NCCN

Anal Carcinoma, Version 2.2018

Clinical Practice Guidelines in Oncology

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Overview

An estimated 8,580 new cases (2,960 men and 5,620 women) of anal cancer involving the anus, anal canal, or anorectum will occur in the United States in 2018, accounting for approximately 2.7% of digestive system cancers.¹ It has been estimated that 1,160 deaths due to anal cancer will occur in the United States in 2018.¹ Although considered to be

Abstract

The NCCN Guidelines for Anal Carcinoma provide recommendations for the management of patients with squamous cell carcinoma of the anal canal or perianal region. Primary treatment of anal cancer usually includes chemoradiation, although certain lesions can be treated with margin-negative local excision alone. Disease surveillance is recommended for all patients with anal carcinoma because additional curative-intent treatment is possible. A multidisciplinary approach including physicians from gastroenterology, medical oncology, surgical oncology, radiation oncology, and radiology is essential for optimal patient care.

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NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Anal Carcinoma Panel are not printed in this issue of JNCCN but can be accessed online at NCCN.org.**

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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 871. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

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

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a rare type of cancer, the incidence rate of invasive anal carcinoma in the United States increased by approximately 1.9-fold for men and 1.5-fold for women from the period of 1973 through 1979 to 1994 through 2000 and has continued to increase since that time (see “Risk Factors,” online, in these guidelines at NCCN.org).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 1992–2001.⁵

This discussion summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN 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.⁶ Other types of cancers occurring in the anal region, such as adenocarcinoma or melanoma, are addressed in other

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

Management of Anal Carcinoma

Clinical Presentation/Evaluation

Approximately 45% of patients with anal carcinoma present with rectal bleeding, and approxi-

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^aTo view the most recent version of these guidelines, visit NCCN.org.
[†]Available online, in these guidelines, at NCCN.org.

^aThe 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.
^bFor melanoma histology, see the NCCN Guidelines for Melanoma^a; for adenocarcinoma, see the NCCN Guidelines for Rectal Cancer (elsewhere in this issue).
^cCT should be with IV and oral contrast. Pelvic MRI with contrast.
^dPET/CT scan does not replace a diagnostic CT. PET/CT performed skull base to mid-thigh.
^eSee Principles of Surgery (ANAL-A[†]).
^fModifications to cancer treatment should not be made solely on the basis of HIV status. See NCCN Guidelines for Cancer in People Living with HIV^a.
^gSee Principles of Chemotherapy (ANAL-B[†]).
^hSee Principles of Radiation Therapy (ANAL-C[†]).

ANAL-1

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^fModifications to cancer treatment should not be made solely on the basis of HIV status.
^gSee Principles of Chemotherapy (ANAL-B[†]).
^hSee Principles of Radiation Therapy (ANAL-C[†]).
ⁱThe perianal region starts at the anal verge and includes the perianal skin over a 5-cm radius from the squamous mucocutaneous junction.

ANAL-2

†Available online, in these guidelines, at NCCN.org.

^eSee Principles of Surgery (ANAL-A[†]).

⁹See Principles of Chemotherapy (ANAL-B†).

^hSee Principles of Radiation Therapy (ANAL-C†).

³Based on the results of the ACT-II study, it may be appropriate to follow patients who have not achieved a complete clinical response with persistent anal cancer up to 6 months following completion of radiation therapy and chemotherapy as long as there is no evidence of progressive disease during this period of follow-up. Persistent disease may continue to regress even at 26 weeks from the start of treatment. James RD, Glynne-Jones R, Meadows HM, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous cell carcinoma of the anus (Act II): a randomised, phase 3, open-label, 2x2 factorial trial. *Lancet Oncol* 2013;14:516-524.

^kConsider muscle flap reconstruction.

¹See Principles of Survivorship (ANAL-D†).

ANAL-3

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[†]Available online, in these guidelines, at NCCN.org.

^gSee Principles of Chemotherapy (ANAL-B[†]).

^hSee Principles of Radiation Therapy (ANAL-C[†]).

^jBased on the results of the ACT-II study, it may be appropriate to follow patients who have not achieved a complete clinical response with persistent anal cancer up to 6 months following completion of radiation therapy and chemotherapy as long as there is no evidence of progressive disease during this period of follow-up. Persistent disease may continue to regress even at 26 weeks from the start of treatment. James RD, Glynne-Jones R, Meadows HM, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous cell carcinoma of the anus (Act II): a randomised, phase 3, open-label, 2x2 factorial trial. *Lancet Oncol* 2013;14:516-524.

^kConsider muscle flap reconstruction.

^lSee Principles of Survivorship (ANAL-D[†]).

^mUtilize imaging studies as per initial workup.

ANAL-4

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mately 30% have either pain or the sensation of a rectal mass.⁷ After confirmation of squamous cell carcinoma by biopsy, the recommendations of the NCCN Anal Carcinoma Panel for the clinical evaluation of patients with anal canal or perianal cancer are very similar.

The panel recommends a thorough examination/evaluation, including a careful digital rectal examination (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,⁸ chest CT scan is performed to evaluate for pulmonary metastasis. Gynecologic exam, including cervical cancer screening, is suggested for female patients due to the association of anal cancer and HPV.⁹

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 people living with HIV (PLWH).¹⁰ Furthermore, 1 of every 7 people in the United States who are infected with HIV are not aware of their infection status,¹¹ and infected individuals who are unaware of their HIV status do not receive the clinical care they need to reduce HIV-related morbidity and mortality and may unknowingly transmit HIV.¹² HIV testing may be particularly important in patients with cancer, because identification of HIV infection has the potential to improve clinical outcomes.¹³ The Centers for Disease Control and Prevention (CDC) recommends HIV screening for all patients in all health care settings unless the patient declines testing (opt-out screening).¹⁴

PET/CT scanning 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.^{15–20} 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.¹⁶ 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.²¹ The use of PET or PET/CT led to upstaging in 5% to 38% of patients and downstaging in 8% to 27% of patients. The authors reported that treatment plan modifications occurred in 12% to 59% of patients and were namely changes in radiation doses or fields. Another systematic review and meta-analysis found PET/CT to change nodal status and TNM stage in 21% and 41% of patients, respectively.²² 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.²³ This increase in lymph node positivity was associated with improvements in overall survival (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.” This suggests that 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 $<30\%$, suggesting that it is possible some patients are being misclassified and overtreated with the increased use of highly sensitive imaging.

Primary Treatment of Nonmetastatic Anal Carcinoma

In the past, patients with invasive anal carcinoma were routinely treated with an abdominoperineal resection (APR); however, local recurrence rates were

high, 5-year survival was only 40% to 70%, and the morbidity with a permanent colostomy was considerable.⁷ In 1974, Nigro et al²⁴ observed complete tumor regression in some patients with anal carcinoma treated with preoperative 5-FU–based concurrent chemotherapy and radiation (chemoRT) including either mitomycin or porfiromycin, suggesting that it might be possible to cure anal carcinoma without surgery and permanent colostomy. Subsequent nonrandomized studies using similar regimens and varied doses of chemoRT provided support for this conclusion.^{25,26} Results of randomized trials evaluating the efficacy and safety of administering chemotherapy with radiation therapy (RT) support the use of combined modality therapy in the treatment of anal cancer.²⁷ Summaries of clinical trials involving patients with anal cancer have been presented,^{28,29} and several key trials are discussed subsequently.

Chemotherapy: A phase III study from the EORTC compared the use of chemoRT (5-FU plus mitomycin) to RT alone in the treatment of anal carcinoma. Results from this trial showed that patients in the chemoRT arm had an 18% higher rate of locoregional control at 5 years and a 32% longer colostomy-free interval.³⁰ The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) randomized ACT I trial confirmed that chemoRT with 5-FU and mitomycin was more effective in controlling local disease than RT alone (relative risk, 0.54; 95% CI, 0.42–0.69; $P < .0001$), although no significant differences in OS were observed at 3 years.³¹ A recently published follow-up study on these patients shows that a clear benefit of chemoRT remains after 13 years, including a benefit in OS.³² 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 (hazard ratio [HR], 0.67; 95% CI, 0.51–0.88, $P = .004$).

A few studies have addressed the efficacy and safety of specific chemotherapeutic agents in the chemoRT regimens used in the treatment of anal carcinoma.^{33–35} 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 disease-free survival (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.³⁵ The OS rate at

4 years was the same for the 2 groups, however, reflecting the ability to treat patients with recurrent disease with additional chemoRT or an APR.

Capecitabine, an oral fluoropyrimidine prodrug, is an accepted alternative to 5-FU in the treatment of colon and rectal cancer.^{36–39} Capecitabine has therefore been assessed as an alternative to 5-FU in chemoRT regimens for nonmetastatic anal cancer.^{40–43} A retrospective study compared 58 patients treated with capecitabine with 47 patients treated with infusional 5-FU; both groups also received mitomycin and radiation.⁴² 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 compared 27 patients treated with capecitabine to 62 patients treated with infusional 5-FU; as in the other study, both groups also received mitomycin and radiation.⁴¹ 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.⁴⁴ Although data for this regimen are limited, the panel recommends mitomycin/capecitabine plus radiation as an alternative to mitomycin/5-FU plus radiation 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.³⁴

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.⁴⁵ 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 radiotherapy. A continuous course (ie, no treatment gap) of radiation of 50.4 Gy was administered in both arms, and patients in each arm were further randomized to receive 2 cycles of maintenance therapy with 5-FU and cisplatin or no maintenance therapy. At a median follow-up of 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 show 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 non-metastatic anal carcinoma was also evaluated in the randomized phase III Intergroup RTOG 98-11 trial. The role of induction chemotherapy was also assessed. In this study, 682 patients were randomly assigned to receive either: 1) induction 5-FU plus cisplatin for 2 cycles followed by concurrent chemoRT with 5-FU and cisplatin; or 2) concurrent chemoRT with 5-FU and mitomycin.^{33,46} A significant difference was seen in the primary endpoint, 5-year DFS, in favor of the mitomycin group (57.8% vs 67.8%; $P=.006$).⁴⁶ Five-year OS was also significantly better in the mitomycin arm (70.7% vs 78.3%; $P=.026$).⁴⁶ 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 and in 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.^{28,47} 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.⁴⁸

Results from ACCORD 03 also suggest that there is no benefit of a course of chemotherapy given before chemoRT.⁴⁹ 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.⁵⁰

A recent retrospective analysis, however, suggests that induction chemotherapy preceding chemoRT may be beneficial for the subset of patients with T4 anal cancer.⁵¹ The 5-year colostomy-free survival rate was significantly better in patients with T4 cancer who received induction 5-FU/cisplatin compared with those who did not (100% vs 38% $\pm$ 16.4%; $P=.0006$).

The combination of 5-FU, mitomycin C, and cisplatin has also been studied in a phase II trial, but it was found to be too toxic.⁵² In addition, a trial assessing the safety and efficacy of capecitabine/oxaliplatin with radiation in the treatment of localized anal cancer has been completed, but final results have not yet been reported (ClinicalTrials.gov identifier: NCT00093379). Preliminary results from this trial seem promising.⁵³

Cetuximab is an epidermal growth factor receptor (EGFR) inhibitor, whose anti-tumor activity depends on the presence of wild-type *KRAS*.⁵⁴ Because *KRAS* mutations appear to be very rare in anal cancer,^{55,56} the use of an EGFR 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. Preliminary results from these trials, reported in 2012, were encouraging with acceptable toxicity and 2-year PFS rates of 92% (95% CI, 81%–100%) and 80% (95% CI, 61%–90%) in the immunocompetent and PLWH populations, respectively.⁵⁷

Longer-term 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.⁵⁸ 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.⁵⁹ Grade 4 toxicity and treatment-associated death 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-FU, cisplatin, and radiation.⁶⁰ 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.⁶¹ 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.⁶²

RT: The optimal dose and schedule of RT for anal carcinoma also continues to be explored; it 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.⁶³ In another study, in which most 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%, $P=.012$).⁶⁴ In a third study of patients with T3, T4, or lymph node–positive tumors, RT doses of ≥ 54 Gy administered with limited treatment breaks (less than 60 days) were associated with increased local control.⁶⁵ 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.⁴⁹ No benefit was seen with the higher dose of radiation. These results are supported by much earlier results from the RTOG 92-08 trial⁶⁶ and suggest that doses of >59 Gy provide no additional benefit to patients with anal cancer.

There is evidence that treatment interruptions, either planned or required by treatment-related toxicity, can compromise the effectiveness of treatment.¹⁹ 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,⁶⁷ 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).⁴⁵ Although results of these and other studies have supported the benefit of delivery of chemoRT over shorter time periods,^{68–70} treatment breaks in the delivery of chemoRT are required in up to 80% of patients because chemoRT-related toxicities are common.⁷⁰ 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 54–60 Gy are administered in 6–7 weeks.⁸

Some of the reported late side effects of chemoRT include increased frequency and urgency of defecation, chronic perineal dermatitis, dyspareunia, and impotence.^{71,72} In some cases, severe late RT complications, such as anal ulcers, stenosis, and necrosis, may necessitate surgery involving colostomy.⁷² In addition, results from a retrospective cohort study of data from the SEER registry showed the risk of subsequent pelvic fracture to be 3-fold higher in older women undergoing RT for anal cancer compared with older women with anal cancer who did not receive RT.⁷³

An increasing body of literature suggests that toxicity can be reduced with advanced radiation delivery techniques.^{19,74–84} Intensity-modulated RT (IMRT) uses detailed beam shaping to target specific volumes and limit the exposure of normal tissue.⁸³ Multiple pilot studies have shown 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.^{33,83} No decrease in treatment effectiveness or local control rates was seen 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 RT, IMRT was less toxic and showed better efficacy in 3-year OS, locoregional control, and PFS.⁸⁵ 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 RT, despite the fact that the IMRT group had a higher average N stage.⁸⁶

The only prospective study assessing IMRT for anal cancer is the phase II dose-painted IMRT study, RTOG 0529. This trial did not meet its primary endpoint of reducing grade 2+ combined acute genitourinary and gastrointestinal adverse events by 15% compared with the chemoRT/5-FU/mitomycin arm from RTOG 98-11, which used conventional radiation.⁸⁷ Of 52 evaluable patients, the grade 2+ combined acute adverse event rate was 77%; the rate in RTOG 98-11 was also 77%. However, significant reductions were seen in grade 2+ hematologic events (73% vs 85%; $P=.032$), grade 3+ gastrointestinal events (21% vs 36%; $P=.008$), and grade 3+ dermatologic events (23% vs 49%; $P<.0001$). Clinical outcomes of RTOG 0529 will be reported in the future and are of great interest because of the risk of underdosing (marginal miss) associated with highly conformal RT.⁸⁷

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 health care utilization costs (ie, hospitalizations and emergency department visits) are higher for those receiving conformal radiation (median, \$711 vs \$4,957 at 1 year; $P=.02$).⁸⁸

Recommendations regarding RT doses follow the multifield technique used in the RTOG 98-11 trial.³³ PET/CT should be considered for treatment planning.⁸⁹ 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 posteroanterior exit field. Patients with disease clini-

cally 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.⁹⁰ IMRT requires expertise and careful target design to avoid reduction in local control by marginal miss.¹⁹ The clinical target volumes for anal cancer used in the RTOG 0529 trial have been described in detail.⁹⁰ Also see <https://www.rtog.org/> for more details of the contouring atlas defined by RTOG.

For untreated patients presenting with synchronous local and metastatic disease, chemoRT can be considered for local control, 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 anal cancer, 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 (T1NX).⁹¹ Such lesions are being seen with increasing frequency because anal cancer screening in high-risk populations is becoming more common. These lesions are often completely excised at the time of biopsy, and local surgical resection with negative margins may be adequate treatment. 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.⁹² 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 superficially invasive and invasive groups.

Local excision is also used for T1N0, well-differentiated perianal cancer (also see “Recommendations for the Primary Treatment of Perianal Cancer,” page 864). In these cases, a 1-cm margin is recommended. A retrospective cohort study that included 2,243 adults from the National Cancer Data Base diagnosed with T1N0 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; $P < .001$).⁹³ No significant difference in 5-year OS was seen based on management strategy (85.3% for local excision; 86.8% for chemoRT; $P = .93$).

Radical surgery in anal cancer (APR) is reserved for local recurrence or disease persistence (see “Treatment of Locally Progressive or Recurrent Anal Carcinoma,” page 865).

Treatment of Anal Cancer in PLWH: As discussed in the full version of these guidelines (see “Risk Factors,” available online at NCCN.org), PLWH have been reported to be at increased risk for anal carcinoma.^{27,94-97} Some evidence suggests that antiretroviral therapy may be associated with a decrease in the incidence of high-grade anal intraepithelial neoplasia and its progression to anal cancer.^{98,99} However, the incidence of anal cancer in PLWH has not decreased much, if at all, over time.^{95,97,100,101}

Most evidence regarding outcomes in PLWH with anal cancer comes from retrospective comparisons, a few of which found worse outcomes in PLWH.^{102,103} For example, a recent 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.¹⁰³ However, no differences in rates of complete response or 5-year OS were seen between the groups in that study. Most studies, however, have found outcomes to be similar in PLWH and HIV-negative patients.¹⁰⁴⁻¹¹¹ 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.¹⁰⁶ 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.¹¹⁰ A recent 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.¹¹² 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 PLWH (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 post-treatment 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 antiretroviral therapy 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 for patients with nonmetastatic anal canal cancer. Mitomycin/5-FU or mitomycin/capecitabine is administered concurrently with radiation.^{33,41-43} Alternatively, 5-FU/cisplatin can be given with concurrent radiation (category 2B).¹¹³ Most studies have delivered 5-FU as a protracted 96- to 120-hour infusion during the first and fifth weeks of RT, and bolus injection of mitomycin is typically given on the first or second day of the 5-FU infusion.⁸ Capecitabine is given orally, Monday through Friday, for 4 or 6 weeks, with bolus injection of mitomycin and concurrent radiation.^{41,43}

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.¹¹⁴ Patients who were male, elderly, 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.¹¹⁵ Males, blacks, 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,

female 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 for patients with T1, N0 well-differentiated perianal cancers is by local excision with adequate margins. The American Society of Colon and Rectal Surgeons defines an adequate margin as 1 cm.¹¹⁶ 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).^{33,41–43,113}

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.¹¹⁷ Because anal carcinoma is a rare cancer and only 10%–20% of patients with anal carcinoma present with extrapelvic metastatic disease,¹¹⁷ 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.

First-Line Treatment of Metastatic Anal Cancer:

Older studies showed that chemotherapy with a fluoropyrimidine-based regimen plus cisplatin benefited some patients with metastatic anal carcinoma, and metastatic disease is often treated with 5-FU/cisplatin.^{113,117–120} The efficacies of other regimens have also been assessed for the metastatic setting.^{119,121–123} In the 2018 version of these guidelines, the panel added carboplatin plus paclitaxel as an option for initial treatment of patients with metastatic anal cancer. This regimen has been assessed in several small, retrospective studies, in which it was found to be safe with evidence of durable responses.^{119,122,123} The ongoing phase II International Multicentre InterAACT study (clinicaltrials.gov NCT02051868) is comparing this regimen to cisplatin plus 5-FU in patients with unresectable locally recurrent or metastatic anal squamous cell carcinoma.

The panel also added FOLFOX as an option for metastatic anal cancer in 2018. The safety of FOLFOX in patients with anal cancer has been demonstrated in a case report.¹²⁴ 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.

Palliative RT can be administered with chemotherapy for local control of a symptomatic bulky primary.⁸⁹

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 in the refractory metastatic setting.¹²⁵ 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 1b trial of the anti-PD-1 antibody pembrolizumab in 24 patients with PD-L1–positive advanced squamous cell carcinoma of the anal canal.¹²⁶ 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.^{125,126}

Although further studies of PD-1/PD-L1 inhibitors are warranted, the panel added nivolumab and pembrolizumab as options for patients with metastatic anal cancer who have progressed 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,¹²⁷ and as discussed previously, responses to PD-1/PD-L1 inhibitors occur in 20% to 24% of patients.^{125,126} 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.¹²⁷

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.

Surveillance Following Primary Treatment

After primary treatment of nonmetastatic anal cancer, the surveillance and follow-up treatment recommendations for perianal and anal canal cancer are

the same. 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.⁴⁵ Interestingly, 72% of patients in this trial who did not show a complete response at 11 weeks from the start of treatment had experienced a complete response by 26 weeks.¹²⁸ Based on these results, the panel believes it may be appropriate to follow patients who have not shown a complete clinical response with persistent anal cancer for up to 6 months after completion of radiation and chemotherapy, as long as there is no evidence of progressive disease during this period of follow-up. Persistent disease may continue to regress even at 26 weeks 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. If biopsy-proven disease progression occurs, further intensive treatment is indicated (see "Treatment of Locally Progressive or Recurrent Anal Carcinoma," on this page).

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 3–6 months for 5 years, including DRE, anoscopic evaluation, and inguinal node palpation. Annual chest, abdominal, and pelvic CT with contrast is recommended for 3 years for patients who initially had locally advanced disease (ie, T3/T4 tumor) or node-positive cancers.

Treatment of Locally Progressive or Recurrent Anal Carcinoma

Despite the effectiveness of chemoRT in the primary treatment of anal carcinoma, rates of locoregional failure of 10% to 30% have been reported.^{129,130} 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 the

section on "Prognostic Factors," in the full NCCN Guidelines for Anal Cancer at NCCN.org).¹³¹

Evidence of progression found on DRE should be followed up using biopsy as well as restaging with CT and/or PET/CT imaging. Patients with biopsy-proven locally progressive disease are candidates for radical surgery with an APR and colostomy.¹³⁰

A recent multicenter retrospective cohort study looked at the cause-specific colostomy rates in 235 patients with anal cancer who were treated with radiotherapy or chemoRT from 1995 to 2003.¹³² 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, and local excision before RT 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.¹³³

In studies involving a minimum of 25 patients undergoing an APR for anal carcinoma, 5-year survival rates of 39% to 66% have been observed.^{129,130,134–137} Complication rates were reported to be high in some of these studies. Factors associated with worse prognosis following APR include an initial presentation of node-positive disease and RT doses <55 Gy used in the treatment of primary disease.¹³⁰

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 recent 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.¹³⁸ This technique is not recommended during surgery in patients with recurrent anal cancer.

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.^{139,140} 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, mitomycin/capecitabine, or 5-FU/cisplatin (category 2B for 5-FU/cisplatin), 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 previously discussed).

Surveillance Following Treatment of Recurrence:

Following APR, patients should undergo re-evaluation every 3–6 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, abdomen, and pelvis CT 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 after APR was 43%.¹⁴¹ 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%.^{141,142}

After treatment of inguinal node recurrence, patients should have a DRE and inguinal node palpation every 3–6 months for 5 years. In addition, anoscopy every 6–12 months and annual chest, abdominal, and pelvic CT with contrast imaging are recommended for 3 years.

Survivorship

The panel recommends that a prescription for survivorship and transfer of care to the primary care physician be written.¹⁴³ 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.¹⁴⁴

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, reduced libido).^{145–148} Anal cancer survivors also report significantly reduced global quality of life, with increased frequency of somatic symptoms including fatigue, dyspnea, pain, and insomnia.^{145,149,150} 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 health care professionals who work with survivors of adult-onset cancer in the post-treatment period, including those in specialty cancer survivor clinics and primary care practices. The NCCN Guidelines for Survivorship 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 continuous infusion 5-FU/mitomycin-based RT, capecitabine/mitomycin-based RT, or 5-FU/cisplatin-based RT (category 2B for 5-FU/cisplatin) in most cases. The exceptions are small, well-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 locoregional progressive disease after primary treatment should undergo an APR. Following complete remission of disease, patients with a local recurrence should be treated with an APR with a groin dissection if there is clinical evidence of inguinal nodal metastasis, and patients with a regional recurrence in the inguinal nodes can be treated with an inguinal node dissection, with consideration of RT with or without chemotherapy if no prior RT to the groin was given. Patients with evidence of extrapelvic metastatic disease should be treated with up to 2 lines of 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 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	Date Completed
Mahmoud M. Al-Hawary, MD	None	None	None	4/13/18
Al B. Benson III, MD	None	Boehringer Ingelheim GmbH; Bristol-Myers Squibb Company; Celgene Corporation; Eli Lilly and Company; EMD Serono, Inc.; Exelixis Inc.; Genentech, Inc.; Genomic Health, Inc.; ImClone Systems Incorporated; Merck & Co., Inc.; Oncosil Medical; sanofi-aventis U.S. LLC; Spectrum Pharmaceuticals, Inc.; and Taiho Pharmaceuticals Co., Ltd.	None	2/20/18
Lynette Cederquist, MD	None	None	None	12/4/17
Yi-Jen Chen, MD, PhD	None	None	None	6/6/18
Kristen K. Ciombor, MD	AbbVie, Inc.; Amgen Inc.; Array Biopharma Inc.; Bayer HealthCare; Boston Biomedical, Inc.; Bristol-Myers Squibb Company; Daiichi Sankyo Co.; Incyte Corporation; MedImmune Inc.; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; NuCana; Pfizer Inc.; and sanofi-aventis U.S. LLC	None	None	5/16/18
Stacey Cohen, MD	None	None	None	6/11/18
Harry S. Cooper, MD	None	None	None	7/4/17
Dustin Deming, MD	Abbott Laboratories; and Merck & Co., Inc.	Bristol-Myers Squibb Company; and Novocure Ltd	None	8/1/17
Paul F. Engstrom, MD	None	None	None	6/4/18
Jean L. Grem, MD	Elion Oncology; and ICON	None	None	5/25/18
Axel Grothey, MD	None	Bayer HealthCare; Boehringer Ingelheim GmbH; Bristol-Myers Squibb Company; Genentech, Inc.; and Guardant Health Inc.	None	9/15/17
Howard S. Hochster, MD	None	Amgen Inc.; Bayer HealthCare; Boehringer Ingelheim GmbH; Bristol-Myers Squibb Company; Eisai Inc.; Eli Lilly and Company; Genentech, Inc.; Merck & Co., Inc.; and Taiho Pharmaceuticals Co., Ltd.	None	8/3/17
Sarah Hoffe, MD	None	None	None	7/27/17
Steven Hunt, MD	None	None	None	6/1/18
Ahmed Kamel, MD	Boston Scientific Corporation	Boston Scientific Corporation; and Sirtex Medical	Bard Peripheral Vascular; and Boston Scientific Corporation	3/12/18
Natalie Kirilcuk, MD	None	None	None	3/21/18
Smitha Krishnamurthi, MD	CytomX Therapeutics, Inc.; and Regeneron Pharmaceuticals, Inc.	None	None	4/30/18
Wells A. Messersmith, MD	Alexo Therapeutics, Inc.; D3 Pharma Limited; Genentech, Inc.; Gilead Sciences, Inc.; Immunomedics, Inc.; Incyte Corporation; Millennium Pharmaceuticals, Inc.; OncoMed Pharmaceuticals, Inc.; Pfizer Inc.; Purdue Pharma LP; and Roche Laboratories, Inc.	Purdue Pharma LP	None	8/29/17
Jeffrey Meyerhardt, MD, MPH	Ignity, Inc.	Chugai Pharmaceutical Co., Ltd	None	3/16/18
Mary F. Mulcahy, MD	None	None	None	4/26/18
James D. Murphy, MD, MS	None	None	None	4/23/18
Steven Nurkin, MD, MS	None	None	None	6/3/18
Leonard Saltz, MD	Taiho Pharmaceutical Co., Ltd.	None	None	4/4/18
Sunil Sharma, MD	None	Arrien Pharmaceuticals; and Novartis Pharmaceuticals Corporation	ARIAD Pharmaceuticals, Inc.; Blend Therapeutics; Clovis Oncology; Exelixis Inc.; Guardant Health Inc.; and LSK Biopharma	10/18/17
David Shibata, MD	None	None	None	10/19/17
John M. Skibber, MD	None	None	None	4/13/18
Constantinos T. Sofocleous, MD, PhD, FSIR, FCIRES ^a	None	Sirtex Medical Inc.	Sirtex Medical Inc.	8/1/17
Elena M. Stoffel, MD, MPH	Cancer Prevention Pharmaceuticals	None	None	11/22/17
Eden Stotsky-Himelfarb, BSN, RN	None	None	None	6/11/18
Alan P. Venook, MD	Halozyne, Inc.	AstraZeneca Pharmaceuticals LP; Eisai Inc.; Genentech, Inc.; Roche Laboratories, Inc.; and Taiho Pharmaceuticals Co., Ltd.	None	6/4/18
Christopher G. Willett, MD	Extrinsic Health	Extrinsic Health	None	9/22/17
Evan Wutrick, MD	None	None	None	6/22/17

The NCCN Guidelines Staff have no conflicts to disclose.

^aThe following individuals have disclosed that they have an Employment/Governing Board, Patent, Equity, or Royalty:
Constantinos T. Sofocleous, MD, PhD, FSIR, FCIRES: Ethicon, Inc.