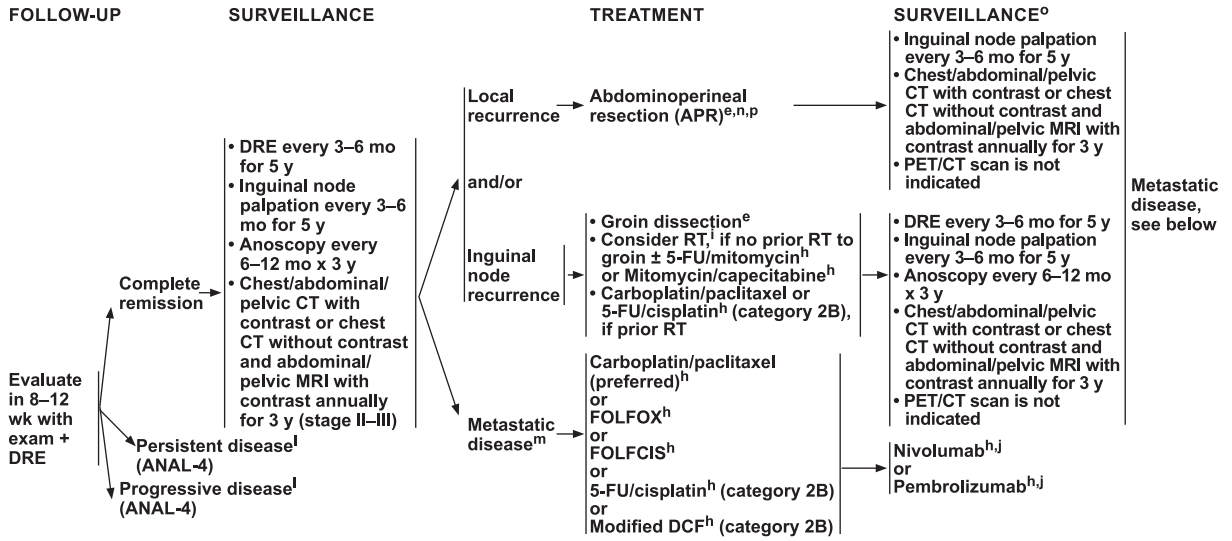
with HPV-16 detected in 73% of them. In contrast, high-risk HPV was not detected in any of the rectal adenocarcinoma specimens analyzed.[12] In addition, results of a systematic review of 35 peer-reviewed anal cancer studies that included HPV DNA testing results published up until July 2007 showed the prevalence of HPV-16/18 to be 72% in patients with invasive anal cancer.[21] Population and registry studies have found similar HPV prevalence rates in anal cancer specimens.[22,23] A 2012 report from the US CDC estimated that 86%–97% of cancers of the anus are attributable to HPV infection.[24]

Suppression of the immune system by the use of immunosuppressive drugs or HIV infection likely facilitates persistence of HPV infection of the anal region.[25,26] Studies have shown that people living with HIV (PLWH) have an approximately 15- to 35-fold increased likelihood of being diagnosed with anal cancer compared with the general population.[27–30] In PLWH, the standardized incidence rate of anal carcinoma per 100,000 person-years in the United States, estimated to be 19.0 in 1992 through 1995, increased to 78.2 during 2000 through 2003.[26] This result likely reflects both the survival benefits of modern antiretroviral therapy (ART) and the lack of an impact of ART on the progression of anal cancer precursors. The incidence rate of anal cancer has been reported to be 131 per 100,000 person-years in males who have sex with males (MSM) with HIV in North America, and in the range of 3.9 to 30 per 100,000 person-years in females living with HIV.[31,32] An analysis of the French Hospital Database on HIV showed a highly elevated risk of anal cancer in PLWH, including in those who were on therapy and whose CD4+T-cell counts were high.[33] The data also revealed an increasing incidence of anal cancer in the PLWH population over time. However, some evidence suggests that prolonged ART (>24 months) may be associated with a decrease in the incidence of high-grade anal intraepithelial neoplasia (AIN).[34]

A meta-analysis of anal cancer incidence across risk groups found that the incidence of anal cancer in solid organ transplant recipients increased both by age and years since transplant.[19] Incidence rates rose from 0.0 and 3.1 per 100,000 person-years in men and women >30 years to 13.4 and 25.9 per 100,000 person-years in men and women ≥60 years. Years since transplant appeared to identify an even higher risk than age, with an incidence rate of 24.5 and 29.6 per 100,000 person-years in males and females ≥10 years posttransplant, respectively. This study also assessed risk in patients with autoimmune diseases and found incidence rates of 10, 6, and 3 per 100,000 person-years for patients with systemic



[e] Principles of Surgery (ANAL-A*).
[h] Principles of Systemic Therapy (ANAL-B).
[i] Principles of Radiation Therapy (ANAL-C*).
[j] NCCN Guidelines for the Management of Immunotherapy-Related Toxicities†.
[l] 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 RT 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 from the start of treatment. James RD, et al. Lancet Oncol 2013;14:516-524.
[m] Palliative RT may be considered in symptomatic patients. Records of previous RT should be carefully reviewed and considered prior to potential re-irradiation of previously irradiated fields. Principles of Radiation Therapy (ANAL-C*).
[n] Consider muscle flap reconstruction.
[o] Principles of Survivorship (ANAL-D*)
[p] Consider the use of immunotherapy (nivolumab or pembrolizumab) (category 2B) before proceeding to APR. Institutional experience has demonstrated that some patients receive a good response and can avoid surgery.

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lupus erythematosus, ulcerative colitis, and Crohn's disease, respectively.

Risk Reduction

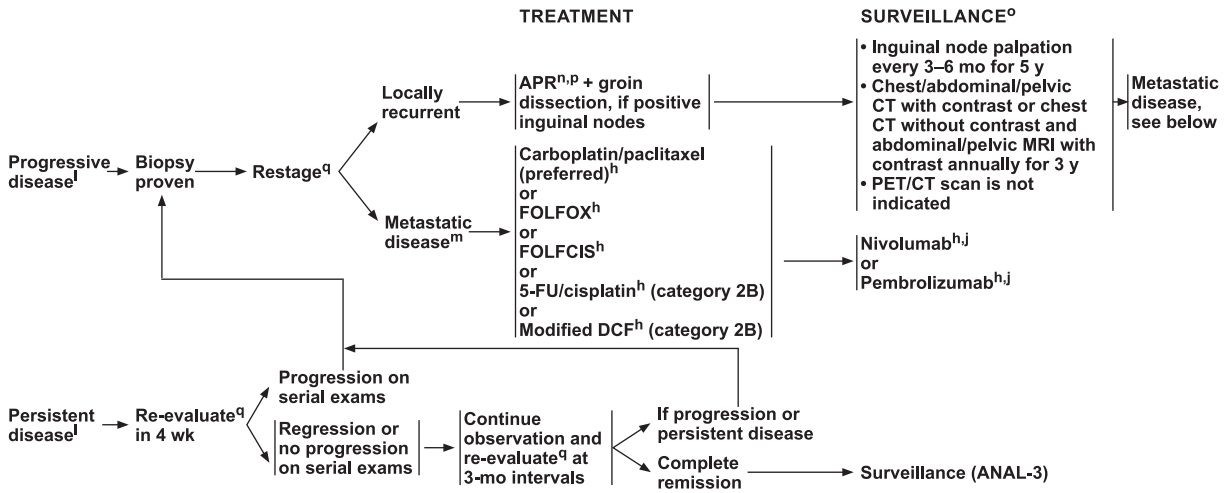
High-grade AIN can be a precursor to anal cancer,[35–38] and treatment of high-grade AIN may prevent the development of anal cancer.[39] AIN can be identified by cytology, HPV testing, digital rectal examination (DRE), high-resolution anoscopy, and/or biopsy.[40,41] The spontaneous regression rate of high-grade AIN is not known, and estimates suggest that the progression rates of AIN to cancer in MSM might be quite low.[42–45] However, a prospective cohort study of 550 HIV-positive MSM found the rate of conversion of high-grade AIN to anal cancer to be 18% (7/38) at a median follow-up of 2.3 years, despite treatment.[38] In this study, screening led to the identification of high-grade AIN and/or anal cancer in 8% of the cohort.

Routine screening for AIN in individuals at high risk such as PLWH or MSM is controversial, because randomized controlled trials showing that such screening programs are efficacious at reducing anal cancer incidence and mortality are lacking, whereas the potential benefits are quite large.[46–52] Systematic reviews and meta-analyses have suggested that anal cytology is effective in detection of AIN, particularly for individuals at high risk.[53–55] Most guidelines do not recommend anal cancer screening even in people at high risk at this time or state that there may be some benefit with anal cytology.[51,56] Few guidelines recommend screening for anal cancer with DRE in PLWH.[57]

Guidelines for the treatment of AIN have been developed by several groups, including the American Society of Colon and Rectal Surgeons (ASCRS).[51,56,58,59] Treatment recommendations vary widely because high-level evidence in the field is limited.[58] One randomized controlled trial in 246 HIV-positive MSM found that electrocautery was superior to both topical imiquimod and topical fluorouracil in the treatment of AIN overall.[60] The subgroup with perianal AIN, as opposed to intra-anal AIN, appeared to show better response to imiquimod. Regardless of treatment, recurrence rates were high, and careful follow-up is likely needed. A large randomized phase III trial compared topical or ablative treatment with active monitoring in 4,459 PLWH with high-grade AIN.[61] With a median follow-up of 25.8 months, 9 cases of anal cancer were diagnosed in the treatment group compared with 21 cases in the active monitoring group. The rate of progression to anal cancer was 57% lower with treatment compared with active monitoring (95% CI, 6–80; P=.03).

HPV Immunization

A quadrivalent HPV vaccine is available and has been shown to be effective in preventing persistent cervical



[h] Principles of Systemic Therapy (ANAL-B).
[j] NCCN Guidelines for the Management of Immunotherapy-Related Toxicities†.
[l] 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 RT 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 from the start of treatment. James RD, Lancet Oncol 2013;14:516-524.
[m] Palliative RT may be considered in symptomatic patients. Records of previous RT should be carefully reviewed and considered prior to potential re-irradiation of previously irradiated fields. Principles of Radiation Therapy (ANAL-C*).
[n] Consider muscle flap reconstruction.
[o] Principles of Survivorship (ANAL-D*).
[p] Consider the use of immunotherapy (nivolumab or pembrolizumab) (category 2B) before proceeding to APR. Institutional experience has demonstrated that some patients receive a good response and can avoid surgery.
[q] Use imaging studies as per initial workup.

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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.[62–64] The vaccine has also been shown to be efficacious in young males at preventing genital lesions associated with HPV-6, -11, -16, or -18 infection.[65] A 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 MSM.[66] In this study, 602 healthy MSM 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, 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 is known to have the ability to progress to anal cancer,[35–37] these results suggest that use of the quadrivalent HPV vaccine in MSM may reduce the risk of anal cancer in this population.

A bivalent HPV vaccine against HPV-16 and -18 is also available.[67] In a randomized, double-blind controlled trial of female patients in Costa Rica, the vaccine was 83.6% effective against initial anal HPV-16/18 infection (95% CI, 66.7–92.8).[68,69] It has also been shown to be effective at preventing high-grade cervical intraepithelial neoplasia in young people.[70] The effect on precancerous anal lesions has not yet been reported.

A 9-valent HPV vaccine is also now available, protecting against HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58.[71] Targeting the additional strains over the quadrivalent vaccine is predicted to prevent an additional 464 cases of anal cancer annually.[72] This vaccine was compared with the quadrivalent vaccine in an international, randomized phase IIb–III study that included more than 14,000 female patients.[73] The 9-valent vaccine was noninferior to the quadrivalent vaccine for antibody response to HPV-6, -11, -16, and -18 and prevented infection and disease related to the other viral strains included in the vaccine. The calculated efficacy of the 9-valent vaccine was 96.7% (95% CI, 80.9–99.8) for the prevention of high-grade cervical, vulvar, or vaginal disease related to those strains.

The Advisory Committee on Immunization Practices (ACIP) recommends routine use of the 9-valent vaccine in children aged 11 and 12 years, as well as catch-up vaccination for individuals through 26 years of age who have not been previously vaccinated.[74–77] The American Academy of Pediatrics concurs with this vaccination schedule.[78] ASCO released a statement regarding HPV vaccination for cancer prevention with the goal of increasing vaccine update.[79] In 2018, the FDA expanded use of the 9-valent vaccine to include individuals aged 27

PRINCIPLES OF SYSTEMIC THERAPY – LOCALIZED CANCER

Chemo/RT for Localized Cancer	
Preferred Regimens	**Other Recommended Regimens**
• 5-FU + mitomycin + RT • Capecitabine + mitomycin + RT	• 5-FU + cisplatin + RT

Systemic Therapy Regimens and Dosing – Localized Cancer

- 5-FU + mitomycin + RT[1,2]
  - Continuous infusion 5-FU 1000 mg/m²/day IV days 1–4 and 29–32
    Mitomycin 10 mg/m² IV bolus days 1 and 29 (capped at 20 mg) with RT
    or
  - Continuous infusion 5-FU 1000 mg/m²/day IV days 1–4 and 29–32
    Mitomycin 12 mg/m² on day 1 (capped at 20 mg) with RT
- Capecitabine + mitomycin + RT[3,4]
  - Capecitabine 825 mg/m² PO BID[a]
    Mitomycin 10 mg/m² days 1 and 29 (capped at 20 mg) with RT
    or
  - Capecitabine 825 mg/m² PO BID days 1–5[a]
    Mitomycin 12 mg/m² IV bolus day 1 (capped at 20 mg) with RT
- 5-FU + cisplatin + RT[5]
  - Cisplatin 75 mg/m² day 1
    Continuous infusion 5-FU 1000 mg/m²/day IV days 1–4
    Repeat every 4 weeks with RT

[a] Monday–Friday, on each day that RT is given throughout the duration of RT (typically 28–30 treatment days depending on stage).

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through 45 years,[80] and the ACIP voted in 2019 to recommend vaccination, based on shared clinical decision-making, for individuals in this age range who are not adequately vaccinated.

Anatomy/Histology

The anal region is comprised of the anal canal and the perianal region, dividing anal cancers into 2 categories. The anal canal is the more proximal portion of the anal region. The 9th Edition of the AJCC Cancer Staging Manual includes a definition of anal canal cancer as tumors that develop from mucosa that cannot be entirely seen when the buttocks are gently pressed.[81] The corresponding definition for perianal cancer is tumors that (1) arise within the skin distal to or at the squamous mucocutaneous junction; (2) can be visualized completely when the buttocks are gently pressed; and (3) are within 5 cm of the anus.[81] Various other 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.[14,82] The anal margin, conversely, is lined with skin. 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.[14,82] 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 anorectal ring and extends to the anal verge (ie, squamous mucocutaneous junction with the perianal skin).[83]

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.[14,82,84] 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.[82] Tumors can involve both the anal canal and the anal margin.

Pathology

Most primary cancers of the anal canal are of squamous cell histology.[82] The second edition of the WHO classification system of anal carcinoma designated all squamous cell

PRINCIPLES OF SYSTEMIC THERAPY – METASTATIC CANCER

First-Line Therapy for Metastatic Cancer		Subsequent Therapy
Preferred Regimens	Other Recommended Regimens	Preferred Regimens
• Carboplatin + paclitaxel	• 5-FU + cisplatin • FOLFCIS • mFOLFOX6[b] • Modified DCF	• Nivolumab • Pembrolizumab if neither previously received

Chemo/RT to the Primary Site for Local Control
• 5-FU + RT • Capecitabine + RT

Systemic Therapy Regimens and Dosing – Metastatic Cancer

- Carboplatin + paclitaxel
  - Carboplatin AUC 5 IV day 1
    Paclitaxel 175 mg/m² IV day 1
    Repeat every 21 days[6]
    or
  - Carboplatin AUC 5 IV day 1
    Paclitaxel 80 mg/m² IV days 1, 8, 15
    Repeat every 28 days[7]
- 5-FU + cisplatin
  - Cisplatin 60 mg/m² day 1
    Continuous infusion 5-FU 1000 mg/m²/day
    IV days 1–4
    Repeat every 3 weeks[8]
    or
  - Cisplatin 75 mg/m² day 1
    Continuous infusion 5-FU 750 mg/m²/day
    IV days 1–5
    Repeat every 4 weeks[9]
- FOLFCIS[10]
  Cisplatin 40 mg/m² IV over 30 minutes on day 1*
  Leucovorin 400 mg/m² IV day 1*
  5-FU 400 mg/m² IV bolus on day 1,
  then 1000 mg/m²/day x 2 days
  (total 2000 mg/m² over 46–48 hours)
  IV continuous infusion
  Repeat every 2 weeks
  *Cisplatin and leucovorin are given concurrently
- mFOLFOX6[11]
  Oxaliplatin 85 mg/m² IV day 1
  Leucovorin 400 mg/m² IV day 1
  5-FU 400 mg/m² IV bolus on day 1,
  then 1200 mg/m²/day x 2 days
  (total 2400 mg/m² over 46–48 hours)
  IV continuous infusion
  Repeat every 2 weeks
- Modified DCF[12]
  Docetaxel 40 mg/m² IV day 1
  Cisplatin 40 mg/m² IV day 1
  Fluorouracil 1200 mg/m²/day x 2 days
  (total 2400 mg/m² over 46–48 hours)
  Repeat every 2 weeks
- Nivolumab[13]
  Nivolumab 240 mg IV every 2 weeks
  or Nivolumab 3 mg/kg IV every 2 weeks
  or Nivolumab 480 mg IV every 4 weeks
- Pembrolizumab[14]
  Pembrolizumab 200 mg IV every 3 weeks
  or Pembrolizumab 2 mg/kg IV every 3 weeks
  or Pembrolizumab 400 mg IV every 6 weeks

Chemo/RT
- 5-FU + RT
  - 5-FU 225 mg/m² IV over 24 hours (continuous infusion) daily on days 1–5 or 1–7 for 5 weeks with RT[15-17]
- Capecitabine + RT
  - Capecitabine 825 mg/m² PO twice daily on days 1–5 with RT[18-20,a]

[a] Monday–Friday, on each day that RT is given throughout the duration of RT (typically 28–30 treatment days depending on stage).
[b] Discontinuation of oxaliplatin should be strongly considered after 3 to 4 months of therapy (or sooner for unacceptable neurotoxicity) while maintaining other agents until time of progression. Oxaliplatin may be reintroduced if it was discontinued for neurotoxicity rather than for disease progression.

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carcinoma variants of the anal canal as cloacogenic and identified subtypes as large-cell keratinizing, large-cell nonkeratinizing (transitional), or basaloid.[85] It has been reported that squamous cell cancers in the more proximal region of the anal canal are more likely to be nonkeratinizing and less differentiated.[14] 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,[86,87] and all subtypes have been included under a single generic heading of "squamous cell carcinoma."[81,86] 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 nonkeratinizing tumors; it has been reported that both keratinizing and nonkeratinizing tumors have a similar natural history and prognosis[86]; and a mixture of cell types frequently characterize histologic specimens of squamous cell carcinomas of the anal canal.[82,86,88] 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.[82]

Perianal squamous cell carcinomas are more likely than those of the anal canal to be well-differentiated and keratinizing large-cell types,[89] but they are not characterized in the guidelines according to cell type. The presence of skin appendages (eg, hair follicles, sweat glands) in perianal tumors can distinguish them from anal canal tumors. However, it is not always possible to distinguish between anal canal and perianal 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.[81,82] 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. Therefore, distal anal cancers present with a higher incidence of inguinal node metastases. Because 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.[82]

The College of American Pathologists publishes protocols for the pathologic examination and reporting of anal tumors following excision or transabdominal resection. The most recent updates were made in April 2020 and February 2020, respectively.[90,91]

Staging

The TNM staging system for anal canal cancer developed by the AJCC is detailed in the guidelines.[81] Because 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. 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," page 660).

In the past, these guidelines have used the AJCC TNM skin cancer system for the staging of perianal cancer because the 2 types of cancers have a similar biology. However, the seventh edition of the AJCC Cancer Staging Manual included substantial changes to the cutaneous squamous cell carcinoma stagings,[92] making them much less appropriate for the staging of perianal cancers. Furthermore, many perianal cancers have involvement of the anal canal or have high-grade, precancerous 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 PLWH, could be significantly undertreated. For these reasons, these guidelines use the AJCC anus staging system for both anal canal and perianal tumors.

The prognosis of anal carcinoma is related to the size of the primary tumor and the presence of lymph node metastases.[14] According to the SEER database,[93] 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.[93] 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.[94] 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.[94] An analysis of more than 600 patients with nonmetastatic anal carcinoma from the RTOG 98-11 trial also found that the tumor and node categories impacted clinical outcomes such as overall survival (OS), disease-free survival (DFS), and colostomy failure, with the worst prognoses for patients with T4,N0 and T3–4,N+ disease.[95]

By the eighth edition of the AJCC Cancer Staging Manual, the former N2 and N3 categories by locations of positive nodes were removed.[96] New categories of N1a, N1b, and N1c were defined and then further refined in the 9th edition.[81] N1a now represents metastasis in inguinal, mesorectal, superior rectal, internal iliac, or obturator nodes. N1b represents metastasis in external iliac nodes. N1c represents metastasis in external iliac with any N1a nodes. 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 biopsy of inguinal nodes can be considered 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 less than 0.5 cm,[97] suggesting that routine radiologic evaluation with CT and PET/CT scan may not be reliable in the determination of lymph node involvement (discussed in more detail in "Clinical Presentation/Evaluation," page 660).

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 DFS in patients with anal cancer treated with 5-FU and radiation and either mitomycin or cisplatin.[98] Male sex, positive nodes, and tumor size >5 cm were independently prognostic for worse OS. A secondary analysis of this trial found that tumor diameter could also be prognostic for colostomy rate and time to colostomy.[99] 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.[100] Similarly, 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 OS.[101]

Data suggest that HPV- and/or p16-positivity are prognostic for improved OS in patients with anal carcinoma.[102–105] In a retrospective study of 143 tumor samples, p16-positivity was an independent prognostic factor for OS (hazard ratio [HR], 0.07; 95% CI, 0.01–0.61; P=.016).[103] Another study involving 95 patients found similar results.[102]

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.[14] 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 perianal cancer are very similar (see ANAL-1 and ANAL-2, pages 654 and 655).

The panel recommends a thorough examination/evaluation, including a careful DRE, an anoscopic examination, and palpation of the inguinal lymph nodes, with fine-needle aspiration 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. Because veins of the anal region are part of the venous network associated with systemic circulation,[82] chest CT scan is performed to evaluate for pulmonary metastasis. Gynecologic examination, including cervical cancer screening, is suggested due to the association of anal cancer and HPV.[12] A discussion of infertility risks and counseling on fertility preservation, if appropriate, should be performed before the start of treatment.

HIV testing should be performed if the patient's HIV status is unknown, because the risk of anal carcinoma has been reported to be higher in PLWH.[16] Furthermore, about 13% of people in the United States who are infected with HIV are not aware of their infection status,[106] and individuals who are unaware of their HIV-positive status do not receive the clinical care they need to reduce HIV-related morbidity and mortality and may unknowingly transmit HIV.[107] HIV testing may be particularly important in patients with cancer, because identification of HIV infection has the potential to improve clinical outcomes.[108] The CDC recommends HIV screening for all patients in all health care settings unless the patient declines testing (opt-out screening).[109]

PET/CT scanning, or PET/MRI if available, can be considered to verify staging before treatment. 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.[110–115] A systematic review and meta-analysis of 7 retrospective and 5 prospective studies calculated pooled estimates of sensitivity and specificity for detection of lymph node involvement by PET/CT to be 56% (95% CI, 45%–67%) and 90% (95% CI, 86%–93%), respectively.[111] A more recent meta-analysis of 17 clinical studies calculated the pooled sensitivity and specificity for detection of lymph node involvement by PET/CT at 93% and 76%, respectively.[116] The use of PET or PET/CT led to upstaging in 5%–38% of patients and downstaging in 8%–27% of patients. Another systematic review and meta-analysis found PET/CT to change nodal status and TNM stage in 21% and 41% of patients, respectively.[117] PET/CT results can also impact radiation therapy planning, as systematic reviews and meta-analyses have shown that treatment plan modifications occurred in 12%–59% of patients based on PET/CT results.[116,118] The panel does not consider PET/CT to be a replacement for a diagnostic CT.

According to a systematic review and meta-regression, the proportion of patients who are node-positive by pretreatment clinical imaging has increased from 15.3% (95% CI, 10.5–20.1) in 1980 to 37.1% (95% CI, 34.0–41.3) in 2012 ($P<.0001$), likely resulting from the increased use of more sensitive imaging techniques.[119] This increase in lymph node positivity was associated with improvements in OS for both the lymph-node–positive and the lymph-node–negative groups. Because the proportion of patients with T3/T4 disease remained constant and therefore disease is not truly being diagnosed at more advanced stages over time, the authors attribute the improved OS results to the "Will Rogers effect": The average survival of both groups increases as patients with worse-than-average survival in the node-negative group migrate to the node-positive group, in which their survival is better than average. Thus, the survival of individuals has not necessarily improved over time, even though the average survival of each group has. Using simulated scenarios, the authors further conclude that the actual rate of true node-positivity is likely less than 30%, suggesting that it is possible some patients are being misclassified and overtreated with the increased use of highly sensitive imaging.

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%–70%, and the morbidity with a permanent colostomy was considerable.[14] In 1974, Nigro et al[120] observed complete tumor regression in some patients with anal carcinoma treated with preoperative 5-FU–based concurrent chemotherapy and RT (chemoRT) including either mitomycin or porfiromycin, suggesting that it might be possible to cure anal carcinoma without surgery and permanent colostomy. Subsequent nonrandomized studies using similar regimens and varied doses of chemoRT provided support for this conclusion.[121,122] 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.[17] Summaries of clinical trials involving patients with anal cancer have been presented,[123,124] and several key trials are discussed subsequently.

Chemotherapy

A phase III study from the EORTC compared the use of chemoRT (5-FU + 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.[100] The United Kingdom Coordinating Committee on Cancer Research randomized ACT I trial confirmed that chemoRT with 5-FU and mitomycin was more effective in controlling local disease than RT alone (relative risk [RR], 0.54; 95% CI, 0.42–0.69; $P<.0001$), although no significant differences in OS were observed at 3 years.[125] A published follow-up study involving these patients showed that a clear benefit of chemoRT remains after 13 years, including a benefit in OS.[126] 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 systematic review and meta-analysis comparing outcomes in patients with stage I anal carcinoma found an increased 5-year OS in patients treated with chemoRT compared with RT alone (RR, 1.18; 95% CI, 1.10–1.26; $P<.00001$) but no significant difference in 5-year DSF (RR, 1.01; 95% CI, 0.92–1.11; $P=.87$.[127] Conversely, a population-based cohort analysis of Medicare-eligible (>65 years of age or with an eligible disability) patients with stage I anal cancer showed no difference in OS, cause-specific survival, colostomy-free survival, or DFS with chemoRT versus RT alone after adjustment using propensity score methods.[128] Therefore, this study concludes that RT alone may allow for adequate oncologic outcomes for highly select patients with stage I anal cancer, although it is important to note that this study did not differentiate between anal canal and perianal cancers. Current NCCN Guidelines recommendations are noted in subsequent sections ("Recommendations for the Primary Treatment of Anal Canal Cancer," page 666 and "Recommendations for the Primary Treatment of Perianal Cancer," page 667).

A few studies have addressed the efficacy and safety of specific chemotherapeutic agents in the chemoRT regimens used in the treatment of anal carcinoma.[98,129,130] 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.[130] The OS rate at 4 years was the same for the 2 groups, however, reflecting the ability to treat patients with recurrent cancer with additional chemoRT or an APR. The phase II JROSG 10-2 trial of 31 patients with squamous cell anal cancer treated with concurrent chemoRT with 5-FU and mitomycin in Japan has reported 2-year DFS, OS, local control, and colostomy-free survival of 77.4%, 93.5%, 83.9%, and 80.6%, respectively.[131]

Capecitabine, an oral fluoropyrimidine prodrug, is an accepted alternative to 5-FU in the treatment of colon and rectal cancer.[132–135] Capecitabine has been assessed as an alternative to 5-FU in chemoRT regimens for nonmetastatic anal cancer.[136–139] Doses throughout the radiation course on treatment days may offer improved radiation sensitization compared with 2 courses of 5-FU infusion during the chemoRT course. A retrospective study compared results for 58 patients treated with capecitabine to 47 patients treated with infusional 5-FU; both groups also received mitomycin and concurrent RT.[138] No significant differences were seen in clinical complete response, 3-year locoregional control, 3-year OS, or colostomy-free survival between the 2 groups. Another retrospective study involved 27 patients treated with capecitabine and 62 patients treated with infusional 5-FU; as in the other study, both groups also received mitomycin and RT.[137] Grade 3/4 hematologic toxicities were significantly lower in the capecitabine group, with no oncologic outcomes reported. A phase II study found that chemoRT with capecitabine and mitomycin was safe and resulted in a 6-month locoregional control rate of 86% (95% CI, 0.72–0.94) in patients with localized anal cancer.[140] Although data for this regimen are limited, the panel recommends mitomycin/capecitabine + RT as an alternative to mitomycin/5-FU + RT in the setting of stage I through III anal cancer.

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.[129]

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.[141] In this study, more than 900 patients with newly diagnosed anal cancer were randomly assigned to primary treatment with either 5-FU/mitomycin or 5-FU/cisplatin with RT. 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 5.1 years, no differences were seen in the primary endpoint of complete response rate in either arm for the chemoRT comparison or in the primary endpoint of progression-free survival (PFS) 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. 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 after primary treatment with chemoRT in patients with anal cancer.

Cisplatin as a substitute for mitomycin in the treatment of patients with nonmetastatic 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 + cisplatin for 2 cycles followed by concurrent chemoRT with 5-FU and cisplatin; or (2) concurrent chemoRT with 5-FU and mitomycin.[98,142] 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).[142] Five-year OS was also significantly better in the mitomycin arm (70.7% vs 78.3%; *P*=.026).[142] In addition, 5-year colostomy-free survival showed a trend toward statistical significance (65.0% vs 71.9%; *P*=.05), again in favor of the mitomycin group. Because 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, it is difficult to attribute the differences to the substitution of cisplatin for mitomycin or to the use of induction chemotherapy.[123,143] However, because ACT II demonstrated that the 2 chemoRT regimens are equivalent, some have suggested that results from RTOG 98-11 suggest that induction chemotherapy is probably detrimental.[144]

Results from ACCORD 03 also suggest that there is no benefit of a course of chemotherapy given before chemoRT.[145] 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 OS. 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 systematic review of randomized trials also showed no benefit to a course of induction chemotherapy.[146]

A retrospective analysis, however, suggests that induction chemotherapy preceding chemoRT may be beneficial for the subset of patients with T4 anal cancer.[147] The 5-year colostomy-free survival rate was significantly better in patients with T4 anal cancer who received induction 5-FU/cisplatin compared with those who did not (100% vs 38 ± 16.4%, *P*=.0006).

The combination of 5-FU, mitomycin C, and cisplatin has also been studied in a phase II trial but was found to be too toxic.[148] The safety and efficacy of capecitabine/oxaliplatin with radiation for the treatment of localized anal cancer has been investigated in a phase II study, which reported that the regimen was safe, with promising efficacy, although larger trials would be needed to confirm these results.[149]

There has also been interest in the use of biologic therapies for the treatment of anal cancer. A phase III trial is investigating the use of the PD-1 inhibitor, nivolumab, following combined modality therapy for high-risk anal carcinoma (ClincalTrials.gov identifier: NCT03233711).[150] This trial has completed enrollment of 344 participants, and results are pending. Cetuximab is an epidermal growth factor receptor inhibitor, whose antitumor activity is dependent on the presence of wild-type *KRAS*.[151] Because *KRAS* mutations appear to be very rare in anal cancer,[152,153] the use of an epidermal growth factor receptor inhibitor such as cetuximab has been considered to be a promising avenue of investigation. The phase II ECOG 3205 and AIDS Malignancy Consortium 045 trials evaluated the safety and efficacy of cetuximab with cisplatin/5-FU and radiation in immunocompetent (E3205) patients and PLWH (AMC045) with anal squamous cell carcinoma.[154,155] Results from E3205 and AMC045 were published in 2017. In a post hoc analysis of E3205, the 3-year locoregional failure rate was 21% (95% CI, 7%–26%) by Kaplan-Meier estimate.[154] The toxicities associated with the regimen were substantial, with grade 4 toxicity occurring in 32% of the study population and 3 treatment-associated deaths (5%). In AMC045, the 3-year locoregional failure rate was 20% (95% CI, 10%–37%) by Kaplan-Meier estimate.[155] Grade 4 toxicity and treatment-associated rates were similar to those seen in E3205, at 26% and 4%, respectively. Two other trials that have assessed the use of cetuximab in this setting have also found it to increase toxicity, including a phase I study of cetuximab with 5-fluorouracil, cisplatin, and radiation.[156] The ACCORD 16 phase II trial, which was designed to assess response rate after chemoRT with cisplatin/5-FU and cetuximab, was terminated prematurely because of extremely high rates of serious adverse events.[157] The 15 evaluable patients from ACCORD 16 had a 4-year DFS rate of 53% (95% CI, 28%–79%), and 2 of the 5 patients who completed the planned treatments had locoregional recurrences.[158]

For older patients or those who are unlikely to tolerate mitomycin, the optimal chemotherapy regimen remains uncertain. Some NCCN Panel members have used a combination of weekly cisplatin and daily 5-FU on days of RT[159] for chemoRT in localized anal cancer. Other potential strategies for this patient population may include capecitabine + RT or RT alone (without chemotherapy). However, due to a lack of data supporting this approach and differing strategies among panel members, there are not yet defined recommendations for patients with anal cancer who are not candidates for intensive therapy. Use of a geriatric assessment to guide management and elicitation of the patient's goals and objectives with regard to their cancer diagnosis is critical to inform shared decision-making discussions in these

situations (See the NCCN Guidelines for Older Adult Oncology at NCCN.org).

Radiation Therapy

Before the start of RT, patients should be counseled on infertility risks and given information regarding sperm banking or oocyte, egg, or ovarian tissue banking, as appropriate. In addition, patients should be counseled on risks for early treatment-induced menopause and changes to sexual function. See the NCCN Guidelines for Survivorship and the NCCN Guidelines for Adolescent and Young Adult Oncology (available at NCCN.org) for more information. Patients should be considered for vaginal dilators daily during treatment, which can reduce RT doses to sexual organs at risk,[160] and instructed on the symptoms of vaginal stenosis.

The optimal dose and schedule of RT for anal carcinoma 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.[161] 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).[162] In a third study of patients with T3, T4, or lymph node-positive tumors, RT doses of ≥54 Gy administered with limited treatment breaks (<60 days) were associated with increased local control.[163] 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.[145] No benefit was seen with the higher dose of radiation. These results are supported by much earlier results from the RTOG 92-08 trial[164] and suggest that doses >59 Gy provide no additional benefit to patients with anal cancer. The randomized, phase II DECREASE study (NCT04166318) is currently evaluating how well lower-dose chemoRT works in comparison with standard-dose chemoRT for patients with stage I or IIA anal cancer.[165] Patients on this study are randomized to either 28 fractions (standard-dose) or 20 or 23 fractions (deintensified dose) of intensity-modulated RT (IMRT). Study completion is expected in 2025.

There is evidence that treatment interruptions, either planned or required due to treatment-related toxicity, can compromise the effectiveness of treatment.[114] 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 locoregional failure rates and lower colostomy-free survival rates when compared with patients who only had treatment breaks for severe skin toxicity,[166] 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 colostomy-free survival rates observed in that study (74% at 3 years).[141] A post hoc analysis from the ACT II trial revealed worse outcomes if the planned RT dose was extended to more than 42 days, with a significant increase in the risk of PFS event (P=.01) and worse OS (P=.006).[167] Although results of these and other studies have supported the benefit of delivery of chemoRT over shorter time periods,[168–170] treatment breaks in the delivery of chemoRT are required in up to 80% of patients because chemoRT-related toxicities are common.[170] 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.[82]

Some of the reported late side effects of chemoRT include increased frequency and urgency of defecation, chronic perineal dermatitis, dyspareunia, and impotence.[171,172] In some cases, severe late RT complications, such as anal ulcers, stenosis, and necrosis, may necessitate surgery involving colostomy.[172] 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 female patients ≥65 years undergoing RT for anal cancer compared with female patients of the same age with anal cancer who did not receive RT.[173]

An increasing body of literature suggests that toxicity can be reduced with advanced radiation delivery techniques.[114,174–184] IMRT uses detailed beam shaping to target specific volumes and limit the exposure of normal tissue.[183] 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 with patients in the 5-FU/mitomycin arm of the randomized RTOG 98-11 study, which used conventional 3D RT, the rates of grade 3–4 dermatologic toxicity were 38%/0% for IMRT-treated patients compared with 43%/5% for those undergoing conventional RT.[98,183] 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 OS, locoregional control, and PFS.[185] In a larger retrospective comparison, no significant differences in local recurrence-free survival, distant metastasis-free survival, colostomy-free survival, and OS at 2 years were seen between patients receiving IMRT and those receiving 3D conformal radiotherapy, despite the fact that the IMRT group had a higher average N stage.[186]

RTOG 0529 was a prospective clinical trial investigating if dose-painted IMRT/5-FU/mitomycin could decrease the rate of gastrointestinal and genitourinary adverse effects compared with patients treated with conventional radiation/5-FU/mitomycin from RTOG 98-11. This trial did not meet its primary endpoint of reducing grade 2+ combined acute genitourinary and gastrointestinal adverse events by 15% compared with conventional radiation on RTOG 98-11.[187] 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%; $P<.0001$). Subsequently, long-term outcomes and toxicities of patients with anal cancer treated with dose-painted IMRT as per RTOG 0529 have been reported.[188,189] Of 99 eligible patients identified in the 2017 publication, 92% had a clinically complete response after a median follow-up of 49 months.[189] The 4-year OS was 85.5% and the 4-year event-free survival was 75.5%. The rate of grade ≥2 nonhematologic late toxicities was 15%. In a longer-term follow-up with 52 eligible patients, the 8-year OS was 68% and the 8-year DFS was 62%.[188] The rate of grade 2 late adverse events was 55%, 16% for grade 3, 0 for grade 4, and 4% for grade 5 events.

A retrospective cohort study using the 2014 linkage of the SEER-Medicare database showed that IMRT is associated with higher total costs than 3D conformal radiation (median total cost, $35,890 vs $27,262; $P<.001$), but unplanned healthcare utilization costs (ie, hospitalizations and emergency department visits) are higher for those receiving conformal radiation (median, $711 vs $4,957 at 1 year; $P=.02$).[190]

Recommendations regarding RT doses follow the multifield technique used in the RTOG 98-11 trial.[98] After clinical and radiologic staging, CT-based simulation is performed for radiation treatment planning. If available, MRI pelvis, PET/CT, or PET/MRI (if available) at the time of simulation may be helpful to define local and regional target structures. 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 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 T2–T4 should receive an additional boost of 9 to 14 Gy. The consensus of the panel is that IMRT is preferred over 3D conformal RT in the treatment of anal carcinoma.[191] IMRT requires expertise and careful target design to avoid reduction in local control by marginal miss.[114] The clinical target volumes for anal cancer used in the RTOG 0529 trial have been described in detail.[191] Also see the RTOG Consensus Panel document (available at https://www.nrgoncology.org/Portals/0/Scientific%20Program/CIRO/Atlases/AnorectalContouringGuidelines.pdf) for more details of the contouring atlas defined by RTOG.

For untreated patients presenting with synchronous local and metastatic disease, chemoRT to the primary site can be considered for local control after first-line chemotherapy, as described in these guidelines. For recurrence in the primary site or nodes after previous chemoRT, surgery should be performed if possible, and, if not, palliative chemoRT can be considered based on symptoms, extent of recurrence, and prior treatment.

Surgical Management

Local excision is used for anal cancer in 2 situations. The first is for superficially invasive squamous cell carcinoma (SISCCA), which is defined as anal cancer that has been completely excised, with ≤3-mm basement membrane invasion and a maximal horizontal spread of ≤7 mm (T1, NX).[192] SISCCA are generally found incidentally in the setting of a biopsy or excision of what is thought to be a benign lesion such as a condyloma, hemorrhoid, or anal skin tag. Such lesions are being seen with increasing frequency because anal cancer screening in populations at high risk is becoming more common. For SISCCA that are noted to have histologically negative margins in carefully selected patients followed up by an experienced provider and/or team, local excision alone with a structured surveillance plan may represent adequate treatment. A careful surveillance plan is necessary because observational studies have reported detection of high-grade squamous intraepithelial lesions in 74% of patients after local excision.[193] A retrospective study described characteristics, treatment, and outcomes of 17 patients with completely excised invasive anal cancer, 7 of whom met the criteria for classification as superficially invasive.[194] Those with positive margins (≤2 mm for anal canal cancer and <1 cm for perianal cancer) received local radiation, and all patients underwent surveillance. After a median follow-up of 45 months, no differences were seen in 5-year OS (100% for the entire cohort) or 5-year cancer recurrence-free survival rates (87% for the entire cohort) between the groups with superficially invasive and invasive cancer.

Local excision is also used for T1,N0, well-differentiated or select T2,N0 perianal (anal margin) cancer that does not involve the sphincter (also see "Recommendations for the Primary Treatment of Perianal Cancer," page 667). In these

cases, a 1-cm margin is recommended. A retrospective cohort study that included 2,243 adults from the National Cancer Database diagnosed with T1,N0 anal canal cancer between 2004 and 2012 found that the use of local excision in this population increased over time (17.3% in 2004 to 30.8% in 2012; $P<.001$).[195] No significant difference in 5-year OS was seen based on management strategy (85.3% for local excision; 86.8% for chemoRT; $P=.93$). Many patients with T1 or selected T2 perianal cancers will have concomitant high-grade squamous intraepithelial lesions of the anal canal, therefore it is important to look for such anal canal involvement when conservative management (local excision) is being considered.

Radical surgery in anal cancer (APR) is reserved for local recurrence or disease persistence (see "Treatment of Locally Progressive or Recurrent Anal Carcinoma," page 667).

Treatment of Anal Cancer in Patients Living With HIV/AIDS

As discussed previously (see "Risk Factors," page 654), PLWH have been reported to be at increased risk for anal carcinoma.[17,27–30] Some evidence suggests that ART may be associated with a decrease in the incidence of high-grade AIN and its progression to anal cancer.[34,196] However, the incidence of anal cancer in PLWH has not decreased much, if at all, over time.[26,28,30,33]

Most evidence regarding outcomes in PLWH with anal cancer comes from retrospective comparisons, a few of which found worse outcomes in PLWH.[197–199] For example, a cohort comparison of 40 PLWH with anal canal cancer and 81 HIV-negative patients with anal canal cancer found local relapse rates to be 4 times higher in PLWH at 3 years (62% vs 13%) and found significantly higher rates of severe acute skin toxicity for PLWH.[198] However, no differences in rates of complete response or 5-year OS were observed between the groups in that study. Another systematic review and meta-analysis of 40 studies including 3,720 patients with localized squamous cell carcinoma of the anus who were treated with chemoRT, 34% of whom were HIV-positive, found a greater risk of grade 3 and higher cutaneous toxicities (RR = 1.34), and worse 3-year DFS (RR = 1.32) and OS (RR = 1.77) rates, in PLWH compared with those who were HIV-negative.[199]

Most studies, however, have found outcomes to be similar in PLWH and HIV-negative patients.[200–207] In a retrospective cohort study of 1,184 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 PLWH was compared with the group of patients testing negative for HIV.[202] Another study of 36 consecutive patients with anal cancer, including 19 immunocompetent and 17 immunodeficient (14 PLWH) patients showed no difference in the efficacy or toxicity of chemoRT.[206] A population-based study of almost 2 million patients with cancer, including 6,459 PLWH, found no increase in cancer-specific mortality for anal cancer in PLWH.[208] Although the numbers of PLWH in these studies have been small, the efficacy and safety results appear similar regardless of HIV status.

Overall, the panel believes that PLWH who have anal cancer should be treated as per these guidelines and that modifications to treatment of anal cancer should not be made solely on the basis of HIV status. Additional considerations for PLWH who have anal cancer are outlined in the NCCN Guidelines for Cancer in People Living with HIV (available at NCCN.org), including the use of normal tissue-sparing radiation techniques, the consideration of nonmalignant causes for lymphadenopathy, and the need for more frequent posttreatment surveillance anoscopy for PLWH. Poor performance status in PLWH and anal cancer may be from HIV, cancer, or other causes. The reason for poor performance status should be considered when making treatment decisions. Treatment with ART may improve poor performance status related to HIV.

Recommendations for the Primary Treatment of Anal Canal Cancer

Currently, concurrent chemoRT is the recommended primary treatment of patients with nonmetastatic anal canal cancer as well as for patients with positive para-aortic lymph nodes that can be included in the radiation field, although only limited retrospective data support use in this setting.[209] Mitomycin/5-FU or mitomycin/capecitabine is administered concurrently with radiation.[98,137–139] Alternatively, 5-FU/cisplatin can be given with concurrent radiation (category 2B).[210] 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.[82] Capecitabine is given orally, Monday through Friday, on each day that RT is given, for 4 or 6 weeks, with bolus injection of mitomycin and concurrent radiation.[137,139] See ANAL-B 1 of 3 (page 658) for more information on these regimens.

An analysis of the National Cancer Database found that only 61.5% of patients with stage I anal canal cancer received chemoRT as recommended in these guidelines.[211] Patients who were male, with age ≥70 years, had smaller or lower-grade tumors, or who had been evaluated at academic facilities were more likely than others to be treated with excision alone. In a separate analysis of the National Cancer Database, 88% of patients with stage II–III anal canal cancer received chemoRT.[212] Males, Black patients, those with multiple comorbidities, and

those treated in academic facilities were less likely to receive combined modality treatment.

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 before treatment. In addition, patients should be considered for vaginal dilators and should be instructed on the symptoms of vaginal stenosis.

Recommendations for the Primary Treatment of Perianal Cancer

Perianal lesions can be treated with either local excision or chemoRT depending on the clinical stage. Primary treatment of patients with T1,N0 well-differentiated or select smaller T2,N0 perianal (anal margin) cancer that does not involve the sphincter is by local excision with adequate margins. The ASCRS defines an adequate margin as 1 cm.[56] If the margins are not adequate, re-excision is the preferred treatment option. Local RT with or without continuous infusion 5-FU/mitomycin, mitomycin/capecitabine, or 5-FU/cisplatin (category 2B) can be considered as alternative treatment options when surgical margins are inadequate. For all other perianal cancers, the treatment options are the same as for anal canal cancer (see previous sections).[98,137–139,210]

Surveillance Following Primary Treatment

Following primary treatment of nonmetastatic anal cancer, the surveillance and follow-up treatment recommendations for perianal and anal canal cancer are the same (see ANAL-3, page 656). Patients are re-evaluated using 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 OS or PFS.[141] Interestingly, 72% of patients in this trial who did not show a complete response at 11 weeks from the start of treatment had achieved a complete response by 26 weeks. The 5-year survival was superior in patients who experienced complete response at 26 weeks.[213] Based on these results, the panel believes it may be appropriate to follow patients who have not experienced 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 for up to 6 months from the start of treatment, and APR can thereby be avoided in some patients. In these patients, observation and re-evaluation should be performed at 3-month intervals. The panel recommends against the use of PET/CT imaging as part of this re-evaluation strategy due to concerns for false-positivity from local inflammation from RT leading to unnecessary surgeries. If biopsy-proven disease progression occurs, further intensive treatment is indicated (see "Treatment of Locally Progressive or Recurrent Anal Carcinoma," next section).

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 undergo evaluation every 3 to 6 months for 5 years, including DRE and inguinal node palpation. Anoscopic evaluation is recommended every 6 to 12 months for 3 years. Annual chest, abdominal, and pelvic CT with contrast or chest CT without contrast and abdominal/pelvic MRI with contrast is recommended for 3 years for patients who initially had stage II–III disease.

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%–30% have been reported.[214,215] Some of the disease characteristics that have been associated with higher recurrence rates after chemoRT include higher T stage and higher N stage (also see "Prognostic Factors," page 660).[216]

Evidence of progression found on DRE should be followed by biopsy as well as restaging with CT and/or PET/CT imaging (see ANAL-4, page 657). Patients with biopsy-proven locally progressive disease are candidates for radical surgery with an APR and colostomy.[215] In an attempt to avoid surgery, the use of immunotherapy with nivolumab or pembrolizumab may be considered prior to APR (category 2B) as some patients may have a good response. However, it should be noted that this approach is based on institutional experience only and there are currently no published data supporting its use in this setting of otherwise curative intent surgery.

A multicenter retrospective cohort study looked at the cause-specific colostomy rates in 235 patients with anal cancer who were treated with radiotherapy or chemoRT from 1995 to 2003.[217] 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.[218]

In studies involving a minimum of 25 patients undergoing an APR for anal carcinoma, 5-year survival rates of 39%–66% have been observed.[214,215,219–223] Complication

rates were reported to be high in some of these studies. Factors associated with worse prognosis after APR include an initial presentation of node-positive disease and RT doses <55 Gy used in the treatment of primary disease.[215]

The general principles for APR technique are similar to those for distal rectal cancer and include the incorporation of meticulous total mesorectal excision. However, APR for anal cancer may require wider lateral perianal margins than are required for rectal cancer. A retrospective analysis of the medical records of 14 patients who received intraoperative RT during APR revealed that intraoperative RT is unlikely to improve local control or to give a survival benefit.[224]

Because of the necessary exposure of the perineum to radiation, patients with anal cancer are prone to poor perineal wound healing. 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 results in decreased perineal wound complications.[225,226] Reconstructive tissue flaps for the perineum, such as the vertical rectus or local myocutaneous flaps, should therefore be considered for patients with anal cancer undergoing an APR.

Inguinal node dissection is recommended for recurrence in that area and for patients who require an APR but have already received groin radiation. Inguinal node dissection can be performed with or without an APR depending on whether disease is isolated to the groin or has occurred in conjunction with recurrence or persistence at the primary site.

Patients who develop inguinal node metastasis who do not undergo an APR can be considered for palliative RT to the groin with or without 5-FU/mitomycin or mitomycin/capecitabine if no prior RT to the groin was given. Radiation therapy technique and doses are dependent on dosing and technique of prior treatment (see the guidelines pages). If RT was given previously, 5-FU/cisplatin chemotherapy may be given (category 2B).

Surveillance Following Treatment of Recurrence

Following APR, patients should undergo re-evaluation every 3 to 6 months for 5 years, including clinical evaluation for nodal metastasis (ie, inguinal node palpation). In addition, it is recommended that these patients undergo annual chest, abdominal, and pelvic CT with contrast or chest CT without contrast and abdominal/pelvic MRI with contrast for 3 years. In one retrospective study of 105 patients with anal canal carcinoma who had an APR between 1996 and 2009, the overall recurrence rate following APR was 43%.[227] Those with T3/4 tumors or involved margins were more likely to experience recurrence. The 5-year survival rate after APR has been reported to be 60%–64%.[227,228]

Following treatment of inguinal node recurrence, patients should have a DRE and inguinal node palpation every 3 to 6 months for 5 years. In addition, anoscopy every 6 to 12 months and annual chest, abdominal, and pelvic CT with contrast or chest CT without contrast and abdominal/pelvic MRI with contrast are recommended for 3 years.

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.[229] Since anal carcinoma is a rare cancer and only 10%–20% of patients with anal carcinoma present with extrapelvic metastatic disease,[229] only limited data are available on this population of patients. Despite this fact, evidence indicates that systemic therapy has some benefit in patients with metastatic anal carcinoma. See ANAL-B 2 of 3 (page 659) for more information on the systemic therapy regimens recommended for metastatic anal cancer.

Palliative chemoRT to the primary site can be administered after upfront chemotherapy for local control of a symptomatic bulky primary. In fact, an analysis of the National Cancer Database reported that patients with newly diagnosed metastatic anal cancer who received definitive pelvic RT in addition to chemotherapy had longer median OS than those who received chemotherapy alone (21.3 vs 15.9 months; HR, 0.70; 95% CI, 0.61-0.81; $P<.001$).[230] A retrospective analysis of 106 patients with squamous cell carcinoma reported that resection or ablation of liver metastases can result in long-term survival and that patients with anal cancer had better outcomes than those with nonanal squamous cell carcinoma, although this approach is not currently included in the NCCN Guidelines for Anal Carcinoma.[231]

First-Line Treatment of Metastatic Anal Cancer

Based on results from the phase II International Multicentre InterAACT study, carboplatin in combination with paclitaxel has been noted as the preferred regimen for first-line treatment of metastatic anal cancer by the NCCN Panel.[232] In this trial, 91 patients with previously untreated, unresectable, locally recurrent or metastatic anal squamous cell carcinoma were randomized to either carboplatin + paclitaxel or cisplatin + 5-FU. Although response rates were similar between carboplatin + paclitaxel and cisplatin + 5-FU (59% and 57%, respectively), carboplatin + paclitaxel showed lower toxicity compared with cisplatin + 5-FU (71% vs 76% grade ≥3 toxicity and 36% vs 62% [$P=.016$] serious adverse events). Median PFS and OS were 8.1 and 20 months for carboplatin + paclitaxel and 5.7 and 12.3 months for cisplatin + 5-FU (HR for OS, 2.0; 95% CI, 1.15–3.47; $P=.014$).[232] The results from the InterAACT trial are in agreement with older studies that showed that chemotherapy with a

fluoropyrimidine-based regimen + cisplatin[210,233–235] or a platinum-based therapy + paclitaxel[234,236,237] benefited some patients with metastatic anal carcinoma.

Other recommended treatment options include 5-FU, leucovorin, and cisplatin (FOLFCIS); 5-FU, leucovorin, and oxaliplatin (FOLFOX); 5-FU + cisplatin (category 2B reflecting its similar efficacy, but higher toxicity, when compared with carboplatin + paclitaxel in a randomized trial); or modified docetaxel, cisplatin, and 5-FU (DCF, category 2B). A retrospective study of 53 patients with advanced anal squamous cell carcinoma who received FOLFCIS as first-line therapy showed that this regimen was safe and effective in this patient population. The response rate was 48%, PFS was 7.1 months, and OS was 22.1 months.[238] The safety of FOLFOX in patients with anal cancer has been demonstrated in a case report.[239] Despite the limited data for FOLFOX in this setting, the panel added it based on consensus and its current use as a standard option at many NCCN Member Institutions. With use of FOLFOX, the panel recommends strong consideration of discontinuation of oxaliplatin after 3-4 months (or sooner for unacceptable neurotoxicity) while maintaining other agents until time of disease progression.[240] Oxaliplatin may be reintroduced if it was discontinued for neurotoxicity rather than for disease progression.

DCF is another regimen that has been evaluated for metastatic anal cancer.[241,242] A single-arm phase II trial evaluated this regimen in patients with previously untreated, advanced anal squamous cell carcinoma. This trial demonstrated the efficacy of DCF (both standard and modified regimens) in this setting and reported better tolerability of modified DCF compared with the standard regimen.[241] The median PFS was 10.7 months for the standard DCF regimen and 11.0 months for the modified regimen. For the standard regimen, 83% of patients had at least one grade 3–4 AE, while 53% had at least one grade 3–4 adverse event when treated with modified DCF. The most common grade 3–4 adverse events were neutropenia, diarrhea, asthenia, anemia, lymphopenia, mucositis, and vomiting. Based on these results, the panel added modified DCF as an option for metastatic anal cancer, with the category 2B designation reflecting concerns voiced by some panel members about potentially higher toxicity with modified DCF compared with the other regimens recommended for metastatic anal cancer.

Several ongoing clinical trials are investigating whether checkpoint inhibitors could have a role in the first-line treatment of metastatic anal cancer. NCT04444921 is a randomized, phase 3 trial comparing chemotherapy alone (carboplatin and paclitaxel) to chemotherapy + nivolumab for treatment-naïve metastatic anal cancer.[243] This study is expected to enroll 205 participants and complete in 2023. POD1UM-303/InterAACT2 is a similar, phase 3 global study (Clinicaltrials.gov identifier: NCT04472429) investigating the addition of the checkpoint inhibitor, retifanlimab, to carboplatin/paclitaxel chemotherapy and comparing it to chemotherapy alone.[244] This trial expects to enroll 300 participants with previously untreated metastatic anal carcinoma and expected completion is in 2024.

Second-Line Treatment of Metastatic Anal Cancer

A single-arm, multicenter phase 2 trial assessed the safety and efficacy of the anti-PD-1 antibody nivolumab for refractory metastatic anal cancer.[245] Two complete responses and 7 partial responses were seen among the 37 enrolled participants who received at least one dose, for a response rate of 24% (95% CI, 15–33). The KEYNOTE-028 trial is a multicohort, phase Ib trial of the anti-PD-1 antibody pembrolizumab in 24 patients with PD-L1–positive advanced squamous cell carcinoma of the anal canal.[246] Four partial responses were seen, for a response rate of 17% (95% CI, 5%–37%), and 10 patients (42%) had stable disease, for a disease control rate of 58%. In both trials, toxicities were manageable, with 13% and 17% experiencing grade 3 adverse events with nivolumab and pembrolizumab, respectively.[245,246] The phase II KEYNOTE-158 study investigated the use of pembrolizumab in patients with noncolorectal microsatellite instability-high/deficient mismatch repair cancers, including patients with anal cancer (cohort A).[247,248] A total of 112 patients with anal cancer were enrolled and treated, 67% of whom had PD-L1-positive disease.[248] A total of 11% of patients (95% CI, 6–18) had an objective response, with responses in 15% (95% CI, 8%–25%) of patients with PD-L1-positive disease and in 3% (95% CI, 0%–17%) with PD-L1-negative disease. Serious treatment-related adverse events were noted in 11% of patients, with 25% of patients having immune-mediated events. This study demonstrated the clinical benefit of pembrolizumab for patients with previously treated advanced anal squamous cell carcinoma.

A phase II clinical trial (ClinicalTrials.gov identifier: NCT02314169) is also underway investigating the efficacy and safety of nivolumab, with or without ipilimumab, for patients with refractory metastatic anal canal cancer.[249] This trial has an estimated enrollment of 137 participants and is expected to complete in February 2024. Other trials have investigated novel second-line agents for metastatic anal cancer, including the phase 2 PODIUM-202 trial of retifanlimab for advanced or metastatic squamous cell carcinoma of the anal canal that progressed after platinum-based chemotherapy.[250]

Although further studies of PD-1/PD-L1 inhibitors are warranted, the panel added nivolumab and pembrolizumab as preferred options for patients with metastatic anal cancer who have experienced progression on first-line chemotherapy in the 2018 version of these guidelines. Microsatellite instability/mismatch repair testing is not required. Microsatellite instability is uncommon

in anal cancer,[251] and as discussed previously, responses to PD-1/PD-L1 inhibitors occur in 20%–24% of patients.[245,246] Anal cancers may be responsive to PD-1/PD-L1 inhibitors because they often have high PD-L1 expression and/or a high tumor mutational load despite being microsatellite stable.[251]

The panel also notes that platinum-based chemotherapy should not be given in second line if disease progressed on platinum-based therapy in first line.

Survivorship

The panel recommends that a prescription for survivorship and transfer of care to the primary care physician be written.[252] The oncologist and primary care provider should have defined roles in the surveillance period, with roles communicated to the patient. The care plan should include an overall summary of treatments received, including surgeries, radiation treatments, and chemotherapy. The possible expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment should be described. Finally, surveillance and health behavior recommendations should be part of the care plan.

Disease-preventive measures, such as immunizations; early disease detection through periodic screening for second primary cancers (eg, breast, cervical, or prostate cancers); and routine good medical care and monitoring are recommended (see the NCCN Guidelines for Survivorship, available at NCCN.org). Additional health monitoring should be performed as indicated under the care of a primary care physician. Survivors are encouraged to maintain a therapeutic relationship with a primary care physician throughout their lifetime.[253]

Other recommendations include monitoring for late sequelae of anal cancer or the treatment of anal cancer. Late toxicity from pelvic radiation can include bowel dysfunction (ie, increased stool frequency, fecal incontinence, flatulence, rectal urgency), urinary dysfunction, and sexual dysfunction (ie, impotence, dyspareunia, vaginal stenosis, vaginal dryness, reduced libido).[254–258] Anal cancer survivors also report significantly reduced global quality of life, with increased frequency of somatic symptoms including fatigue, dyspnea, nausea, appetite loss, pain, and insomnia.[254,258–260] Therefore, survivors of anal cancer should be screened regularly for distress.

The NCCN Guidelines for Survivorship (available at NCCN.org) provide screening, evaluation, and treatment recommendations for common consequences of cancer and cancer treatment to aid healthcare professionals who work with survivors of adult-onset cancer in the posttreatment period, including those in specialty cancer survivor clinics and primary care practices. These guidelines include many topics with potential relevance to survivors of anal cancer, including anxiety, depression, and distress; cognitive dysfunction; fatigue; pain; sexual dysfunction; sleep disorders; healthy lifestyles; and immunizations. Concerns related to employment, insurance, and disability are also discussed.

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 perianal cancer and anal canal cancer are very similar and include chemoRT in most cases. The exception is small, well or moderately differentiated perianal lesions and superficially invasive lesions, which can be treated with margin-negative local excision alone. Follow-up clinical evaluations are recommended for all patients with anal carcinoma because additional curative-intent treatment is possible. Patients with biopsy-proven evidence of locally recurrent or persistent disease after primary treatment should undergo an APR with groin dissection if there is clinical evidence of inguinal nodal metastasis. 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 systemic therapy. The panel endorses the concept that treating patients in a clinical trial has priority over standard or accepted therapy.

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Individual Disclosures for the Anal Carcinoma Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Specialties
Mahmoud M. Al-Hawary, MD	None	None	None	Diagnostic/Interventional radiology
Nilofer Azad, MD	Agios, Inc.; Array; Atlas; Bayer HealthCare; Bristol-Myers Squibb Company; Celgene Corporation; Daiichi- Sankyo Co.; Debio; Eli Lilly and Company; EMD Serono; Incyte Corporation; Merck & Co., Inc.; Taiho Pharmaceuticals Co., Ltd.	AstraZeneca Pharmaceuticals LP; GlaxoSmithKline; Incyte Corporation; Mirati; QED	AstraZeneca Pharmaceuticals LP	Medical oncology
Al B. Benson III, MD	Astellas Pharma US, Inc.; Boehringer Ingelheim GmbH; Boston Scientific Corporation; Bristol-Myers Squibb Company; GSK; Mirati; Mirati Therapeutics, Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Tempus; Terumo; Therabionic	Therabionic; Apexigen; Artemida; BioScend; Bristol-Myers Squibb Company; Grail; HalioDx; Janssen Oncology; Merck Sharpe & Dohme; Natera; Pfizer Inc./Hospira Inc.; TUKYSA; Xencor	None	Medical oncology
Yi-Jen Chen, MD, PhD	None	None	None	Radiotherapy/Radiation oncology
Kristen K. Ciombor, MD	Array; Bristol-Myers Squibb Company; Calithera; Daiichi- Sankyo Co.; Genentech, Inc.; Incyte Corporation; Merck & Co., Inc.; Nucana; Pfizer Inc.	Incyte Corporation; Personalis; Pfizer Inc.; Replimune; SeaGen	None	Medical oncology
Stacey Cohen, MD	GlaxoSmithKline	Bayer HealthCare; Cancer Study Group; Delcath; Eisai Inc.; Guidepoint; Helsell Fettermann; Istari Oncology	None	Medical oncology
Harry S. Cooper, MD	None	None	None	Pathology
Dustin Deming, MD	Aadi Biosciences; Arcus; Bristol-Myers Squibb Company; Curegenix; Eli Lilly and Company; EMD Serono; Genentech, Inc.; Ipsen; Merck & Co., Inc.; Natera; Pfizer Inc.; Promega; Revolution Medicine; Seattle Genetics, Inc.; STRATA Oncology	Bayer HealthCare; Eli Lilly and Company; Illumina; Pfizer Inc.; Promega; Seattle Genetics, Inc.	None	Medical oncology
Ignacio Garrido-Laguna, MD, PhD	Amgen Inc.; Genentech, Inc.; GlaxoSmithKline; Halozyme, Inc.; MedImmune Inc.; Navire; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Seattle Genetics, Inc.; SOTIO, LLC; Tolero; Trishula; Yingli	Cancer Study Group; Jazz Pharmaceuticals Inc.; Kanaph Therapeutics; OncXerna	None	Medical oncology
Jean L. Grem, MD	Processa Pharmaceuticals	None	None	Medical oncology
J. Randolph Hecht, MD	A2; Amgen Inc.; Astellas Pharma US, Inc.; Bold; Camrus; Crinetics; Exelixis Inc.; Gilead Sciences, Inc.; NGM; TESARO, Inc.; Tizona	Actym; Astellas Pharma US, Inc.; Deciphera Pharmaceuticals, Inc.; Exelixis Inc.; Gilead Sciences, Inc.; IGM; Mirati; Notch; Rafael; ZelamBio	None	Medical oncology
Sarah Hoffe, MD	Galera, second trial, GRECO-2; Varian Medical Systems, Inc.; ViewRay	Beyond the White Coat; Galera; University of South Florida	MyCareGorithm; Rittenhouse , I have signed a paper for future stock options but have not been received anything to this date	Radiotherapy/Radiation oncology
Joleen Hubbard, MD	None	Bayer HealthCare; BeiGene; Incyte Corporation; Merck & Co., Inc.; Taiho Pharmaceuticals Co., Ltd.	None	Medical oncology; Hematology/ Hematology oncology
Steven Hunt, MD	No commercial interest. This is a lab developed system for photoacoustic imaging of tumors.	None	None	Surgery/Surgical oncology
Hisham Hussan, MD	None	None	None	Gastroenterology
William Jeck, MD[a]				Pathology
Kimberly L. Johung, MD, PhD	None	None	None	Radiotherapy/Radiation oncology
Nora Joseph, MD	None	None	None	Pathology
Natalie Kirilcuk, MD	None	None	None	Surgery/Surgical oncology
Smitha Krishnamurthi, MD	Agenus; Aravive Biologics, Inc; BioMed Valley; Bristol-Myers Squibb Company; Natera; Pfizer Inc.	None	None	Medical oncology; Internal medicine
Jennifer Maratt, MD	None	None	None	Gastroenterology
Wells A. Messersmith, MD	ALX Oncology; Amgen Inc.; BeiGene; CanBAS; Criterium; Exelixis Inc.; Experimental Drug Development Centre (Singapore); Fate Therapeutics; Mirati; NGM; Pfizer Inc.; PureTech; QED Therapeutics; Rascal Therapeutics; Zymeworks	takeda	None	Medical oncology
Jeffrey Meyerhardt, MD, MPH	None	None	None	Medical oncology
Eric D. Miller, MD, PhD	EMD Serono	None	None	Radiotherapy/Radiation oncology
Mary F. Mulcahy, MD	None	None	None	Hematology/Hematology oncology; Medical oncology
Steven Nurkin, MD, MS	None	Merck & Co., Inc.	None	Surgery/Surgical oncology
Michael J. Overman, MD[a]	None	None	3dmed; AbbVie, Inc.; agilvax; Eisai Inc.; Gilead Sciences, Inc.; gritstone; Janssen Pharmaceutica Products, LP; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Phanes; Takeda Pharmaceuticals North America, Inc.	Medical oncology; Hematology/ Hematology oncology
Aparna Parikh, MD	AbbVie, Inc.; Bayer HealthCare; Bristol-Myers Squibb Company; C2i; Checkmate; CVS; Daiichi-Sankyo Co.; Delcath; Eli Lilly and Company; erasca; Foundation Medicine; Genentech, Inc.; Inivata; Karkinos; Mirati; Novartis Pharmaceuticals Corporation; Parithera; Pfizer Inc.; PMV Pharma; Puretech; Saga; Scare; Seagen; Taiho Pharmaceuticals Co., Ltd.; Up to Date; Value Analytics Lab	C2i equity but no valuation yet; Parithera; Xcures; XGenomes equity but no valuation yet	None	Medical oncology
Hitendra Patel, MD	None	Epinoma	None	Medical oncology
Katrina Pedersen, MD, MS[a]	Arcus; BioLineRx; Boston Biomedical; Bristol-Myers Squibb Company; Daiichi- Sankyo Co.; HCW Biologics; Incyte Corporation; Ipsen; MedImmune Inc.; Merck & Co., Inc.; Natera; Nouscom; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Pierre-Fabre; Rafael; Roche Laboratories, Inc.	AstraZeneca Pharmaceuticals LP; GlaxoSmithKline; Novartis Pharmaceuticals Corporation; SAGA Diagnostics; Taiho Pharmaceuticals Co., Ltd.	WebMD/MedScape	Medical oncology
Leonard Saltz, MD	None	Genor Biopharma	None	Medical oncology; Hematology/ Hematology oncology; Internal medicine
Charles Schneider, MD	None	None	None	Medical oncology
David Shibata, MD	None	None	None	Medical oncology
John M. Skibber, MD	None	None	None	Surgery/Surgical oncology
Constantinos T. Sofocleous, MD, PhD	Boston Scientific Corporation; Ethicon, Inc.; Memorial Sloan Kettering IMRAS; NIH/NCI; SIRTEX; Society of Interventional Oncology	Ethicon, Inc.; Medtronic, Inc.; TERUMO; Varian Medical Systems, Inc.	None	Diagnostic/Interventional radiology
Eden Stotsky-Himelfarb, BSN, RN	None	None	None	Medical oncology; Surgery/Surgical oncology; Patient advocate
Anna Tavakkoli, MD, MSc	None	None	None	Gastroenterology
Alan P. Venook, MD	Amgen Inc.	Amgen Inc.; Bayer HealthCare; Bristol-Myers Squibb Company; Exact Sciences; Exelixis Inc.; GlaxoSmithKline; Merck & Co., Inc.; Pfizer Inc.	None	Medical oncology; Hematology/ Hematology oncology
Christopher G. Willett, MD	None	None	None	Radiotherapy/Radiation oncology
Grant Williams, MD, MSPH	None	None	None	Medical oncology

The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosures relating to employment/governing board, patent, equity, or royalty:
William Jeck, MD: Seattle Genetics, Inc.
Michael J. Overman, MD: UpToDate
Katrina Pedersen, MD, MS: UpToDate