National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Anal Carcinoma

Version 2.2021 — June 30, 2021

NCCN.org

Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Anal Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

***Al B. Benson, III, MD/Chair †**
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

***Alan P. Venook, MD/Vice-Chair † ‡**
UCSF Helen Diller Family Comprehensive Cancer Center

Mahmoud M. Al-Hawary, MD ф
University of Michigan Rogel Cancer Center

Mustafa A. Arain, MD ¤
UCSF Helen Diller Family Comprehensive Cancer Center

Yi-Jen Chen, MD, PhD §
City of Hope National Medical Center

Kristen K. Ciombor, MD †
Vanderbilt-Ingram Cancer Center

Stacey Cohen, MD †
Fred Hutchinson Cancer Research Center/ Seattle Cancer Care Alliance

Harry S. Cooper, MD ≠
Fox Chase Cancer Center

Dustin Deming, MD †
University of Wisconsin Carbone Cancer Center

Linda M. Farkas, MD ¶
UT Southwestern Simmons Comprehensive Cancer Center

Ignacio Garrido-Laguna, MD, PhD †
Huntsman Cancer Institute at the University of Utah

Jean L. Grem, MD †
Fred & Pamela Buffett Cancer Center

Andrew Gunn, MD ф
O'Neal Comprehensive Cancer Center at UAB

NCCN
Kristina Gregory, RN, MSN
Lisa Gurski, PhD

J. Randolph Hecht, MD †
UCLA Jonsson Comprehensive Cancer Center

Sarah Hoffe, MD §
Moffitt Cancer Center

Joleen Hubbard, MD ‡
Mayo Clinic Cancer Center

Steven Hunt, MD ¶
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Kimberly L. Johung, MD §
Yale Cancer Center/ Smilow Cancer Hospital

Natalie Kirilcuk, MD ¶
Stanford Cancer Institute

Smitha Krishnamurthi, MD † Þ
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Wells A. Messersmith, MD †
University of Colorado Cancer Center

Jeffrey Meyerhardt, MD, MPH †
Dana-Farber Brigham and Women's Cancer Center

Eric D. Miller, MD, PhD §
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Mary F. Mulcahy, MD ‡ †
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Steven Nurkin, MD, MS ¶
Roswell Park Comprehensive Cancer Center

Michael J. Overman, MD † ‡
The University of Texas MD Anderson Cancer Center

Aparna Parikh, MD †
Massachusetts General Hospital Cancer Center

Hitendra Patel, MD †
UC San Diego Moores Cancer Center

Katrina Pedersen, MD, MS †
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Leonard Saltz, MD † ‡ Þ
Memorial Sloan Kettering Cancer Center

Charles Schneider, MD †
Abramson Cancer Center at the University of Pennsylvania

David Shibata, MD ¶
The University of Tennessee Health Science Center

John M. Skibber, MD ¶
The University of Texas MD Anderson Cancer Center

Constantinos T. Sofocleous, MD, PhD ф
Memorial Sloan Kettering Cancer Center

Elena M. Stoffel, MD, MPH ¤
University of Michigan Rogel Cancer Center

Eden Stotsky-Himelfarb, BSN, RN † ¶ ¥
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Christopher G. Willett, MD §
Duke Cancer Institute

Continue

ф Diagnostic/Interventional radiology
¤ Gastroenterology
‡ Hematology/Hematology oncology
Þ Internal medicine
† Medical oncology
≠ Pathology
¥ Patient advocate
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
* Discussion Section Writing Committee

NCCN Guidelines Panel Disclosures

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Anal Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

NCCN Anal Carcinoma Panel Members
Summary of the Guidelines Updates

Workup and Treatment - Anal Canal Cancer (ANAL-1)
Workup and Treatment - Perianal Cancer (ANAL-2)
Follow-up Therapy and Surveillance (ANAL-3)

Principles of Surgery (ANAL-A)
Principles of Systemic Therapy (ANAL-B)
Principles of Radiation Therapy (ANAL-C)
Principles of Survivorship (ANAL-D)

Staging (ST-1)

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Anal Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 2.2021 of the NCCN Guidelines for Anal Carcinoma from Version 1.2021 include:
MS-1: Discussion section updated to reflect the changes in the algorithm.

Updates in Version 1.2021 of the NCCN Guidelines for Anal Carcinoma from Version 2.2020 include:

ANAL-1
- Workup: "Consider" removed before "Fertility risk discussion."
- Treatment for Metastatic Disease
  - 5-FU/Cisplatin recommendation changed from a category 2A to a category 2B (also applies to ANAL-2, ANAL-3, ANAL-4)
- Footnote i added: Carboplatin/paclitaxel is the only regimen supported by randomized data and may be preferred over 5-FU/cisplatin due to toxicity profiles. (also applies to ANAL-2, ANAL-3, ANAL-4)
- Footnote j added: See NCCN Guidelines for the Management of Immunotherapy-Related Toxicities. (also applies to ANAL-2, ANAL-3, ANAL-4)

ANAL-3
- Surveillance
  - CT clarified for stage II—III.
- Treatment
  - Inguinal node recurrence
    - ◊ Carboplatin/paclitaxel added as a treatment option.

ANAL-4
- Footnote q added: Consider the use of immunotherapy (nivolumab or pembrolizumab) (category 2B) before proceeding to APR. Institutional experience has demonstrated some patients receive a good response and can avoid surgery.

ANAL-A
- Radical Surgery
  - Bullet 1; sub-bullet 2 modified: General principles for APR are similar to those for distal rectal cancer and include the incorporation of ~~meticulous~~ total mesorectal excision (TME).

ANAL-B 1 of 2
- The following clarification added to nivolumab and pembrolizumab: if not previously received.

ANAL-B 2 of 2
- Reference 7 updated.

ANAL-C 1 of 5
- The following statement removed:
  - Please note: Prior to the start of radiation therapy (RT), premenopausal female patients should be counseled on early treatment-induced menopause and sexual function, as well as infertility risks. See NCCN Guidelines for Survivorship.
- General Principles
  - Bullet 2 modified: Image-guided RT (IGRT) with kilovoltage (kV) imaging ~~and~~ *or* cone beam CT imaging should be routinely used during the course of treatment with IMRT and stereotactic body RT (SBRT).
  - Bullet 3 added: Consider SBRT for patients with oligometastatic disease.

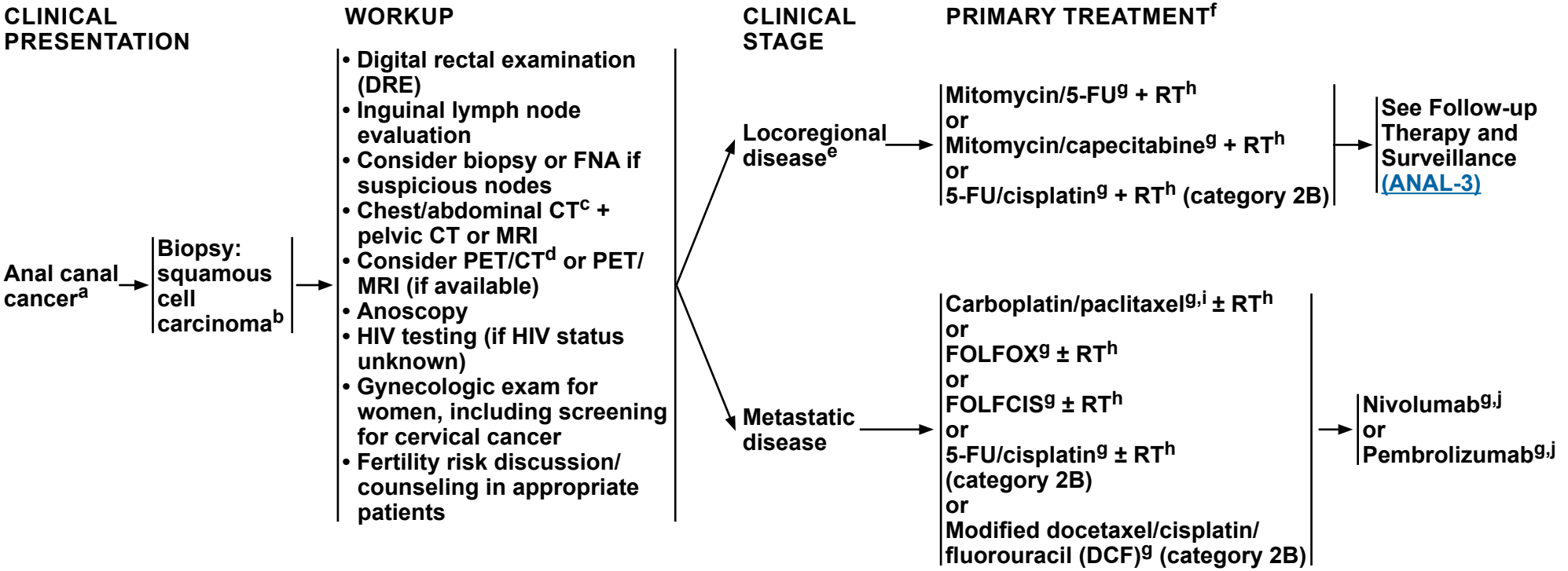
ANAL-C 2 of 5
- Target Volume Definition
  - Sub-bullet 4 modified with removal of the following sentence: Additionally, the entire mesorectum is included within the volume defined as gross disease CTV.

ANAL-C 5 of 5
- Side Effect Management changed to Supportive Care
  - Bullet 2 modified: Female patients should be counseled on *sexual dysfunction and* infertility risks and given information regarding oocyte, egg, or ovarian tissue banking prior to treatment.
  - Bullet 3 modified: Male patients should be counseled on *sexual dysfunction and* infertility risks and given information regarding sperm banking.

National Comprehensive Cancer Network®

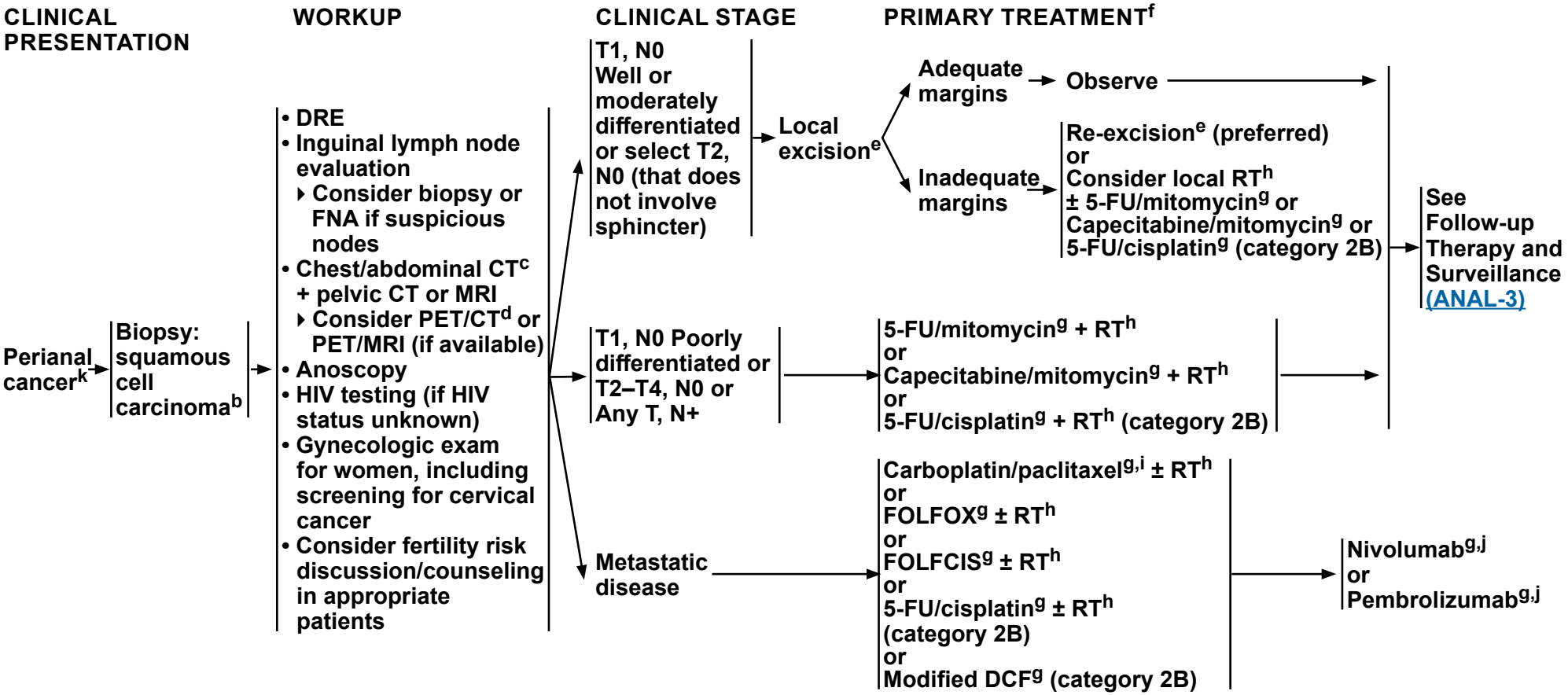
NCCN Guidelines Version 2.2021
Anal Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion



[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] See Principles of Surgery (ANAL-A).
[f] Modifications to cancer treatment should not be made solely on the basis of HIV status. See NCCN Guidelines for Cancer in People with HIV.
[g] See Principles of Systemic Therapy (ANAL-B).
[h] See Principles of Radiation Therapy (ANAL-C).
[i] Carboplatin/paclitaxel is the only regimen supported by randomized data and may be preferred over 5-FU/cisplatin due to toxicity profiles.
[j] See NCCN Guidelines for the Management of Immunotherapy-Related Toxicities.

Note: All recommendations are category 2A unless otherwise indicated.
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.



[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 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] See Principles of Surgery (ANAL-A).

[f] Modifications to cancer treatment should not be made solely on the basis of HIV status. See NCCN Guidelines for Cancer in People with HIV.

[g] See Principles of Systemic Therapy (ANAL-B).

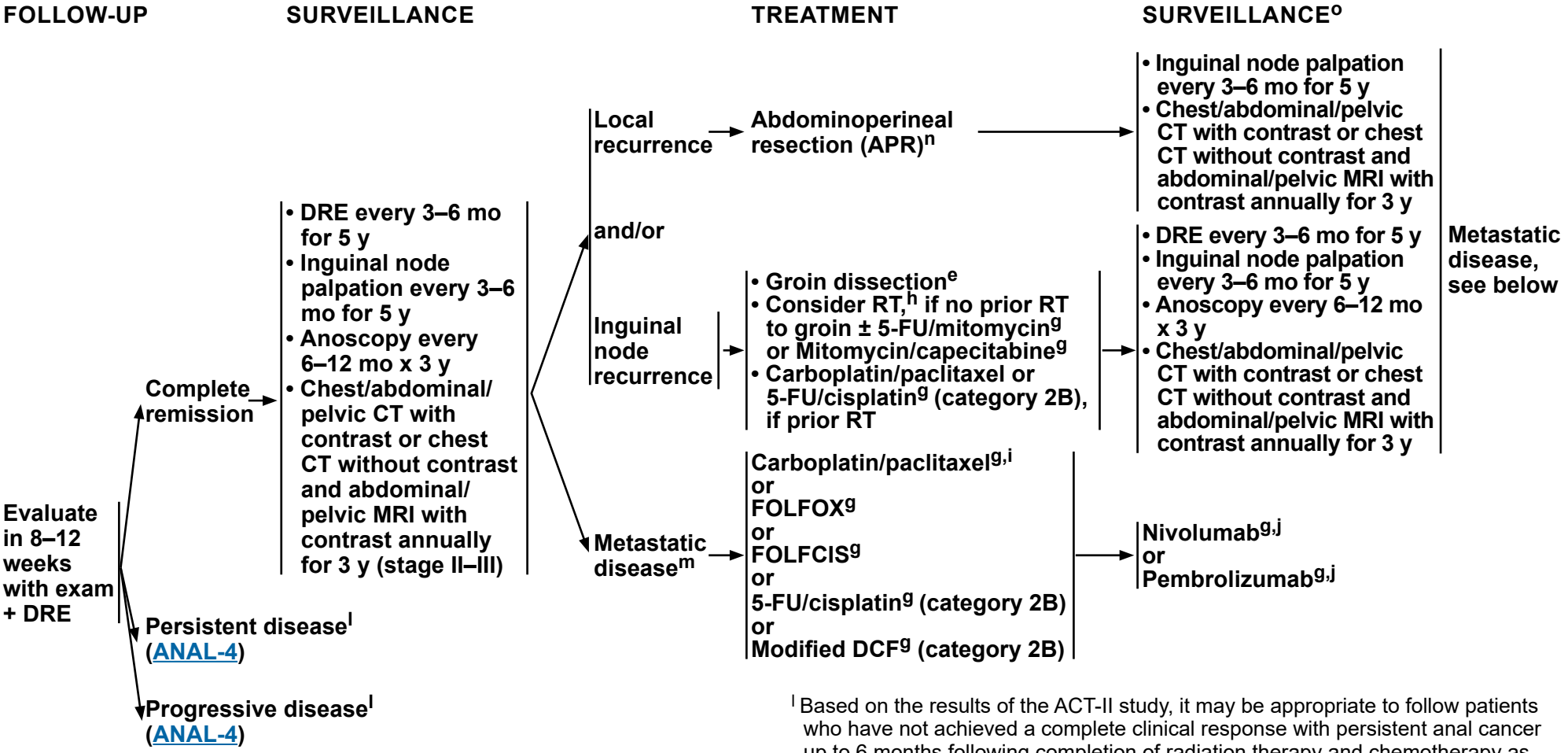
[h] See Principles of Radiation Therapy (ANAL-C).

[i] Carboplatin/paclitaxel is the only regimen supported by randomized data and may be preferred over 5-FU/cisplatin due to toxicity profiles.

[j] See NCCN Guidelines for the Management of Immunotherapy-Related Toxicities.

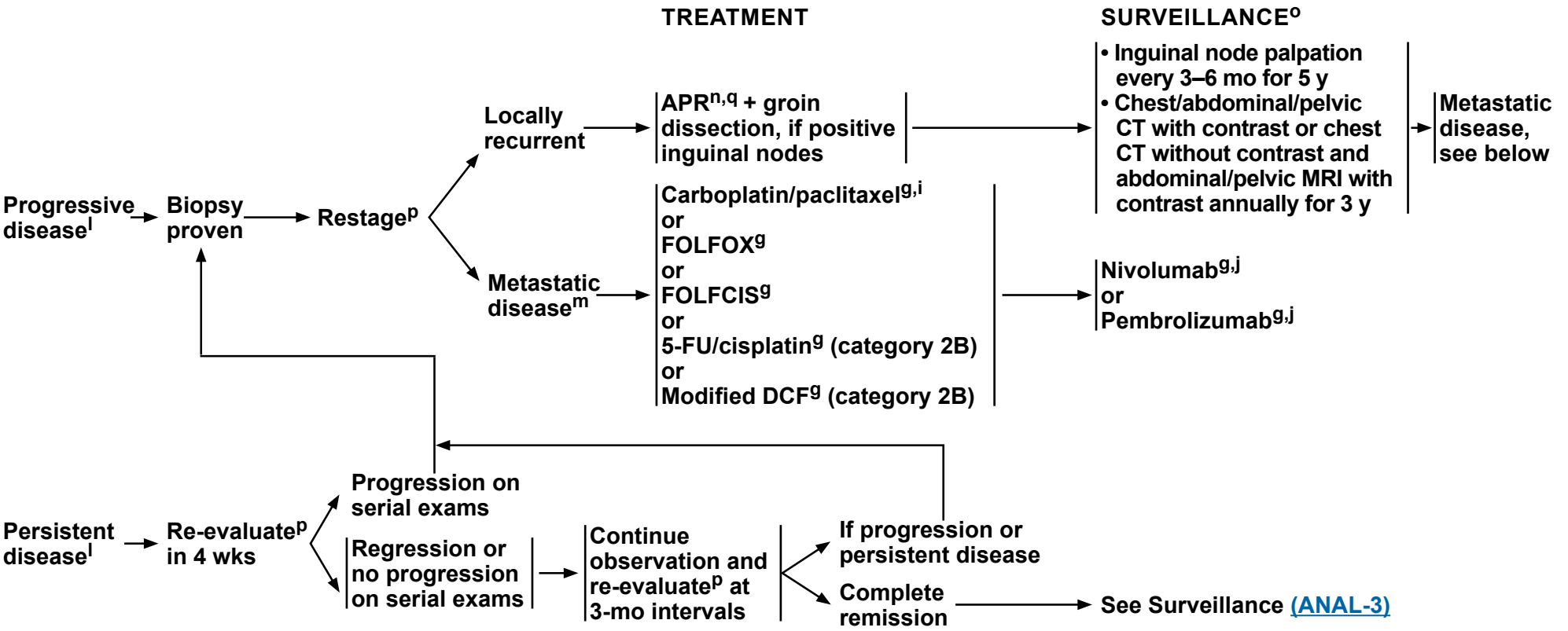
[k] The perianal region starts at the anal verge and includes the perianal skin over a 5-cm radius from the squamous mucocutaneous junction.

Note: All recommendations are category 2A unless otherwise indicated.
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.



[e] See Principles of Surgery (ANAL-A).
[g] See Principles of Systemic Therapy (ANAL-B).
[h] See Principles of Radiation Therapy (ANAL-C).
[i] Carboplatin/paclitaxel is the only regimen supported by randomized data and may be preferred over 5-FU/cisplatin due to toxicity profiles.
[j] See 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 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, 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. See Principles of Radiation Therapy (ANAL-C).
[n] Consider muscle flap reconstruction.
[o] See Principles of Survivorship (ANAL-D).

Note: All recommendations are category 2A unless otherwise indicated.
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.



[g] See Principles of Systemic Therapy (ANAL-B).
[i] Carboplatin/paclitaxel is the only regimen supported by randomized data and may be preferred over 5-FU/cisplatin due to toxicity profiles.
[j] See 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 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, 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. See Principles of Radiation Therapy (ANAL-C).
[n] Consider muscle flap reconstruction.
[o] See Principles of Survivorship (ANAL-D).
[p] Utilize imaging studies as per initial workup.
[q] Consider the use of immunotherapy (nivolumab or pembrolizumab) (category 2B) before proceeding to APR. Institutional experience has demonstrated some patients receive a good response and can avoid surgery.

Note: All recommendations are category 2A unless otherwise indicated.
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.

PRINCIPLES OF SURGERY

Local Excision

- **Superficially Invasive Squamous Cell Carcinoma (SISCCA)**
  - **For completely excised anal cancer (removed at time of biopsy) with ≤3-mm basement membrane invasion and a maximal horizontal spread of ≤7 mm, local surgical resection with negative margins may be adequate treatment.**
- **Perianal Cancer**
  - **T1N0, moderately to well-differentiated or select T2N0 squamous cell carcinoma (SCC) of the perianal region may be adequately treated by local excision with 1-cm margins.**
    - ◊ **Local surgical excision of select, smaller T2 lesions may be considered**
      - **– Where the tumor forms a discrete lesion arising from the perianal skin that is clearly separate from the anal canal**
      - **– Where negative margin excision can be accomplished without compromise of the adjacent sphincter muscles**
      - **– Where there is no evidence of regional nodal involvement**

Radical Surgery

- **Local Recurrence/Persistence**
  - **APR is the primary treatment.**
  - **General principles for APR are similar to those for distal rectal cancer and include the incorporation of total mesorectal excision (TME).**
  - **APR for anal cancer may require wider lateral perianal margins.**
  - **Due to the necessary exposure of the perineum to radiation, patients are prone to poor perineal wound healing and may benefit from the use of reconstructive tissue flaps for the perineum such as the vertical rectus or local myocutaneous flaps.**
- **Inguinal Recurrence**
  - **Patients who have already received groin radiation should undergo an inguinal node dissection.**
  - **Groin dissection can be done with or without APR depending on whether disease is isolated to the groin or is in conjunction with recurrence/persistence at the primary site.**

Note: All recommendations are category 2A unless otherwise indicated.
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.

PRINCIPLES OF SYSTEMIC THERAPY

Localized Cancer		Metastatic Cancer		Subsequent Therapy
Preferred Regimens	**Other Recommended Regimens**	**Preferred Regimens**	**Other Recommended Regimens**	**Preferred Regimens**
• 5-FU + mitomycin + RT • Capecitabine + mitomycin + RT	• 5-FU + cisplatin + RT	• Carboplatin + paclitaxel	• 5-FU + cisplatin • FOLFCIS • mFOLFOX6 • Modified DCF	• Nivolumab • Pembrolizumab if not previously received

Systemic Therapy Regimens and Dosing

- 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
    Concurrent radiotherapy (See ANAL-C)
    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)
    Concurrent radiotherapy (See ANAL-C)
- Capecitabine + mitomycin + RT[3,4]
  - Capecitabine 825 mg/m² PO BID, Monday–Friday, on each day that RT is given, throughout the duration of RT (typically 28 treatment days)
    Mitomycin 10 mg/m² days 1 and 29
    Concurrent radiotherapy (See ANAL-C)
    or
  - Capecitabine 825 mg/m² PO BID days 1–5 weekly x 6 weeks
    Mitomycin 12 mg/m² IV bolus day 1
    Concurrent radiotherapy (See ANAL-C)
- 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
  Concurrent radiotherapy (See ANAL-C)
- 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

Note: All recommendations are category 2A unless otherwise indicated.
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.

References

PRINCIPLES OF SYSTEMIC THERAPY
REFERENCES

[1] Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. JAMA 2008;299:1914-1921.
[2] 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, 2 x 2 factorial trial. Lancet Oncol 2013;14:516-524.
[3] Goodman KA, Julie D, Cercek A, et al. Capecitabine with mitomycin reduces acute hematologic toxicity and treatment delays in patients undergoing definitive chemoradiation using intensity modulated radiation therapy for anal cancer. Int J Radiat Oncol Biol Phys 2017;98:1087-1095.
[4] Thind G, Johal B, Follwell M, Kennecke HF. Chemoradiation with capecitabine and mitomycin-C for stage I-III anal squamous cell carcinoma. Radiat Oncol 2014;9:124.
[5] Gunderson LL, Winter KA, Ajani JA, et al. Long-term update of US Intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol 2012;30:4344-4351.
[6] Kim R, Byer J, Fulp WJ, et al. Carboplatin and paclitaxel treatment is effective in advanced anal cancer. Oncology 2014;87:125-32.
[7] Rao S, Sclafani F, Eng C, et al. International rare cancers initiative multicenter randomized phase II trial of cisplatin and 5-fluorouracil versus carboplatin and paclitaxel in advanced anal cancer:InterAAct. J Clin Oncol 2020;38:2510-2518.
[8] Sclafani F, Adams RA, Eng C, et al. InterAACT: An international multicenter open label randomized phase II advanced anal cancer trial comparing cisplatin (CDDP) plus 5-fluorouracil (5-FU) versus carboplatin (CBDCA) plus weekly paclitaxel (PTX) in patients with inoperable locally recurrent (ILR) or metastatic disease. J Clin Oncol 2015;33:3_suppl, TPS792.
[9] Eng C, Chang GJ, You YN, et al. The role of systemic chemotherapy and multidisciplinary management in improving the overall survival of patients with metastatic squamous cell carcinoma of the anal canal. Oncotarget 2014;5:11133-11142.
[10] Mondaca S, Chatila WK, Bates D, et al. FOLFCIS treatment and genomic correlates of response in advanced anal squamous cell cancer. Clin Colorectal Cancer 2019;18:e39-e52.
[11] Matsunaga M, Miwa K, Oka Y, et al. Successful treatment of metastatic anal canal adenocarcinoma with mFOLFOX + bevacizumab. Case Rep Oncol 2016;9:249-254.
[12] Kim S, Francois E, Andre T, et al. Docetaxel, cisplatin, and fluorouracil chemotherapy for metastatic or unresectable locally recurrent anal squamous cell carcinoma (Epitopes-HPV02): a multicentre, single-arm, phase 2 study. Lancet Oncol 2018;19:1094-1106.
[13] Morris VK, Salem ME, Nimeiri H, et al. Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicenter, single-arm, phase 2 study. Lancet Oncol 2017;18:446-453.
[14] Ott PA, Piha-Paul SA, Munster P, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal. Ann Oncol 2017;28:1036-1041.

Note: All recommendations are category 2A unless otherwise indicated.
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.

PRINCIPLES OF RADIATION THERAPY[1]

General Principles

- The consensus of the panel is that intensity-modulated RT (IMRT) is preferred over 3D conformal RT in the treatment of anal carcinoma.[2] IMRT requires expertise and careful target design to avoid reduction in local control by so-called "marginal-miss."[3] The clinical target volumes (CTV) for anal cancer used in the RTOG-0529 trial have been described in detail.[2] The outcome results of RTOG-0529 have been reported.[4] Also see The RTOG Consensus Panel Contouring Atlas for more details of the contouring atlas defined by RTOG. The information below provides details regarding simulation, target volume definition, dose prescription, organs at risk (OARs), IMRT constraints, quality assurance, and image guidance delivery.
- Image-guided RT (IGRT) with kilovoltage (kV) imaging or cone beam CT imaging should be routinely used during the course of treatment with IMRT and stereotactic body RT (SBRT).
- Consider SBRT for patients with oligometastatic disease.

Treatment Information

- Simulation
  - After clinical and radiologic staging, CT-based simulation is performed for radiation treatment planning. If available, PET/CT or PET/MRI (if available) at the time of simulation may be helpful to define local and regional target structures. Patients can be simulated in the supine or prone position and there are benefits to each approach in the appropriate clinical setting. Prone setup with a false tabletop allows for improved small bowel avoidance and may be useful in individuals with a large pannus and pelvic node involvement. Supine setup is usually more reproducible with less setup variability, potentially allowing for reduced planning target volume (PTV) margins and smaller treatment fields. Patients are typically simulated for anal cancer IMRT planning in the supine position with legs slightly abducted (frog-legged) with semi-rigid immobilization in vacuum-locked bag or alpha-cradle. Patients are instructed to maintain a full bladder for simulation and treatment.
  - In males, the external genitalia are typically positioned inferiorly such that setup is reproducible. In females, a vaginal dilator can be placed to help delineate the genitalia and move the vulva and lower vagina away from the primary tumor. A radiopaque marker should be placed at the anal verge and perianal skin involvement can be outlined with radio-opaque catheters. It may be helpful to place a catheter with rectal contrast in the anal canal at the time of simulation for tumor delineation.
  - In patients with adequate renal function, IV contrast facilitates identification of the pelvic and groin vasculature (which approximates at-risk nodal regions). Oral contrast identifies small bowel as an avoidance structure during treatment planning. For tumors involving the perianal skin or superficial inguinal nodes, bolus should be placed as necessary for adequate dosing of gross disease in these areas. Routine use of bolus may not be necessary as the tangential effect of IMRT may minimize skin sparing. In situations where adequate dosing of superficial targets is uncertain, in vivo diode dosimetry with the first treatment fraction can ensure appropriate dose at the skin surface.

[1] Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal. JAMA 2008;299:1914-1921.
[2] Myerson RJ, Garofalo MC, El Naqa I, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring atlas. Int J Radiat Oncol Biol Phys 2009;74:824-830.
[3] Pepek JM, Willett CG, Czito BG. Radiation therapy advances for treatment of anal cancer. J Natl Compr Canc Netw 2010;8:123-129.
[4] Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 2013;86:27-33.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
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.

PRINCIPLES OF RADIATION THERAPY[1]

Treatment Information, (continued)

- **Target Volume Definition**
  - **Target volume definition should be performed per ICRU 50 recommendations. Gross tumor volume (GTV) should include all primary tumor and involved lymph nodes, utilizing information from physical examination, endoscopic findings, diagnostic imaging, and simulation planning study for delineation. CTV should include the GTV plus areas at risk for microscopic spread from the primary tumor and at-risk nodal areas. If the primary tumor cannot be determined with available information (such as after local excision), the anal canal may be used as a surrogate target.**
  - **The pelvic and inguinal nodes should be routinely treated in all patients.**
  - **When using IMRT, a separate CTV volume for each planned treatment dose tier is contoured. One approach has been to define three tiers: a gross disease only volume, a high-risk elective nodal volume (including gross disease), and low-risk elective nodal volume (including gross disease). These volumes are determined by the presence or absence of tumor based on physical exam, biopsy, diagnostic and planning studies, and risk of nodal spread depending on tumor stage at presentation. The rationale for this approach is based on the shrinking fields technique. In RTOG-0529, a gross disease volume with a single elective nodal volume are used to deliver the prescribed course (dose-painting).**
  - **In defining the gross disease CTV around the primary tumor, an approximately 2.5-cm margin around GTV should be used with manual editing to avoid muscle or bone at low risk for tumor infiltration. To define the gross disease CTV around involved nodes, a 1-cm expansion should be made beyond the contoured involved lymph node with manual editing to exclude areas at low risk for tumor infiltration.**
  - **At-risk nodal regions include mesorectal, presacral, internal and external iliac, and inguinal nodes. The mesorectal volume encompasses the rectum and surrounding lymphatic tissue. The presacral nodal volume is typically defined as an approximately 1-cm strip over the anterior sacral prominence. To contour the internal and external iliac nodes, it is recommended to generally contour the iliac arteries and veins with approximately 0.7-cm margin (1–1.5 cm anteriorly on external iliac vessels) to include adjacent lymph nodes. In order to include the obturator lymph nodes, external and internal iliac volume contours should be joined parallel to the pelvic sidewall. The inguinal node volume extends beyond the external iliac contour along the femoral artery from approximately the upper edge of the superior pubic rami to approximately 2 cm caudad to saphenous/femoral artery junction. The inguinal node volume should be contoured as a compartment with general margins. The medial and lateral borders may be defined by adductor longus and sartorius muscles, respectively. Several recently published atlases are helpful to review when defining elective nodal CTVs.[5,6] The above descriptions are generalizations and each plan should be individualized based on the anatomy of each patient and tumor distribution.**

[1] Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal. JAMA 2008;299:1914-1921.
[5] Myerson RJ, Garofalo MC, El Naqa I, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring atlas. Int J Radiation Oncology Biol Phys 2009;74:824-830.
[6] Ng M, Leong T, Chander S, et al. Australasian Gastrointestinal Trials Group (AGITG) contouring atlas and planning guidelines for intensity-modulated radiotherapy in anal cancer. Int J Radiation Oncology Biol Phys 2012;83:1455-1462.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
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.

PRINCIPLES OF RADIATION THERAPY[1]

Treatment Information (continued)

- **Target Volume Definition**
  - **The high-risk elective nodal volume typically includes the gross disease CTV plus the entire mesorectum, presacral nodes, and bilateral internal and external iliac lymph nodes inferior to the sacroiliac joint. In patients with gross inguinal nodal involvement, the bilateral or unilateral inguinal nodes may be included in the high-risk elective nodal volume. The low-risk elective nodal volume should include the gross disease CTV, high-risk elective nodal CTV, and presacral, bilateral internal, and external iliac nodes above the inferior border of the sacroiliac joint to the bifurcation of the internal and external iliac vessels at approximately L5/S1 vertebral body junction. If there is no obvious involvement of the bilateral inguinal nodes, these are included in the low-risk elective nodal volume.**
  - **PTV should account for effects of organ and patient movement and inaccuracies in beam and patient setup. PTV expansions should typically be about 0.5–1.0 cm depending on use of image guidance and physician practice with treatment setup for each defined CTV. To account for differences in bladder and rectal filling, a more generous CTV to PTV margin is applied in these regions. These volumes may be manually edited to limit the borders to the skin surface for treatment planning purposes.**
- **Dose Prescription**
  - **With IMRT treatment planning, doses are typically prescribed to PTVs. The dose of radiation required to control disease is extrapolated from historical studies that show excellent rates of control with concurrent radiation and chemotherapy. Typically prescribed dose varies by the size of tumor and risk of microscopic spread in elective nodal areas. One approach with "shrinking field technique" is that the low-risk elective nodal PTV volume is typically prescribed to 30.6 Gy in 1.8 Gy daily fractions. The high-risk elective nodal PTV is sequentially prescribed an additional 14.4 Gy in 1.8 Gy daily fractions for a total prescribed dose of 45 Gy. Finally, for T1–2 lesions with residual disease after 45 Gy, T3–4 lesions, or N1 lesions, an additional 5.4–14.4 Gy in 1.8–2 Gy daily fractions is again sequentially prescribed to the gross disease PTV volume (total dose 50.4–59.4 Gy).**
  - **In RTOG-0529, the prescription parameters are different due to the use of only a single elective nodal volume and slightly different dose prescriptions depending on tumor stage. Furthermore, delivery of escalating dose to different target volumes was performed using a simultaneous integrated boost (SIB) dose painting technique with a maximum dose of 1.8 Gy per fraction to the primary tumor and large volume gross nodal involvement and 1.5 Gy per daily fraction to elective nodal areas. Table 1 outlines dose prescriptions by TNM stage according to the RTOG-0529 protocol. The SIB approach offers the convenience of developing a single treatment plan with reduced planning complexity, albeit with a lower biological dose delivered to the elective nodal areas. Utilization of SIB dose painting is a relatively new approach in the treatment of anal cancer and the implications of 1.5 Gy per fraction to the elective nodal region are not well studied in this disease.**
  - **For untreated patients presenting with synchronous local and metastatic disease, a platinum-based regimen is standard practice, and radiation can be considered for local control. The approach to radiation depends on the patient's performance status and extent of metastatic disease. If performance status is good and metastatic disease is limited, treat involved fields, 45–54 Gy to the primary tumor and involved sites in the pelvis, in coordination with plans for a platinum-based regimen. If there is low-volume liver oligometastasis, an SBRT dosing schema after systemic therapy may be appropriate depending on response. If metastatic disease is extensive and life expectancy is limited, a different schedule and dose of radiation should be considered, again in coordination with plans for 5-FU/cisplatin or a platinum-based regimen.**

[1] Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal. JAMA 2008;299:1914-1921.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
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.

PRINCIPLES OF RADIATION THERAPY[1]

Treatment Information (continued)

Table 1: Dose Specification of Primary and Nodal Planning Target Volumes: RTOG-0529[4]

TNM Stage	Primary Tumor PTV Dose	Nodal PTV Dose
T2, N0	50.4 Gy (28 fxs at 1.8 Gy/fx)	42 Gy (28 fxs at 1.5 Gy/fx)
T3–4, N0	54 Gy (30 fxs at 1.8 Gy/fx)	45 Gy (30 fxs at 1.5 Gy/fx)
T any, N+ (≤3 cm)	54 Gy (30 fxs at 1.8 Gy/fx)	50.4 Gy (30 fxs at 1.68 Gy/fx)
T any, N+ (>3 cm)	54 Gy (30 fxs at 1.8 Gy/fx)	54 Gy (30 fxs at 1.8 Gy/fx)

- **Dose Prescription**
  - **The usual scenario of recurrent disease is recurrence in the primary site or nodes after previous radiation therapy and chemotherapy. In this setting, surgery should be performed if possible, and, if not, palliative radiation therapy and chemotherapy can be considered based on symptoms, extent of recurrence, and prior treatment. Radiation therapy technique and doses are dependent on dosing and technique of prior treatment. In the setting of pure palliation, doses of 20–25 Gy in 5 fractions to 30 Gy in 10 fractions can be considered. SBRT can also be considered for treatment of primary and nodal recurrence in the setting of low-volume metastatic disease.**
- **OARs and IMRT Constraints**
  - **It is important to accurately define OARs so that dose to these structures can be minimized during treatment. In anal cancer, 2D and 3D treatment planning techniques are limited in their ability to spare most pelvic normal tissues due to the location of the target. With IMRT, dose to small bowel, bladder, pelvic/femoral bones, and external genitalia can be sculpted and minimized despite close proximity of these organs to target volumes. When contouring these structures, it is typically best to demarcate normal tissues on axial CT at least 2 cm above and below the PTV. Oral contrast is helpful to delineate the small bowel. While there is significant variability in how to contour the small bowel, one approach entails contouring the entire volume of peritoneal space in which the small bowel can move. As with elective nodal volume delineation, contouring atlases offer excellent guidance on defining OARs.[7] Once the OARs have been identified, the chief aim of IMRT planning is to limit the dose to these structures without compromising PTV coverage. The extent to which OARs can be avoided largely depends on the location and extent of tumor involvement at presentation as well as the extent to which the bowel extends into the lower pelvis and a given individual's anatomy.**
  - **Given patient variation with respect to OAR position and areas of tumor involvement, practical dose constraint guidelines are challenging. In tumors without gross nodal involvement it is often possible to limit OAR doses even further. Alternatively, in tumors with gross nodal involvement within the pelvis, compromise of PTV coverage may be necessary to limit doses to normal tissues, such as small bowel. Table 2 outlines dose constraints in RTOG-0529.**

[1] Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal. JAMA 2008;299:1914-1921.
[4] Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 2013;86:27-33.
[7] Gay HA, Barthold HJ, O'Meara E, et al. Pelvic normal tissue contouring guidelines for radiation therapy: a radiation therapy oncology group consensus panel atlas. Int J Radiation Oncol Biol Phys 2012;83:e353-e362.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
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.

PRINCIPLES OF RADIATION THERAPY[1]

Treatment Information (continued)

Table 2: DP-IMRT Dose Constraints for Normal Tissues[6]

Organ	Dose (Gy) at <5% Volume	Dose (Gy) at <35% Volume	Dose (Gy) at <50% Volume
Small bowel*,†	45 (<20 cc)	35 (<150 cc)	30 (<200 cc)
Femoral heads*	44	40	30
Iliac crest	50	40	30
External genitalia	40	30	20
Bladder	50	40	35
Large bowel†	45 (<20 cc)	35 (<150 cc)	30 (<200 cc)

Organs are listed in order of decreasing priority.
* Assigned criteria for major and minor violations were considered as part of the feasibility secondary endpoint.
† Dose constraints are based on absolute volume instead of % volume.

- **Quality Assurance and Image-Guided Treatment Delivery**
  - **Due to the sophistication and complexity of IMRT planning for anal cancer, comprehensive quality assurance measures must be implemented to ensure minimal variability between the designed and delivered treatment plans. Each institution should have a quality assurance program in place for the treatment of anal cancer patients.**
  - **The use of image guidance for radiation treatment delivery has significantly improved confidence in daily treatment setup. This has allowed for shrinking CTV to PTV expansions during the treatment planning process, which in turn further minimizes dose to OARs.**
- **Supportive Care**
  - **Female patients should be considered for vaginal dilators and instructed on the symptoms of vaginal stenosis.**
  - **Female patients should be counseled on sexual dysfunction and infertility risks and given information regarding oocyte, egg, or ovarian tissue banking prior to treatment.**
  - **Male patients should be counseled on sexual dysfunction and infertility risks and given information regarding sperm banking.**

[1] Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal. JAMA 2008;299:1914-1921.
[6] Reprinted from the International Journal of Radiation Oncology, Biology, Physics, Vol. 86/1, Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 2013;86:27-33 with permission from Elsevier.

Note: All recommendations are category 2A unless otherwise indicated.
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.

PRINCIPLES OF SURVIVORSHIP

Anal Carcinoma Surveillance:

- Long-term surveillance should be carefully managed with routine good medical care and monitoring, including cancer screening, routine health care, and preventive care.

Survivorship Care Planning:

The oncologist and primary care provider should have defined roles in the surveillance period, with roles communicated to the patient.[1]

- Develop survivorship care plan that includes:
  - Overall summary of treatment, including all surgeries, radiation treatments, and chemotherapy received.
  - Description of possible expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment.
  - Surveillance recommendations.
  - Delineation of appropriate timing of transfer of care with specific responsibilities identified for primary care physician and oncologist.
  - Health behavior recommendations.

Management of Late/Long-Term Sequelae of Disease or Treatment:[2-6]

- For issues related to distress, pain, neuropathy, fatigue, or sexual dysfunction, see NCCN Guidelines for Survivorship.
- Bowel function changes: chronic diarrhea, incontinence, stool frequency, stool clustering, urgency, cramping
  - Consider anti-diarrheal agents, bulk-forming agents, diet manipulation, pelvic floor rehabilitation, and protective undergarments.
  - Management of an ostomy
    - ◊ Consider participation in an ostomy support group or coordination of care with a health care provider specializing in ostomy care (ie, ostomy nurse).
    - ◊ Screen for distress around body changes (See NCCN Guidelines for Distress Management) and precautions around involvement with physical activity (SPA-A in the NCCN Guidelines for Survivorship).
- Urogenital dysfunction after resection and/or pelvic radiation[7,8]
  - Screen for sexual dysfunction, erectile dysfunction, dyspareunia, and vaginal dryness.
  - Screen for urinary incontinence, frequency, and urgency.
  - Consider referral to urologist or gynecologist for persistent symptoms.
- Potential for pelvic fractures/decreased bone density after pelvic radiation
  - Consider bone density monitoring.

Counseling Regarding Healthy Lifestyle and Wellness:[9]

See NCCN Guidelines for Survivorship

- Undergo all age- and gender-appropriate cancer and preventive health screenings as per national guidelines.
- Maintain a healthy body weight throughout life.
- Adopt a physically active lifestyle (at least 30 minutes of moderate-intensity activity on most days of the week). Activity recommendations may require modification based on treatment sequelae (ie, ostomy, neuropathy).
- Consume a healthy diet with an emphasis on plant sources. Diet recommendations may be modified based on severity of bowel dysfunction.
- Consider daily aspirin 325 mg for secondary prevention.
- Eliminate or limit alcohol consumption; no more than 1 drink/day for women, and 2 drinks/day for men.
- Seek smoking cessation counseling as appropriate.

Additional health monitoring and immunizations 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.

References

Note: All recommendations are category 2A unless otherwise indicated.
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.

PRINCIPLES OF SURVIVORSHIP
REFERENCES

[1] Hewitt M, Greenfield S, Stovall E. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, D.C.:The National Academies Press;2006.
[2] Schneider EC, Malin JL, Kahn KL, et al. Surviving colorectal cancer. Cancer 2007;110:2075-2082.
[3] Sprangers MAG, Taal BG, Aaronson NK, te Velde A. Quality of life in colorectal cancer. Stoma vs. nonstoma patients. Dis Colon Rectum 1995;38:361-369.
[4] Gami B, Harrington K, Blake P, et al. How patients manage gastrointestinal symptoms after pelvic radiotherapy. Aliment Pharmacol Ther 2003;18:987-994.
[5] DeSnoo L, Faithfull S. A qualitative study of anterior resection syndrome: the experiences of cancer survivors who have undergone resection surgery. Eur J Cancer Care (Engl) 2006;15:244-251.
[6] McGough C, Baldwin C, Frost C, Andreyev HJ. Role of nutritional intervention in patients treated with radiotherapy for pelvic malignancy. Br J Cancer 2004;90:2278-2287.
[7] Lange MM, Marijnen CAM, Mass CP, et al. Risk factors for sexual dysfunction after rectal cancer treatment. Eur J Cancer 2009;45:1578-88.
[8] Lange MM, Mass CP, Marijnen CAM, et al. Urinary dysfunction after rectal cancer treatment is mainly caused by surgery. Brit J Cancer 2008;95:1020-28.
[9] Kushi LH, Byers T, Doyle C, et al and The American Cancer Society 2006 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society Guidelines on Nutrition and Physical Activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin 2006;56:254-281.

Note: All recommendations are category 2A unless otherwise indicated.
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.

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Anal Carcinoma (8th ed., 2017)

Table 1. **Definitions for T, N, M**

T	Primary Tumor
TX	Primary tumor not assessed
T0	No evidence of primary tumor
Tis	High-grade squamous intraepithelial lesion (previously termed carcinoma in situ, Bowen disease, anal intraepithelial neoplasia II–III, high-grade anal intraepithelial neoplasia)
T1	Tumor 2 cm or less
T2	Tumor more than 2 cm but not more than 5 cm
T3	Tumor more than 5 cm
T4	Tumor of any size invades adjacent organ(s), such as the vagina, urethra, bladder

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes
N1a	Metastasis in inguinal, mesorectal, or internal iliac lymph nodes
N1b	Metastasis in external iliac lymph nodes
N1c	Metastasis in external iliac with any N1a nodes

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

Table 2. **AJCC Anatomic Stage/Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T1-T2	N1	M0
Stage IIIB	T4	N0	M0
Stage IIIC	T3-T4	N1	M0
Stage IV	Any T	Any N	M1

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

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 indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Discussion

This discussion corresponds to the NCCN Guidelines for Anal Carcinoma. Last updated June 30, 2021

Table of Contents

Overview **MS-2**

Literature Search Criteria and Guidelines Update Methodology **MS-2**

Risk Factors **MS-3**

Risk Reduction MS-3

Anatomy/Histology **MS-5**

Pathology **MS-5**

Staging **MS-6**

Prognostic Factors **MS-7**

Management of Anal Carcinoma **MS-8**

Clinical Presentation/Evaluation MS-8

Primary Treatment of Non-Metastatic Anal Carcinoma MS-9

Treatment of Metastatic Anal Cancer MS-16

Surveillance Following Primary Treatment MS-18

Treatment of Locally Progressive or Recurrent Anal Carcinoma MS-18

Survivorship **MS-20**

Summary **MS-20**

References **MS-21**

Overview

An estimated 9090 new cases (3020 male and 6070 female) of anal cancer involving the anus, anal canal, or anorectum will occur in the United States in 2021, accounting for approximately 2.7% of digestive system cancers.[1] It has been estimated that 1430 deaths due to anal cancer will occur in the United States in 2021.[1] Although considered to be a rare type of cancer, the incidence rate of invasive anal carcinoma in the United States increased by approximately 1.9-fold for males and 1.5-fold for females from the period of 1973 through 1979 to 1994 through 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%/year from 1992 to 2001.[5] An analysis of squamous cell anal cancer incidence from the U.S. Cancer Statistics dataset reported an annual increase of 2.7% between 2001 to 2015 with the greatest increases in age groups 50 years and older.[6] Anal cancer mortality rates (2001–2016) also rose, with an average increase of 3.1% per year. Another analysis of anal cancer incidence data from the National Program of Cancer Registries and SEER programs from 2001 to 2016 showed similar trends, 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 greater than or equal to 50 years of age.[7] Increases in incidence of anal cancer during that time frame were especially noted for females 50 years or age and older.

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, 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.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Anal Carcinoma, an electronic search of the PubMed database was performed to obtain key literature in the field of anal cancer, using the following search terms: (anal cancer) OR (anal squamous cell carcinoma). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[11]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion. NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. When citing data and

recommendations from other organizations, the terms *men*, *male*, *women*, and *female* will be used to be consistent with the cited sources.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

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.[12-19]

The association between anal carcinoma and persistent infection with a high-risk form of HPV (eg, HPV-16; HPV-18) is especially strong.[13,20,21] 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, with HPV-16 detected in 73% of them. In contrast, high-risk HPV was not detected in any of the rectal cancer specimens analyzed.[13] In addition, results of a systematic review of 35 peer-reviewed anal cancer studies that included detection of HPV DNA published up until July 2007 showed the prevalence of HPV-16/18 to be 72% in patients with invasive anal cancer.[21] Population and registry studies have found similar HPV prevalence rates in anal cancer specimens.[22,23] A 2012 report from the U.S. Centers for Disease Control and Prevention (CDC) estimated that 86% to 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 HIV-infected males who have sex with males (MSM) in North America, and in the range of 3.9 to 30 per 100,000 person years in females living with HIV.[31,32] Recent 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]

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 high-risk individuals 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 high-risk individuals.[53-55] Most guidelines do not recommend anal cancer screening even in high-risk individuals 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 respond better to imiquimod. Regardless of treatment, recurrence rates were high, and careful follow-up is likely needed. A large ongoing randomized phase III trial is comparing topical or ablative treatment with active monitoring in PLWH with high-grade AIN. The primary outcome measure is time to anal cancer, and the study is estimated to be completed in 2022 (clinicaltrials.gov NCT02135419).

HPV Immunization

A quadrivalent HPV vaccine is available and has been shown to be effective in preventing persistent cervical infection with HPV-6, -11, -16, or -18 as well as in preventing high-grade cervical intraepithelial neoplasia related to these strains of the virus.[61-63] 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.[64] A recent substudy of a larger double-blind study assessed the efficacy of the vaccine for the prevention of AIN and anal cancer related to infection with HPV-6, -11, -16, or -18 in MSM.[65] In this study, 602 healthy MSM aged 16 to 26 years were randomized to receive the vaccine or a placebo. While none of the participants in either arm developed anal cancer during the 3-year follow-up period, there were 5 cases of grade 2/3 AIN associated with one of the vaccine strains in the vaccine arm and 24 such cases in the placebo arm in the per-protocol population, giving an observed efficacy of 77.5% (95% CI, 39.6–93.3). Since high-grade AIN 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.[66] 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).[67,68] It has also been shown to be effective at preventing high-grade cervical intraepithelial neoplasias in young people.[69] 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.[70] Targeting the additional strains over the quadrivalent vaccine is predicted to prevent an additional 464 cases of anal cancer annually.[71] This vaccine was compared to the quadrivalent vaccine in an international, randomized phase IIb–III study that included more than 14,000 female patients.[72] 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.[73-76] The American Academy of Pediatrics concurs with this vaccination schedule.[77] ASCO released a statement regarding HPV vaccination for cancer prevention with the goal of increasing vaccine update.[78] In 2018, the FDA expanded use of the 9-valent vaccine to include individuals aged 27 through 45 years,[79] 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 two categories. The anal canal is the more proximal portion of the anal region. The 8th 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 is gently pressed.[80] 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 is gently pressed; and 3) are within 5 cm of the anus.[80] 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.[15,81] The anal margin, on the other hand, 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.[15,81] 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).[82]

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.[15,81,83] 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.[81] Tumors can involve both the anal canal and the anal margin.

Pathology

Most primary cancers of the anal canal are of squamous cell histology.[81] The second edition of the WHO classification system of anal carcinoma designated all squamous cell carcinoma variants of the anal canal as cloacogenic and identified subtypes as large-cell keratinizing, large-cell non-keratinizing (transitional), or basaloid.[84] It has been reported that

squamous cell cancers in the more proximal region of the anal canal are more likely to be non-keratinizing and less differentiated.[15] 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,[85,86] and all subtypes have been included under a single generic heading of squamous cell carcinoma.[80,85] Reasons for this change include the following: both cloacogenic (which is sometimes used interchangeably with the term basaloid) and transitional tumors are now considered to be non-keratinizing tumors; it has been reported that both keratinizing and non-keratinizing tumors have a similar natural history and prognosis[85]; and a mixture of cell types frequently characterize histologic specimens of squamous cell carcinomas of the anal canal.[81,85,87] 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.[81]

Perianal squamous cell carcinomas are more likely than those of the anal canal to be well-differentiated and keratinizing large-cell types,[88] 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.[80,81] 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.[81]

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.[89,90]

Staging

The TNM staging system for anal canal cancer developed by the AJCC is detailed in the guidelines.[80] 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*, below).

In the past, these guidelines have used the AJCC TNM skin cancer system for the staging of perianal cancer since the two types of cancers have a similar biology. However, the 7th edition of the AJCC Cancer Staging Manual included substantial changes to the cutaneous squamous cell carcinoma stagings,[91] 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, pre-cancerous lesions in the anal canal. It is important to look for such anal canal involvement, particularly if conservative management (simple excision) is being contemplated. Many patients, particularly 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.[15] According to the SEER database,[92] 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.[92] 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.[93] 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.[93] An analysis of more than 600 patients with non-metastatic 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.[94]

By the 8th edition of AJCC Cancer Staging Manual, the former N2 and N3 categories by locations of positive nodes were removed. New categories of N1a, N1b, and N1c were defined. N1a represents metastasis in inguinal, mesorectal, or internal iliac nodes. N1b represents metastasis in external iliac nodes. N1c represents metastasis in external iliac with any N1a nodes.[80] However, initial therapy of anal cancer does not typically involve surgery, and the true lymph node status may not be determined accurately by clinical and radiologic evaluation. Fine-needle aspiration (FNA) biopsy of inguinal nodes 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,[95] 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*, below).

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.[96] Male sex, positive nodes, and tumor size greater than 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.[97] 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.[98] Similarly, recent multivariate analyses of data from the ACT I trial also showed that positive lymph nodes and male sex are prognostic indicators for higher local regional failure, anal cancer death, and lower OS.[99]

Data suggest that HPV- and/or p16-positivity are prognostic for improved OS in patients with anal carcinoma.[100-103] In a retrospective study of 143 tumor samples, p16-positivity was an independent prognostic factor for OS (HR, 0.07; 95% CI, 0.01–0.61; P = .016).[101] Another study of 95 patients found similar results.[100]

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.[15] 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.

The panel recommends a thorough examination/evaluation, including a careful DRE, an anoscopic examination, and palpation of the inguinal lymph nodes, with FNA and/or excisional biopsy of nodes found to be enlarged by either clinical or radiologic examination. Evaluation of pelvic lymph nodes with CT or MRI of the pelvis is also recommended. These methods can also provide information on whether the tumor involves other abdominal/pelvic organs; however, assessment of T stage is primarily performed through clinical examination. A CT scan of the abdomen is also recommended to assess possible disease dissemination. Since veins of the anal region are part of the venous network associated with systemic circulation,[81] chest CT scan is performed to evaluate for pulmonary metastasis. Gynecologic exam, including cervical cancer screening, is suggested due to the association of anal cancer and HPV.[13] A discussion of infertility risks and counseling on fertility preservation, if appropriate, should be carried out prior to 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.[17] Furthermore, about 13% of people in the United States who are infected with HIV are not aware of their infection status,[104] 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.[105] HIV testing may be particularly important in patients with cancer, because identification of HIV infection has the potential to improve clinical outcomes.[106] The CDC recommends HIV screening for all patients in all health care settings unless the patient declines testing (opt-out screening).[107]

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.[108-113] A systematic review and meta-analysis of seven retrospective and five 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.[109] 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.[114] The use of PET or PET/CT led to upstaging in 5% to 38% of patients and downstaging in 8% to 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.[115] PET/CT results can also impact radiation therapy planning, as systematic reviews and meta-analyses have shown that treatment plan modifications occurred in 12% to 59% of patients based on PET/CT results.[114,116] 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.[117] 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% to 70%, and the morbidity with a permanent colostomy was considerable.[15] In 1974, Nigro and coworkers observed complete tumor regression in some patients with anal carcinoma treated with preoperative 5-FU–based concurrent chemotherapy and radiation (chemoRT) including either mitomycin or porfiromycin, suggesting that it might be possible to cure anal carcinoma without surgery and permanent colostomy.[118] Subsequent nonrandomized studies using similar regimens and varied doses of chemoRT provided support for this conclusion.[119,120] 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.[18] Summaries of clinical trials involving patients with anal cancer have been presented,[121,122] and several key trials are discussed below.

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.[98] 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.[123] A recently published follow-up study on these patients demonstrates that a clear benefit of chemoRT remains after 13 years, including a benefit in OS.[124] 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; $P = .004$). 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.[125] Therefore, this study concludes that radiation 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 Guideline *Recommendations for the Primary Treatment of Anal Canal Cancer* and *Recommendations for the Primary Treatment of Perianal Cancer* can be found below.

A few studies have addressed the efficacy and safety of specific chemotherapeutic agents in the chemoRT regimens used in the treatment of anal carcinoma.[96,126,127] 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.[127] The OS rate at 4 years was the same for the two groups, however, reflecting the ability to treat recurrent patients 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.[128-131] Capecitabine has therefore been assessed as an alternative to 5-FU in chemoRT regimens for non-metastatic anal cancer.[132-135] A retrospective study compared 58 patients treated with capecitabine to 47 patients treated with infusional 5-FU; both groups also received mitomycin and radiation.[134] No significant differences were seen in clinical complete response, 3-year locoregional control, 3-year OS, or colostomy-free survival between the two groups of patients. 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.[133] 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.[136] 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.[126]

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.[137] 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 two 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 observed 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 following 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 two cycles followed by concurrent chemoRT with 5-FU and cisplatin; or 2) concurrent chemoRT with 5-FU and mitomycin.[96,138] 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).[138] Five-year OS was also significantly better in the mitomycin arm (70.7% vs. 78.3%; *P* =

.026).[138] In addition, 5-year colostomy-free survival showed a trend towards statistical significance (65.0% vs. 71.9%; *P* = .05), again in favor of the mitomycin group. Since the two 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.[121,139] However, since ACT II demonstrated that the two chemoRT regimens are equivalent, some have suggested that results from RTOG 98-11 suggest that induction chemotherapy is probably detrimental.[140]

Results from ACCORD 03 also suggest that there is no benefit of a course of chemotherapy given prior to chemoRT.[141] 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.[142]

A recent retrospective analysis, however, suggests that induction chemotherapy preceding chemoRT may be beneficial for the subset of patients with T4 anal cancer.[143] The 5-year colostomy-free survival rate was significantly better in T4 patients who received induction 5-FU/cisplatin compared to those who did not (100% vs. 38 ± 16.4%, *P* = .0006).

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.[144] 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.[145]

There has also been interest in the use of biologic therapies for the treatment of anal cancer. A phase 3 trial is investigating the use of the PD-1 inhibitor, nivolumab, following combined modality therapy for high risk anal carcinoma.[146] This trial is expected to enroll 344 participants and is expected to complete by the end of 2021. Cetuximab is an epidermal growth factor receptor (EGFR) inhibitor, whose anti-tumor activity is dependent on the presence of wild-type *KRAS*.[147] Because *KRAS* mutations appear to be very rare in anal cancer,[148,149] 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) and PLWH (AMC045) with anal squamous cell carcinoma.[150,151] 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.[150] The toxicities associated with the regimen were substantial, with grade 4 toxicity occurring in 32% of the study population and three treatment-associated deaths (5%). In AMC045, the 3-year locoregional failure rate was 20% (95% CI, 10%–37%) by Kaplan-Meier estimate.[151] Grade 4 toxicity and treatment-associated rates were similar to that 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.[152] 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.[153] The 15 evaluable patients from ACCORD 16 had a 4-year DFS rate of 53% (95% CI, 28%–79%), and two of the five patients who completed the planned treatments had locoregional recurrences.[154]

Radiation Therapy

Prior to the start of RT, patients should be counseled on infertility risks and given information regarding sperm, oocyte, egg, or ovarian tissue banking prior to treatment. 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 (AYA) Oncology for more information.

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.[155] 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).[156] In a third study of patients with T3, T4, or lymph node-positive tumors, RT doses of greater than or equal to 54 Gy administered with limited treatment breaks (<60 days) were associated with increased local control.[157] 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.[141] No benefit was seen with the higher dose of radiation. These results are supported by much earlier results from the RTOG 92-08 trial[158] and suggest that doses of greater than 59 Gy provide no additional benefit to patients with anal cancer. The randomized, phase 2 DECREASE study (NCT04166318) is currently looking at how well lower-dose chemoRT works in comparison to standard-dose chemoRT for patients with stage I or IIA anal cancer.[159] Patients on this study are randomized to either 28 fractions (standard-dose) or 20 or 23 fractions (deintensified dose) of IMRT. Study completion is expected in 2025.

There is evidence that treatment interruptions, either planned or required by treatment-related toxicity, can compromise the effectiveness of treatment.[112] 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 to patients who only had treatment breaks for severe skin toxicity,[160] 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).[137] Although results of these and other studies have supported the benefit of delivery of chemoRT over shorter time periods,[161-163] treatment breaks in the delivery of chemoRT are required in up to 80% of patients since chemoRT-related toxicities are common.[163] 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.[81]

Some of the reported late side effects of chemoRT include increased frequency and urgency of defecation, chronic perineal dermatitis, dyspareunia, and impotence.[164,165] In some cases, severe late RT complications, such as anal ulcers, stenosis, and necrosis, may necessitate surgery involving colostomy.[165] 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 female patients undergoing RT for anal cancer compared with older female patients with anal cancer who did not receive RT.[166]

An increasing body of literature suggests that toxicity can be reduced with advanced radiation delivery techniques.[112,167-177] Intensity-modulated radiation therapy (IMRT) utilizes detailed beam shaping to target specific volumes and limit the exposure of normal tissue.[176] Multiple pilot studies have demonstrated reduced toxicity while maintaining local control using IMRT. For example, in a cross-study comparison of a multicenter study of 53 patients with anal cancer treated with concurrent 5-FU/mitomycin chemotherapy and IMRT compared to patients in the 5-FU/mitomycin arm of the randomized RTOG 98-11 study, which used conventional 3-D RT, the rates of grade 3/4 dermatologic toxicity were 38%/0% for IMRT-treated patients compared to 43%/5% for those undergoing conventional RT.[96,176] 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.[178] 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 3-D conformal radiotherapy, despite the fact that the IMRT group had a higher average N stage.[179]

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 to 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 to conventional radiation on RTOG 98-11.[180] 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 anal cancer patients treated with dose-painted IMRT as per RTOG 0529 have been reported.[181] Of 99 eligible patients, 92% of patients had a clinically complete response after a median follow-up of 49 months. The 4-year OS was 85.5% and the 4-year event-free survival was 75.5%. The rate of grade greater than or equal to 2 non-hematologic late toxicities was 15%.

A retrospective cohort study using the 2014 linkage of the SEER-Medicare database showed that IMRT is associated with higher total costs than 3-D 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; $P = .02$).[182]

Recommendations regarding RT doses follow the multifield technique used in the RTOG 98-11 trial.[96] PET/CT should be considered for treatment planning.[183] All patients should receive a minimum RT dose of 45 Gy to the primary cancer. The recommended initial RT dose is 30.6 Gy to the pelvis, anus, perineum, and inguinal nodes; there should be attempts to reduce the dose to the femoral heads. Field reduction off the superior field border and node-negative inguinal nodes is recommended after delivery of 30.6 Gy and 36 Gy, respectively. For

patients treated with an anteroposterior-posteroanterior (AP-PA) rather than multifield technique, the dose to the lateral inguinal region should be brought to the minimum dose of 36 Gy using an anterior electron boost matched to the PA exit field. Patients with disease clinically staged as node-positive or T2–T4 should receive an additional boost of 9 to 14 Gy. The consensus of the panel is that IMRT is preferred over 3-D conformal RT in the treatment of anal carcinoma.[184] IMRT requires expertise and careful target design to avoid reduction in local control by marginal miss.[112] The clinical target volumes for anal cancer used in the RTOG 0529 trial have been described in detail.[184] Also see 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 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 two situations. The first is for superficially invasive anal cancer, which is defined as anal cancer that has been completely excised, with less than or equal to 3-mm basement membrane invasion and a maximal horizontal spread of less than or equal to 7 mm (T1,NX).[185] 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, seven of whom met the criteria for classification as superficially invasive.[186] 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 T1,N0, well-differentiated perianal cancer or select T2,N0 perianal cancer that does not involve the sphincter (also see *Recommendations for the Primary Treatment of Perianal Cancer*, below). In these cases, a 1-cm margin is recommended. A retrospective cohort study that included 2243 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; $P < .001$).[187] 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*, below).

Treatment of Anal Cancer in Patients Living with HIV/AIDS

As discussed above (see *Risk Factors*), PLWH have been reported to be at increased risk for anal carcinoma.[18,27-30] Some evidence suggests that ART may be associated with a decrease in the incidence of high-grade AIN and its progression to anal cancer.[34,188] 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.[189-191] 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 four times higher in PLWH at 3 years (62% vs. 13%) and found significantly higher rates of severe acute skin toxicity for PLWH.[190] 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 3720 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 to those who were HIV-negative.[191]

Most studies, however, have found outcomes to be similar in PLWH and HIV-negative patients.[192-199] In a retrospective cohort study of 1184 veterans diagnosed with squamous cell carcinoma of the anus between 1998 and 2004 (15% of whom tested positive for HIV), no differences with respect to receipt of treatment or 2-year survival rates were observed when the group of PLWH was compared with the group of patients testing negative for HIV.[194] 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.[198] A recent population-based study of almost 2 million patients with cancer, including 6459 PLWH, found no increase in cancer-specific mortality for anal cancer in PLWH.[200] 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, including the use of normal tissue-sparing radiation techniques, the consideration of non-malignant 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 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 for patients with non-metastatic anal canal cancer. Mitomycin/5-FU or mitomycin/capecitabine is administered concurrently with radiation.[96,133-135] Alternatively, 5-FU/cisplatin can be given with concurrent radiation (category 2B).[201] 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.[81] Capecitabine is given orally, Monday through Friday, for 4 or 6 weeks, with bolus injection of mitomycin and concurrent radiation.[133,135]

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.[202] 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.[203] 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 prior to 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 for patients with T1,N0 well-differentiated perianal cancers or select T2,N0 perianal 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 above).[96,133-135,201]

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.[204] Since anal carcinoma is a rare cancer and only 10% to 20% of patients with anal carcinoma present with extrapelvic metastatic disease,[204] 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. Palliative RT can be administered with chemotherapy for local control of a symptomatic bulky primary.[183]

First-Line Treatment of Metastatic Anal Cancer

Based on results from the phase II International Multicentre InterAACT study (clinicaltrials.gov NCT02051868), carboplatin in combination with paclitaxel has been noted as the preferred regimen for first-line treatment of metastatic anal cancer by the NCCN Panel.[205] In this trial, 91 patients with previously untreated, unresectable, locally recurrent or metastatic anal squamous cell carcinoma were randomized to either carboplatin plus paclitaxel or cisplatin plus 5-FU. While response rates were similar between carboplatin plus paclitaxel and cisplatin plus 5-FU (59% and 57%, respectively), carboplatin plus paclitaxel showed lower toxicity compared to cisplatin plus 5-FU (71% vs. 76% grade ≥3 toxicity and 36% vs. 62% [*P* = .016] serious adverse events). Median PFS and OS were 8.1 months and 20 months for carboplatin plus paclitaxel and 5.7 months and 12.3 months for cisplatin plus 5-FU (HR for OS, 2.0; 95% CI, 1.15–3.47; *P* = .014).[205] The results from the InterAACT trial are in agreement with older studies that showed that chemotherapy with a fluoropyrimidine-based regimen plus cisplatin[201,206-208] or a platinum-based therapy plus paclitaxel[207,209,210] 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 plus cisplatin (category 2B reflecting its similar efficacy, but higher toxicity, when compared to carboplatin plus 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.[211] The safety of FOLFOX in patients with anal cancer has been demonstrated in a case report.[212] 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.

DCF is another regimen that has been evaluated for metastatic anal cancer.[213,214] 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 to the standard regimen.[213] 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 to 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 plus nivolumab for treatment-naïve metastatic anal cancer.[215] This study is expected to enroll 205 participants and complete in 2023. POD1UM-303/InterAACT2 is a similar, phase 3 global study (NCT04472429) investigating the addition of the checkpoint inhibitor, retifanlimab, to carboplatin/paclitaxel chemotherapy and comparing it to chemotherapy alone.[216] 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.[217] Two complete responses and seven 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 multi-cohort, 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.[218] 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.[217,218] The phase II KEYNOTE-158 study investigated the use of pembrolizumab in patients with noncolorectal microsatellite instability-high (MSI-H)/ deficient mismatch repair (dMMR) cancers, including one patient with anal cancer.[219] This study demonstrated the clinical benefit of pembrolizumab for patients with previously treated unresectable or metastatic MSI-H/dMMR noncolorectal cancer. A phase 2 clinical trial (NCT02314169) is also underway investigating the efficacy and safety of nivolumab, with or without ipilimumab, for patients with refractory metastatic anal canal cancer.[220] This trial has an estimated enrollment of 137 participants and is expected to complete in February 2022.

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 progressed on first-line chemotherapy in the 2018 version of these guidelines. Microsatellite instability (MSI)/mismatch repair (MMR) testing is not required. MSI is uncommon in anal cancer,[221] and as discussed above, responses to PD-1/PD-L1 inhibitors occur in 20% to 24% of patients.[217,218] 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 (MSS).[221]

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

Following primary treatment of non-metastatic anal cancer, the surveillance and follow-up treatment recommendations for perianal and anal canal cancer are the same. Patients are re-evaluated by DRE between 8 and 12 weeks after completion of chemoRT. Following re-evaluation, patients are classified according to whether they have a complete remission of disease, persistent disease, or progressive disease. Patients with persistent disease but without evidence of progression may be managed with close follow-up (in 4 weeks) to see if further regression occurs.

The National Cancer Research Institute's ACT II study compared different chemoRT regimens and found no difference in OS or PFS.[137] 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.[222] Based on these results, the panel believes it may be appropriate to follow patients who have not achieved a complete clinical response with persistent anal cancer for up to 6 months after completion of radiation and chemotherapy, as long as there is no evidence of progressive disease during this period of follow-up. Persistent disease may continue to regress even at 26 weeks 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*, below).

Although a clinical assessment of progressive disease requires histologic confirmation, patients can be classified as having a complete remission without biopsy verification if clinical evidence of disease is absent. The panel recommends that these patients undergo evaluation every 3 to 6 months for 5 years, including DRE, anoscopic evaluation, and inguinal node palpation. 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% to 30% have been reported.[223,224] Some of the disease characteristics that have been associated with higher recurrence rates following chemoRT include higher T stage and higher N stage (also see the section on *Prognostic Factors*, above).[225]

Evidence of progression found on DRE should be followed by 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.[224]

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.[226] 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.[227]

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.[223,224,228-232] 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 less than 55 Gy used in the treatment of primary disease.[224]

The general principles for APR technique are similar to those for distal rectal cancer and include the incorporation of meticulous total mesorectal excision (TME). 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 radiation therapy (IORT) during APR revealed that IORT is unlikely to improve local control or to give a survival benefit.[233] 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.[234,235] 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 above). 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%.[236] 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% to 64%.[236,237]

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.

Survivorship

The panel recommends that a prescription for survivorship and transfer of care to the primary care physician be written.[238] 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). 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.[239]

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).[240-244] 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.[240,244-246] Therefore, survivors of anal cancer should be screened regularly for distress.

The NCCN Guidelines for Survivorship 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. 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 following 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 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.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin 2021;71:7-33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33433946.

2. Jemal A, Simard EP, Dorell C, et al. Annual Report to the Nation on the Status of Cancer, 1975-2009, featuring the burden and trends in human papillomavirus (HPV)-associated cancers and HPV vaccination coverage levels. J Natl Cancer Inst 2013;105:175-201. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23297039.

3. Johnson LG, Madeleine MM, Newcomer LM, et al. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973-2000. Cancer 2004;101:281-288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15241824.

4. Nelson RA, Levine AM, Bernstein L, et al. Changing patterns of anal canal carcinoma in the United States. J Clin Oncol 2013;31:1569-1575. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23509304.

5. Shiels MS, Kreimer AR, Coghill AE, et al. Anal cancer incidence in the United States, 1977-2011: distinct patterns by histology and behavior. Cancer Epidemiol Biomarkers Prev 2015;24:1548-1556. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26224796.

6. Deshmukh AA, Suk R, Shiels MS, et al. Recent Trends in Squamous Cell Carcinoma of the Anus Incidence and Mortality in the United States, 2001-2015. J Natl Cancer Inst 2020;112:829-838. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31742639.

7. Raed A, Zandu M, Sharma A, et al. Anal Squamous Cell Carcinoma: A Growing Threat to Women's Health and Call for Action [abstract]. American College of Gastroenterology Annual Scientific Meeting 2020;Abstract P0399. Available at: https://www.eventscribe.com/2020/ACG/fsPopup.asp?efp=RElCSUFHUk02NDI2&PosterID=298982&rnd=0.3727714&mode=posterinfo.

8. Glynne-Jones R, Nilsson PJ, Aschele C, et al. Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Radiother Oncol 2014;111:330-339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24947004.

9. Moureau-Zabotto L, Vendrely V, Abramowitz L, et al. Anal cancer: French Intergroup Clinical Practice Guidelines for diagnosis, treatment and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SNFCP). Dig Liver Dis 2017;49:831-840. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28610905.

10. Stewart DB, Gaertner WB, Glasgow SC, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for Anal Squamous Cell Cancers (Revised 2018). Dis Colon Rectum 2018;61:755-774. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29878949.

11. U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: http://www.nlm.nih.gov/bsd/bsd_key.html. Accessed June 07, 2021.

12. Daling JR, Madeleine MM, Johnson LG, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. Cancer 2004;101:270-280. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15241823.

13. Frisch M, Glimelius B, van den Brule AJ, et al. Sexually transmitted infection as a cause of anal cancer. N Engl J Med 1997;337:1350-1358. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9358129.

14. Jimenez W, Paszat L, Kupets R, et al. Presumed previous human papillomavirus (HPV) related gynecological cancer in women diagnosed with anal cancer in the province of Ontario. Gynecol Oncol 2009;114:395-398. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19501390.

15. Ryan DP, Compton CC, Mayer RJ. Carcinoma of the anal canal. N Engl J Med 2000;342:792-800. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10717015.

16. Sunesen KG, Norgaard M, Thorlacius-Ussing O, Laurberg S. Immunosuppressive disorders and risk of anal squamous cell carcinoma: a nationwide cohort study in Denmark, 1978-2005. Int J Cancer 2010;127:675-684. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19960431.

17. Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. J Natl Cancer Inst 2000;92:1500-1510. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10995805.

18. Uronis HE, Bendell JC. Anal cancer: an overview. Oncologist 2007;12:524-534. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17522240.

19. Albuquerque A, Stirrup O, Nathan M, Clifford GM. Burden of anal squamous cell carcinoma, squamous intraepithelial lesions and HPV16 infection in solid organ transplant recipients: A systematic review and meta-analysis. Am J Transplant 2020;20:3520-3528. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32343489.

20. De Vuyst H, Clifford GM, Nascimento MC, et al. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. Int J Cancer 2009;124:1626-1636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19115209.

21. Hoots BE, Palefsky JM, Pimenta JM, Smith JS. Human papillomavirus type distribution in anal cancer and anal intraepithelial lesions. Int J Cancer 2009;124:2375-2383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19189402.

22. Ouhoummane N, Steben M, Coutlee F, et al. Squamous anal cancer: patient characteristics and HPV type distribution. Cancer Epidemiol 2013;37:807-812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24139594.

23. Steinau M, Unger ER, Hernandez BY, et al. Human papillomavirus prevalence in invasive anal cancers in the United States before vaccine introduction. J Low Genit Tract Dis 2013;17:397-403. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23609590.

24. Human papillomavirus-associated cancers - United States, 2004-2008. MMWR Morb Mortal Wkly Rep 2012;61:258-261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22513527.

25. Palefsky JM, Holly EA, Ralston ML, Jay N. Prevalence and risk factors for human papillomavirus infection of the anal canal in human immunodeficiency virus (HIV)-positive and HIV-negative homosexual men. J Infect Dis 1998;177:361-367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9466522.

26. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. Ann Intern Med 2008;148:728-736. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18490686.

27. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. J Natl Cancer Inst 2009;101:1120-1130. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19648510.

28. Colon-Lopez V, Shiels MS, Machin M, et al. Anal Cancer Risk Among People With HIV Infection in the United States. J Clin Oncol 2018;36:68-75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29140774.

29. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet 2007;370:59-67. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17617273.

30. Hernandez-Ramirez RU, Shiels MS, Dubrow R, Engels EA. Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study. Lancet HIV 2017;4:e495-e504. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28803888.

31. Silverberg MJ, Lau B, Justice AC, et al. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. Clin Infect Dis 2012;54:1026-1034. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22291097.

32. Stier EA, Sebring MC, Mendez AE, et al. Prevalence of anal human papillomavirus infection and anal HPV-related disorders in women: a systematic review. Am J Obstet Gynecol 2015;213:278-309. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25797230.

33. Piketty C, Selinger-Leneman H, Bouvier AM, et al. Incidence of HIV-related anal cancer remains increased despite long-term combined antiretroviral treatment: results from the french hospital database on HIV. J Clin Oncol 2012;30:4360-4366. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23091098.

34. Libois A, Feoli F, Nkuize M, et al. Prolonged antiretroviral therapy is associated with fewer anal high-grade squamous intraepithelial lesions in HIV-positive MSM in a cross-sectional study. Sex Transm Infect 2017;93:15-17. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27030607.

35. Berry JM, Jay N, Cranston RD, et al. Progression of anal high-grade squamous intraepithelial lesions to invasive anal cancer among HIV-infected men who have sex with men. Int J Cancer 2014;134:1147-1155. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23934991.

36. Scholefield JH, Castle MT, Watson NF. Malignant transformation of high-grade anal intraepithelial neoplasia. Br J Surg 2005;92:1133-1136. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16044425.

37. Watson AJ, Smith BB, Whitehead MR, et al. Malignant progression of anal intra-epithelial neoplasia. ANZ J Surg 2006;76:715-717. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16916390.

38. Tinmouth J, Peeva V, Amare H, et al. Progression from perianal high-grade anal intraepithelial neoplasia to anal cancer in HIV-positive men who have sex with men. Dis Colon Rectum 2016;59:836-842. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27505112.

39. Gautier M, Brochard C, Lion A, et al. High-grade anal intraepithelial neoplasia: progression to invasive cancer is not a certainty. Dig Liver Dis 2016;48:806-811. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27103359.

40. Berry JM, Palefsky JM, Jay N, et al. Performance characteristics of anal cytology and human papillomavirus testing in patients with high-resolution anoscopy-guided biopsy of high-grade anal intraepithelial neoplasia. Dis Colon Rectum 2009;52:239-247. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19279418.

41. Jay N. Elements of an anal dysplasia screening program. J Assoc Nurses AIDS Care 2011;22:465-477. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22035526.

42. Fuchs W, Wieland U, Skaletz-Rorowski A, et al. The male ScreenING Study: prevalence of HPV-related genital and anal lesions in an urban cohort of HIV-positive men in Germany. J Eur Acad Dermatol Venereol 2016;30:995-1001. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26833895.

43. Jin F, Grulich AE, Poynten IM, et al. The performance of anal cytology as a screening test for anal HSILs in homosexual men. Cancer Cytopathol 2016;124:415-424. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26915346.

44. Machalek DA, Poynten M, Jin F, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. Lancet Oncol 2012;13:487-500. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22445259.

45. Schofield AM, Sadler L, Nelson L, et al. A prospective study of anal cancer screening in HIV positive and negative men who have sex with men; results of Analogy. AIDS 2016;30:1375-1383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26836788.

46. Barroso LF. Anal cancer screening. Lancet Oncol 2012;13:e278-279; author reply e280. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22748260.

47. Goldstone SE, Johnstone AA, Moshier EL. Long-term outcome of ablation of anal high-grade squamous intraepithelial lesions: recurrence and incidence of cancer. Dis Colon Rectum 2014;57:316-323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24509453.

48. Palefsky J, Berry JM, Jay N. Anal cancer screening. Lancet Oncol 2012;13:e279-280; author rreply e280. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22748261.

49. Park IU, Palefsky JM. Evaluation and management of anal intraepithelial neoplasia in HIV-negative and HIV-positive men who have sex with men. Curr Infect Dis Rep 2010;12:126-133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20461117.

50. Roark R. The need for anal dysplasia screening and treatment programs for HIV-infected men who have sex with men: a review of the literature. J Assoc Nurses AIDS Care 2011;22:433-443. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22035523.

51. Scholefield JH, Harris D, Radcliffe A. Guidelines for management of anal intraepithelial neoplasia. Colorectal Dis 2011;13 Suppl 1:3-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21251167.

52. Wentzensen N. Screening for anal cancer: endpoints needed. Lancet Oncol 2012;13:438-440. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22445258.

53. Chen CC, Chou YY. Predictive value of the anal cytology for detecting anal intraepithelial neoplasia or worse: A systematic review and meta-analysis. Diagn Cytopathol 2019;47:307-314. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30605263.

54. Dias Goncalves Lima F, Viset JD, Leeflang MMG, et al. The Accuracy of Anal Swab-Based Tests to Detect High-Grade Anal Intraepithelial Neoplasia in HIV-Infected Patients: A Systematic Review and Meta-analysis. Open Forum Infect Dis 2019;6:ofz191. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31123696.

55. Goncalves JCN, Macedo ACL, Madeira K, et al. Accuracy of Anal Cytology for Diagnostic of Precursor Lesions of Anal Cancer: Systematic Review and Meta-analysis. Dis Colon Rectum 2019;62:112-120. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30451747.

56. Steele SR, Varma MG, Melton GB, et al. Practice parameters for anal squamous neoplasms. Dis Colon Rectum 2012;55:735-749. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22706125.

57. Ong JJ, Chen M, Grulich AE, Fairley CK. Regional and national guideline recommendations for digital ano-rectal examination as a means for anal cancer screening in HIV positive men who have sex with men: a systematic review. BMC Cancer 2014;14:557. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25081485.

58. Alam NN, White DA, Narang SK, et al. Systematic review of guidelines for the assessment and management of high-grade anal intraepithelial neoplasia (AIN II/III). Colorectal Dis 2016;18:135-146. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26559167.

59. Hartschuh W, Breitkopf C, Lenhard B, et al. S1 guideline: anal intraepithelial neoplasia (AIN) and perianal intraepithelial neoplasia (PAIN). J Dtsch Dermatol Ges 2011;9:256-258. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21208377.

60. Richel O, de Vries HJ, van Noesel CJ, et al. Comparison of imiquimod, topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial. Lancet Oncol 2013;14:346-353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23499546.

61. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915-1927. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17494925.

62. Dillner J, Kjaer SK, Wheeler CM, et al. Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial. BMJ 2010;341:c3493. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20647284.

63. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356:1928-1943. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17494926.

64. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med 2011;364:401-411. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21288094.

65. Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med 2011;365:1576-1585. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22029979.

66. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2010;59:626-629. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20508593.

67. Kreimer AR, Gonzalez P, Katki HA, et al. Efficacy of a bivalent HPV 16/18 vaccine against anal HPV 16/18 infection among young women: a nested analysis within the Costa Rica Vaccine Trial. Lancet Oncol 2011;12:862-870. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21865087.

68. Beachler DC, Kreimer AR, Schiffman M, et al. Multisite HPV16/18 vaccine efficacy against cervical, anal, and oral HPV infection. J Natl Cancer Inst 2016;108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26467666.

69. Lehtinen M, Paavonen J, Wheeler CM, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol 2011;13:69-99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22075171.

70. Petrosky E, Bocchini JA, Jr., Hariri S, et al. Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. MMWR Morb Mortal Wkly Rep 2015;64:300-304. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25811679.

71. Saraiya M, Unger ER, Thompson TD, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. J Natl Cancer Inst 2015;107:djv086. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25925419.

72. Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015;372:711-723. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25693011.

73. Markowitz LE, Dunne EF, Saraiya M, et al. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2014;63:1-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25167164.

74. Meites E, Kempe A, Markowitz LE. Use of a 2-Dose Schedule for Human Papillomavirus Vaccination - Updated Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2016;65:1405-1408. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27977643.

75. Kim DK, Riley LE, Harriman KH, et al. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2017. MMWR Morb Mortal Wkly Rep 2017;66:136-138. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28182599.

76. Meites E, Szilagyi PG, Chesson HW, et al. Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2019;68:698-702. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31415491.

77. HPV vaccine recommendations. Pediatrics 2012;129:602-605. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22371460.

78. Bailey HH, Chuang LT, duPont NC, et al. American Society of Clinical Oncology statement: human papillomavirus vaccination for cancer prevention. J Clin Oncol 2016;34:1803-1812. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27069078.

79. U.S. Food & Drug Administration. FDA approves expanded use of Gardasil 9 to include individuals 27 through 45 years old. 2018. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-expanded-use-gardasil-9-include-individuals-27-through-45-years-old. Accessed June 07, 2021.

80. Welton ML, Steele SR, Goodman KA, et al. Anus. In: Amin MB, ed. AJCC Cancer Staging Manual, Eighth Edition: Springer; 2017.

81. Cummings BJ, Ajani JA, Swallow CJ. Cancer of the anal region. In: DeVita Jr. VT, Lawrence TS, Rosenberg SA, et al., eds. Cancer: Principles & Practice of Oncology, Eighth Edition. Philadelphia, PA: Lippincott, Williams & Wilkins; 2008.

82. Pandey P. Anal anatomy and normal histology. Sex Health 2012;9:513-516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23380234.

83. Nivatvongs S, Stern HS, Fryd DS. The length of the anal canal. Dis Colon Rectum 1981;24:600-601. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7318624.

84. Jass JR, Sobin LH. Histological Typing of Intestinal Tumours: Springer-Verlag Berlin Heidelberg; 1989.

85. Fenger C, Frisch M, Marti MC, Parc R. Tumours of the anal canal. In: Hamilton SR, Aaltonen LA, eds. WHO Classification of Tumours, Volume 2: Pathology and Genetics. Tumours of the Digestive System. Lyon: IARC Press; 2000:145-155.

86. Welton ML, Lambert R, Bosman FT. Tumours of the Anal Canal. In: Bosman FT, Carneiro, F., Hruban, R. H., Theise, N.D., ed. WHO Classification of Tumours of the Digestive System. Lyon: IARC; 2010:183-193.

87. Fenger C. Prognostic factors in anal carcinoma. Pathology 2002;34:573-578. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12555997.

88. Oliver GC, Labow SB. Neoplasms of the anus. Surg Clin North Am 1994;74:1475-1490. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7985077.

89. Burgart LJ, Kakar S, Shi C, et al. Protocol for the Examination of Excision Specimens From Patients With Carcinoma of the Anus. 2020. Available at: https://documents.cap.org/protocols/cp-gilower-anus-excision-20-4101.pdf.

90. Burgart LJ, Shi C, Driman DK, et al. Protocol for the Examination of Resection Specimens From Patients With Carcinoma of the Anus. 2020. Available at: https://documents.cap.org/protocols/cp-gilower-anus-resection-20-4100.pdf.

91. Edge SBB, D.R.; Compton, C.C.; Fritz, A.G.; Greene, F.L.; Trotti, A., ed AJCC Cancer Staging Manual (ed 7th Edition). New York: Springer; 2010.

92. Altekruse SF, Kosary CL, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2007. 2010. Available at: http://seer.cancer.gov/csr/1975_2007/.

93. Gerard JP, Chapet O, Samiei F, et al. Management of inguinal lymph node metastases in patients with carcinoma of the anal canal: experience in a series of 270 patients treated in Lyon and review of the

literature. Cancer 2001;92:77-84. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11443612.

94. Gunderson LL, Moughan J, Ajani JA, et al. Anal carcinoma: impact of TN category of disease on survival, disease relapse, and colostomy failure in US Gastrointestinal Intergroup RTOG 98-11 phase 3 trial. Int J Radiat Oncol Biol Phys 2013;87:638-645. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24035327.

95. Wade DS, Herrera L, Castillo NB, Petrelli NJ. Metastases to the lymph nodes in epidermoid carcinoma of the anal canal studied by a clearing technique. Surg Gynecol Obstet 1989;169:238-242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2672386.

96. Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. JAMA 2008;299:1914-1921. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18430910.

97. Ajani JA, Winter KA, Gunderson LL, et al. US intergroup anal carcinoma trial: tumor diameter predicts for colostomy. J Clin Oncol 2009;27:1116-1121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19139424.

98. Bartelink H, Roelofsen F, Eschwege F, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol 1997;15:2040-2049. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9164216.

99. Glynne-Jones R, Sebag-Montefiore D, Adams R, et al. Prognostic factors for recurrence and survival in anal cancer: generating hypotheses from the mature outcomes of the first United Kingdom Coordinating Committee on Cancer Research Anal Cancer Trial (ACT I). Cancer 2013;119:748-755. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23011911.

100. Rodel F, Wieland U, Fraunholz I, et al. Human papillomavirus DNA load and p16 expression predict for local control in patients with anal squamous cell carcinoma treated with chemoradiotherapy. Int J Cancer 2014;136:278-288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24839133.

101. Serup-Hansen E, Linnemann D, Skovrider-Ruminski W, et al. Human papillomavirus genotyping and p16 expression as prognostic factors for patients with American Joint Committee on Cancer stages I to III carcinoma of the anal canal. J Clin Oncol 2014;32:1812-1817. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24821878.

102. Urbute A, Rasmussen CL, Belmonte F, et al. Prognostic Significance of HPV DNA and p16(INK4a) in Anal Cancer: A Systematic Review and Meta-Analysis. Cancer Epidemiol Biomarkers Prev 2020;29:703-710. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32051192.

103. Parwaiz I, MacCabe TA, Thomas MG, Messenger DE. A Systematic Review and Meta-Analysis of Prognostic Biomarkers in Anal Squamous Cell Carcinoma Treated With Primary Chemoradiotherapy. Clin Oncol (R Coll Radiol) 2019;31:e1-e13. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31301958.

104. U.S. Statistics. HIV.gov; 2021. Available at: https://www.hiv.gov/hiv-basics/overview/data-and-trends/statistics. Accessed June 07, 2021.

105. Marks G, Crepaz N, Senterfitt JW, Janssen RS. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. J Acquir Immune Defic Syndr 2005;39:446-453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16010168.

106. Chiao EY, Dezube BJ, Krown SE, et al. Time for oncologists to opt in for routine opt-out HIV testing? JAMA 2010;304:334-339. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20639567.

107. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR Recomm Rep 2006;55:1-17; quiz CE11-14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16988643.

108. Bhuva NJ, Glynne-Jones R, Sonoda L, et al. To PET or not to PET? That is the question. Staging in anal cancer. Ann Oncol 2012;23:2078-2082. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22294527.

109. Caldarella C, Annunziata S, Treglia G, et al. Diagnostic performance of positron emission tomography/computed tomography using fluorine-18 fluorodeoxyglucose in detecting locoregional nodal involvement in patients with anal canal cancer: a systematic review and meta-analysis. Scientific World Journal 2014:196068. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24672298.

110. Cotter SE, Grigsby PW, Siegel BA, et al. FDG-PET/CT in the evaluation of anal carcinoma. Int J Radiat Oncol Biol Phys 2006;65:720-725. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16626889.

111. Mistrangelo M, Pelosi E, Bello M, et al. Role of positron emission tomography-computed tomography in the management of anal cancer. Int J Radiat Oncol Biol Phys 2012;84:66-72. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22592047.

112. Pepek JM, Willett CG, Czito BG. Radiation therapy advances for treatment of anal cancer. J Natl Compr Canc Netw 2010;8:123-129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20064294.

113. Trautmann TG, Zuger JH. Positron Emission Tomography for pretreatment staging and posttreatment evaluation in cancer of the anal canal. Mol Imaging Biol 2005;7:309-313. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16028002.

114. Mahmud A, Poon R, Jonker D. PET imaging in anal canal cancer: a systematic review and meta-analysis. Br J Radiol 2017;90:20170370. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28972796.

115. Jones M, Hruby G, Solomon M, et al. The role of FDG-PET in the initial staging and response assessment of anal cancer: a systematic review and meta-analysis. Ann Surg Oncol 2015;22:3574-3581. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25652048.

116. Albertsson P, Alverbratt C, Liljegren A, et al. Positron emission tomography and computed tomographic (PET/CT) imaging for radiation therapy planning in anal cancer: A systematic review and meta-analysis. Crit Rev Oncol Hematol 2018;126:6-12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29759568.

117. Sekhar H, Zwahlen M, Trelle S, et al. Nodal stage migration and prognosis in anal cancer: a systematic review, meta-regression, and simulation study. Lancet Oncol 2017;18:1348-1359. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28802802.

118. Nigro ND, Vaitkevicius VK, Considine B. Combined therapy for cancer of the anal canal: a preliminary report. Dis Colon Rectum 1974;17:354-356. Available at: http://www.ncbi.nlm.nih.gov/pubmed/4830803.

119. Cummings BJ, Keane TJ, O'Sullivan B, et al. Epidermoid anal cancer: treatment by radiation alone or by radiation and 5-fluorouracil with and without mitomycin C. Int J Radiat Oncol Biol Phys 1991;21:1115-1125. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1938508.

120. Papillon J, Chassard JL. Respective roles of radiotherapy and surgery in the management of epidermoid carcinoma of the anal margin. Series of 57 patients. Dis Colon Rectum 1992;35:422-429. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1568392.

121. Czito BG, Willett CG. Current management of anal canal cancer. Curr Oncol Rep 2009;11:186-192. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19336010.

122. Glynne-Jones R, Lim F. Anal cancer: an examination of radiotherapy strategies. Int J Radiat Oncol Biol Phys 2011;79:1290-1301. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21414513.

123. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research. Lancet 1996;348:1049-1054. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8874455.

124. Northover J, Glynne-Jones R, Sebag-Montefiore D, et al. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I). Br J Cancer 2010;102:1123-1128. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20354531.

125. Buckstein M, Arens Y, Wisnivesky J, et al. A Population-Based Cohort Analysis of Chemoradiation Versus Radiation Alone for Definitive Treatment of Stage I Anal Cancer in Older Patients. Dis Colon Rectum 2018;61:787-794. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29771796.

126. Crehange G, Bosset M, Lorchel F, et al. Combining cisplatin and mitomycin with radiotherapy in anal carcinoma. Dis Colon Rectum 2007;50:43-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17089083.

127. Flam M, John M, Pajak TF, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. J Clin Oncol 1996;14:2527-2539. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8823332.

128. Hofheinz RD, Wenz F, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol 2012;13:579-588. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22503032.

129. O'Connell MJ, Colangelo LH, Beart RW, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. J Clin Oncol 2014;32:1927-1934. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24799484.

130. Twelves C, Scheithauer W, McKendrick J, et al. Capecitabine versus 5-fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results from the X-ACT trial with analysis by age and preliminary evidence of a pharmacodynamic marker of efficacy. Ann Oncol 2012;23:1190-1197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21896539.

131. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352:2696-2704. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15987918.

132. Glynne-Jones R, Meadows H, Wan S, et al. EXTRA--a multicenter phase II study of chemoradiation using a 5 day per week oral regimen of capecitabine and intravenous mitomycin C in anal cancer. Int J Radiat Oncol Biol Phys 2008;72:119-126. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18472366.

133. Goodman K, Rothenstein D, Lajhem C, et al. Capecitabine plus mitomycin in patients undergoing definitive chemoradiation for anal squamous cell carcinoma. Int J Radiat Oncol Biol Phys 2014;90:S32–S33. Available at: http://www.redjournal.org/article/S0360-3016(14)00792-5/fulltext.

134. Meulendijks D, Dewit L, Tomasoa NB, et al. Chemoradiotherapy with capecitabine for locally advanced anal carcinoma: an alternative treatment option. Br J Cancer 2014;111:1726-1733. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25167226.

135. Thind G, Johal B, Follwell M, Kennecke HF. Chemoradiation with capecitabine and mitomycin-C for stage I-III anal squamous cell carcinoma. Radiat Oncol 2014;9:124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24885554.

136. Oliveira SC, Moniz CM, Riechelmann R, et al. Phase II study of capecitabine in substitution of 5-FU in the chemoradiotherapy regimen for patients with localized squamous cell carcinoma of the anal canal. J

Gastrointest Cancer 2016;47:75-81. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26691173.

137. 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, 2 x 2 factorial trial. Lancet Oncol 2013;14:516-524. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23578724.

138. Gunderson LL, Winter KA, Ajani JA, et al. Long-term update of US GI Intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol 2012;30:4344-4351. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23150707.

139. Eng C, Crane CH, Rodriguez-Bigas MA. Should cisplatin be avoided in the treatment of locally advanced squamous cell carcinoma of the anal canal? Nat Clin Pract Gastroenterol Hepatol 2009;6:16-17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19047998.

140. Abbas A, Yang G, Fakih M. Management of anal cancer in 2010. Part 2: current treatment standards and future directions. Oncology (Williston Park) 2010;24:417-424. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20480740.

141. Peiffert D, Tournier-Rangeard L, Gerard JP, et al. Induction chemotherapy and dose intensification of the radiation boost in locally advanced anal canal carcinoma: final analysis of the randomized UNICANCER ACCORD 03 trial. J Clin Oncol 2012;30:1941-1948. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22529257.

142. Spithoff K, Cummings B, Jonker D, et al. Chemoradiotherapy for squamous cell cancer of the anal canal: a systematic review. Clin Oncol (R Coll Radiol) 2014;26:473-487. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24721444.

143. Moureau-Zabotto L, Viret F, Giovaninni M, et al. Is neoadjuvant chemotherapy prior to radio-chemotherapy beneficial in T4 anal carcinoma? J Surg Oncol 2011;104:66-71. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21240983.

144. Sebag-Montefiore D, Meadows HM, Cunningham D, et al. Three cytotoxic drugs combined with pelvic radiation and as maintenance chemotherapy for patients with squamous cell carcinoma of the anus (SCCA): long-term follow-up of a phase II pilot study using 5-fluorouracil, mitomycin C and cisplatin. Radiother Oncol 2012;104:155-160. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22857859.

145. Eng C, Jacome AA, Das P, et al. A Phase II Study of Capecitabine/Oxaliplatin With Concurrent Radiotherapy in Locally Advanced Squamous Cell Carcinoma of the Anal Canal. Clin Colorectal Cancer 2019;18:301-306. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31350201.

146. ClinicalTrials.gov. Nivolumab After Combined Modality Therapy in Treating Patients With High Risk Stage II-IIIB Anal Cancer. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT03233711. Accessed June 15, 2021.

147. U. S. Food & Drug Administration. Prescribing information. ERBITUX® (cetuximab) injection, for intravenous use. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s277s280lbl.pdf. Accessed June 07, 2021.

148. Van Damme N, Deron P, Van Roy N, et al. Epidermal growth factor receptor and K-RAS status in two cohorts of squamous cell carcinomas. BMC Cancer 2010;10:189. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20459770.

149. Zampino MG, Magni E, Sonzogni A, Renne G. K-ras status in squamous cell anal carcinoma (SCC): it's time for target-oriented treatment? Cancer Chemother Pharmacol 2009;65:197-199. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19727729.

150. Garg MK, Zhao F, Sparano JA, et al. Cetuximab plus chemoradiotherapy in immunocompetent patients with anal carcinoma: a phase II Eastern Cooperative Oncology Group-American College of Radiology Imaging Network Cancer Research Group trial (E3205). J Clin Oncol 2017;35:718-726. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28068178.

151. Sparano JA, Lee JY, Palefsky J, et al. Cetuximab plus chemoradiotherapy for HIV-associated anal carcinoma: a phase II AIDS Malignancy Consortium trial. J Clin Oncol 2017;35:727-733. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27937092.

152. Olivatto LO, Vieira FM, Pereira BV, et al. Phase 1 study of cetuximab in combination with 5-fluorouracil, cisplatin, and radiotherapy in patients with locally advanced anal canal carcinoma. Cancer 2013;119:2973-2980. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23674135.

153. Deutsch E, Lemanski C, Pignon JP, et al. Unexpected toxicity of cetuximab combined with conventional chemoradiotherapy in patients with locally advanced anal cancer: results of the UNICANCER ACCORD 16 phase II trial. Ann Oncol 2013;24:2834-2838. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24026540.

154. Levy A, Azria D, Pignon JP, et al. Low response rate after cetuximab combined with conventional chemoradiotherapy in patients with locally advanced anal cancer: long-term results of the UNICANCER ACCORD 16 phase II trial. Radiother Oncol 2015;114:415-416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25769380.

155. Ortholan C, Ramaioli A, Peiffert D, et al. Anal canal carcinoma: early-stage tumors < or =10 mm (T1 or Tis): therapeutic options and original pattern of local failure after radiotherapy. Int J Radiat Oncol Biol Phys 2005;62:479-485. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15890590.

156. Ferrigno R, Nakamura RA, Dos Santos Novaes PER, et al. Radiochemotherapy in the conservative treatment of anal canal carcinoma: retrospective analysis of results and radiation dose effectiveness. Int J Radiat Oncol Biol Phys 2005;61:1136-1142. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15752894.

157. Huang K, Haas-Kogan D, Weinberg V, Krieg R. Higher radiation dose with a shorter treatment duration improves outcome for locally advanced carcinoma of anal canal. World J Gastroenterol 2007;13:895-900. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17352019.

158. John M, Pajak T, Flam M, et al. Dose escalation in chemoradiation for anal cancer: preliminary results of RTOG 92-08. Cancer J Sci Am 1996;2:205-211. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9166533.

159. ClinicalTrials.gov. Lower-Dose Chemoradiation in Treating Patients With Early-Stage Anal Cancer, the DECREASE Study. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04166318. Accessed June 15, 2021.

160. Konski A, Garcia M, Jr., John M, et al. Evaluation of planned treatment breaks during radiation therapy for anal cancer: update of RTOG 92-08. Int J Radiat Oncol Biol Phys 2008;72:114-118. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18472363.

161. Ben-Josef E, Moughan J, Ajani JA, et al. Impact of overall treatment time on survival and local control in patients with anal cancer: a pooled data analysis of Radiation Therapy Oncology Group trials 87-04 and 98-11. J Clin Oncol 2010;28:5061-5066. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20956625.

162. Graf R, Wust P, Hildebrandt B, et al. Impact of overall treatment time on local control of anal cancer treated with radiochemotherapy. Oncology 2003;65:14-22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12837978.

163. Roohipour R, Patil S, Goodman KA, et al. Squamous-cell carcinoma of the anal canal: predictors of treatment outcome. Dis Colon Rectum 2008;51:147-153. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18180997.

164. Allal AS, Sprangers MA, Laurencet F, et al. Assessment of long-term quality of life in patients with anal carcinomas treated by radiotherapy with or without chemotherapy. Br J Cancer 1999;80:1588-1594. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10408404.

165. de Bree E, van Ruth S, Dewit LGH, Zoetmulder FAN. High risk of colostomy with primary radiotherapy for anal cancer. Ann Surg Oncol 2007;14:100-108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17066231.

166. Baxter NN, Habermann EB, Tepper JE, et al. Risk of pelvic fractures in older women following pelvic irradiation. JAMA 2005;294:2587-2593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16304072.

167. Call JA, Prendergast BM, Jensen LG, et al. Intensity-modulated radiation therapy for anal cancer: results from a multi-institutional retrospective cohort study. Am J Clin Oncol 2014;39:8-12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24401669.

168. Chen YJ, Liu A, Tsai PT, et al. Organ sparing by conformal avoidance intensity-modulated radiation therapy for anal cancer: dosimetric evaluation of coverage of pelvis and inguinal/femoral nodes. Int J Radiat Oncol Biol Phys 2005;63:274-281. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16111597.

169. Chuong MD, Freilich JM, Hoffe SE, et al. Intensity-modulated radiation therapy vs. 3D conformal radiation therapy for squamous cell carcinoma of the anal canal. Gastrointest Cancer Res 2013;6:39-45. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23745158.

170. DeFoe SG, Beriwal S, Jones H, et al. Concurrent chemotherapy and intensity-modulated radiation therapy for anal carcinoma--clinical outcomes in a large National Cancer Institute-designated integrated cancer centre network. Clin Oncol (R Coll Radiol) 2012;24:424-431. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22075444.

171. Franco P, Mistrangelo M, Arcadipane F, et al. Intensity-modulated radiation therapy with simultaneous integrated boost combined with concurrent chemotherapy for the treatment of anal cancer patients: 4-year results of a consecutive case series. Cancer Invest 2015;33:259-266. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25950188.

172. Kachnic LA, Tsai HK, Coen JJ, et al. Dose-painted intensity-modulated radiation therapy for anal cancer: a multi-institutional report of acute toxicity and response to therapy. Int J Radiat Oncol Biol Phys 2012;82:153-158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21095071.

173. Lin A, Ben-Josef E. Intensity-modulated radiation therapy for the treatment of anal cancer. Clin Colorectal Cancer 2007;6:716-719. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18039425.

174. Milano MT, Jani AB, Farrey KJ, et al. Intensity-modulated radiation therapy (IMRT) in the treatment of anal cancer: toxicity and clinical outcome. Int J Radiat Oncol Biol Phys 2005;63:354-361. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16168830.

175. Mitchell MP, Abboud M, Eng C, et al. Intensity-modulated radiation therapy with concurrent chemotherapy for anal cancer: outcomes and toxicity. Am J Clin Oncol 2014;37:461-466. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23466576.

176. Salama JK, Mell LK, Schomas DA, et al. Concurrent chemotherapy and intensity-modulated radiation therapy for anal canal cancer patients: a multicenter experience. J Clin Oncol 2007;25:4581-4586. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17925552.

177. Yates A, Carroll S, Kneebone A, et al. Implementing intensity-modulated radiotherapy with simultaneous integrated boost for anal cancer: 3 year outcomes at two Sydney institutions. Clin Oncol (R Coll Radiol) 2015;27:700-707. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26382849.

178. Bazan JG, Hara W, Hsu A, et al. Intensity-modulated radiation therapy versus conventional radiation therapy for squamous cell carcinoma of the anal canal. Cancer 2011;117:3342-3351. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21287530.

179. Dasgupta T, Rothenstein D, Chou JF, et al. Intensity-modulated radiotherapy vs. conventional radiotherapy in the treatment of anal squamous cell carcinoma: a propensity score analysis. Radiother Oncol 2013;107:189-194. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23692961.

180. Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 2013;86:27-33. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23154075.

181. Mitra D, Hong TS, Horick N, et al. Long-term outcomes and toxicities of a large cohort of anal cancer patients treated with dose-painted IMRT per RTOG 0529. Adv Radiat Oncol 2017;2:110-117. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28740921.

182. Chin AL, Pollom EL, Qian Y, et al. Impact of intensity-modulated radiotherapy on health care costs of patients with anal squamous cell carcinoma. J Oncol Pract 2017;13:e992-e1001. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29035618.

183. Benson AB, 3rd, Arnoletti JP, Bekaii-Saab T, et al. Anal Carcinoma, Version 2.2012: featured updates to the NCCN guidelines. J Natl Compr Canc Netw 2012;10:449-454. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22491045.

184. Myerson RJ, Garofalo MC, El Naqa I, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring atlas. Int J Radiat Oncol Biol Phys 2009;74:824-830. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19117696.

185. Darragh TM, Colgan TJ, Cox JT, et al. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Arch Pathol Lab Med 2012;136:1266-1297. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22742517.

186. Arana R, Flejou JF, Si-Mohamed A, et al. Clinicopathological and virological characteristics of superficially invasive squamous-cell carcinoma of the anus. Colorectal Dis 2015;17:965-972. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25784158.

187. Management of stage I squamous cell carcinoma of the anal canal. JAMA Surg 2018;153:209-215. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29049547.

188. Duncan KC, Chan KJ, Chiu CG, et al. HAART slows progression to anal cancer in HIV-infected MSM. AIDS 2015;29:305-311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25686679.

189. Grew D, Bitterman D, Leichman CG, et al. HIV infection is associated with poor outcomes for patients with anal cancer in the highly active antiretroviral therapy era. Dis Colon Rectum 2015;58:1130-1136. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26544809.

190. Oehler-Janne C, Huguet F, Provencher S, et al. HIV-specific differences in outcome of squamous cell carcinoma of the anal canal: a multicentric cohort study of HIV-positive patients receiving highly active antiretroviral therapy. J Clin Oncol 2008;26:2550-2557. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18427149.

191. Camandaroba MPG, de Araujo RLC, Silva VSE, et al. Treatment outcomes of patients with localized anal squamous cell carcinoma according to HIV infection: systematic review and meta-analysis. J Gastrointest Oncol 2019;10:48-60. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30788159.

192. Alfa-Wali M, Dalla Pria A, Nelson M, et al. Surgical excision alone for stage T1 anal verge cancers in people living with HIV. Eur J Surg Oncol 2016;42:813-816. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27012999.

193. Bryant AK, Huynh-Le MP, Simpson DR, et al. Association of HIV status with outcomes of anal squamous cell carcinoma in the era of highly active antiretroviral therapy. JAMA Oncol 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28975226.

194. Chiao EY, Giordano TP, Richardson P, El-Serag HB. Human immunodeficiency virus-associated squamous cell cancer of the anus: epidemiology and outcomes in the highly active antiretroviral therapy era. J Clin Oncol 2008;26:474-479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18202423.

195. Leeds IL, Alturki H, Canner JK, et al. Outcomes of abdominoperineal resection for management of anal cancer in HIV-positive patients: a national case review. World J Surg Oncol 2016;14:208. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27495294.

196. Martin D, Balermpas P, Fokas E, et al. Are there HIV-specific differences for anal cancer patients treated with standard chemoradiotherapy in the era of combined antiretroviral therapy? Clin Oncol (R Coll Radiol) 2017;29:248-255. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28049602.

197. Pappou EP, Magruder JT, Fu T, et al. Prognostic and predictive clinicopathologic factors of squamous anal canal cancer in HIV-positive and HIV-negative patients: does HAART influence outcomes? World J Surg 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28948325.

198. Seo Y, Kinsella MT, Reynolds HL, et al. Outcomes of chemoradiotherapy with 5-Fluorouracil and mitomycin C for anal cancer in immunocompetent versus immunodeficient patients. Int J Radiat Oncol Biol Phys 2009;75:143-149. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19203845.

199. White EC, Khodayari B, Erickson KT, et al. Comparison of toxicity and treatment outcomes in HIV-positive versus HIV-negative patients with squamous cell carcinoma of the anal canal. Am J Clin Oncol 2014;40:386-392. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25513996.

200. Coghill AE, Shiels MS, Suneja G, Engels EA. Elevated cancer-specific mortality among HIV-infected patients in the United States. J Clin Oncol 2015;33:2376-2383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26077242.

201. Faivre C, Rougier P, Ducreux M, et al. [5-fluorouracile and cisplatinum combination chemotherapy for metastatic squamous-cell anal cancer]. Bull Cancer 1999;86:861-865. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10572237.

202. Kole AJ, Stahl JM, Park HS, et al. Predictors of nonadherence to NCCN guideline recommendations for the management of stage I anal canal cancer. J Natl Compr Canc Netw 2017;15:355-362. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28275036.

203. Geltzeiler CB, Tsikitis VL, Kim JS, et al. Variation in the use of chemoradiotherapy for stage II and III anal cancer: analysis of the National Cancer Data Base. Ann Surg Oncol 2016;23:3934-3940. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27444107.

204. Cummings BJ. Metastatic anal cancer: the search for cure. Onkologie 2006;29:5-6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16514247.

205. Rao S, Sclafani F, Eng C, et al. International Rare Cancers Initiative Multicenter Randomized Phase II Trial of Cisplatin and Fluorouracil Versus Carboplatin and Paclitaxel in Advanced Anal Cancer: InterAAct. J Clin Oncol 2020;38:2510-2518. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32530769.

206. Ajani JA, Carrasco CH, Jackson DE, Wallace S. Combination of cisplatin plus fluoropyrimidine chemotherapy effective against liver metastases from carcinoma of the anal canal. Am J Med 1989;87:221-224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2527006.

207. Eng C, Chang GJ, You YN, et al. The role of systemic chemotherapy and multidisciplinary management in improving the overall survival of patients with metastatic squamous cell carcinoma of the anal canal. Oncotarget 2014;5:11133-11142. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25373735.

208. Jaiyesimi IA, Pazdur R. Cisplatin and 5-fluorouracil as salvage therapy for recurrent metastatic squamous cell carcinoma of the anal canal. Am J Clin Oncol 1993;16:536-540. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8256774.

209. Kim R, Byer J, Fulp WJ, et al. Carboplatin and paclitaxel treatment is effective in advanced anal cancer. Oncology 2014;87:125-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25012155.

210. Sclafani F, Morano F, Cunningham D, et al. Platinum-fluoropyrimidine and paclitaxel-based chemotherapy in the treatment of advanced anal cancer patients. Oncologist 2017;22:402-408. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28209745.

211. Mondaca S, Chatila WK, Bates D, et al. FOLFCIS Treatment and Genomic Correlates of Response in Advanced Anal Squamous Cell Cancer. Clin Colorectal Cancer 2019;18:e39-e52. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30316684.

212. Matsunaga M, Miwa K, Oka Y, et al. Successful treatment of metastatic anal canal adenocarcinoma with mFOLFOX6 + bevacizumab. Case Rep Oncol 2016;9:249-254. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27239180.

213. Kim S, Francois E, Andre T, et al. Docetaxel, cisplatin, and fluorouracil chemotherapy for metastatic or unresectable locally recurrent anal squamous cell carcinoma (Epitopes-HPV02): a multicentre, single-arm, phase 2 study. Lancet Oncol 2018;19:1094-1106. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30042063.

214. Kim S, Jary M, Mansi L, et al. DCF (docetaxel, cisplatin and 5-fluorouracil) chemotherapy is a promising treatment for recurrent advanced squamous cell anal carcinoma. Ann Oncol 2013;24:3045-3050. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24114858.

215. ClinicalTrials.gov. Testing the Addition of Nivolumab to Chemotherapy for Patients With Metastatic Anal Cancer. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04444921. Accessed June 15, 2021.

216. ClinicalTrials.gov. Carboplatin-paclitaxel With Retifanlimab or Placebo in Participants With Locally Advanced or Metastatic Squamous Cell Anal Carcinoma (POD1UM-303/InterAACT 2). 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04472429. Accessed June 15, 2021.

217. Morris VK, Salem ME, Nimeiri H, et al. Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study. Lancet Oncol 2017;18:446-453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28223062.

218. Ott PA, Piha-Paul SA, Munster P, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal. Ann Oncol 2017;28:1036-1041. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28453692.

219. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol 2020;38:1-10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31682550.

220. ClinicalTrials.gov. Nivolumab With or Without Ipilimumab in Treating Patients With Refractory Metastatic Anal Canal Cancer. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT02314169. Accessed June 15, 2021.

221. Salem ME, Puccini A, Grothey A, et al. Landscape of tumor mutation load, mismatch repair deficiency, and PD-L1 expression in a large patient cohort of gastrointestinal cancers. Mol Cancer Res 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29523759.

222. Glynne-Jones R, Sebag-Montefiore D, Meadows HM, et al. Best time to assess complete clinical response after chemoradiotherapy in squamous cell carcinoma of the anus (ACT II): a post-hoc analysis of randomised controlled phase 3 trial. Lancet Oncol 2017;18:347-356. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28209296.

223. Schiller DE, Cummings BJ, Rai S, et al. Outcomes of salvage surgery for squamous cell carcinoma of the anal canal. Ann Surg Oncol 2007;14:2780-2789. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17638059.

224. Mullen JT, Rodriguez-Bigas MA, Chang GJ, et al. Results of surgical salvage after failed chemoradiation therapy for epidermoid carcinoma of the anal canal. Ann Surg Oncol 2007;14:478-483. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17103253.

225. Das P, Bhatia S, Eng C, et al. Predictors and patterns of recurrence after definitive chemoradiation for anal cancer. Int J Radiat Oncol Biol Phys 2007;68:794-800. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17379452.

226. Sunesen KG, Norgaard M, Lundby L, et al. Cause-specific colostomy rates after radiotherapy for anal cancer: a danish multicentre cohort study. J Clin Oncol 2011;29:3535-3540. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21825256.

227. Ozsahin M, Santa Cruz O, Bouchaab H, et al. Definitive organ-sparing treatment of anal canal cancer: can we afford to question it? J Clin Oncol 2012;30:673-674; author reply 674-675. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22278906.

228. Allal AS, Laurencet FM, Reymond MA, et al. Effectiveness of surgical salvage therapy for patients with locally uncontrolled anal carcinoma after sphincter-conserving treatment. Cancer 1999;86:405-409. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10430247.

229. Delhorme JB, Severac F, Waissi W, et al. Surgery is an effective option after failure of chemoradiation in cancers of the anal canal and anal margin. Oncology 2017;93:183-190. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28571009.

230. Ellenhorn JD, Enker WE, Quan SH. Salvage abdominoperineal resection following combined chemotherapy and radiotherapy for epidermoid carcinoma of the anus. Ann Surg Oncol 1994;1:105-110. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7834434.

231. Nilsson PJ, Svensson C, Goldman S, Glimelius B. Salvage abdominoperineal resection in anal epidermoid cancer. Br J Surg 2002;89:1425-1429. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12390386.

232. Ko G, Sarkaria A, Merchant SJ, et al. A systematic review of outcomes after salvage abdominoperineal resection for persistent or recurrent anal squamous cell cancer. Colorectal Dis 2019;21:632-650. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30689272.

233. Wright JL, Gollub MJ, Weiser MR, et al. Surgery and high-dose-rate intraoperative radiation therapy for recurrent squamous-cell carcinoma of the anal canal. Dis Colon Rectum 2011;54:1090-1097. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21825888.

234. Chessin DB, Hartley J, Cohen AM, et al. Rectus flap reconstruction decreases perineal wound complications after pelvic chemoradiation and surgery: a cohort study. Ann Surg Oncol 2005;12:104-110. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15827789.

235. Devulapalli C, Jia Wei AT, DiBiagio JR, et al. Primary versus flap closure of perineal defects following oncologic resection: A systematic review and meta-analysis. Plast Reconstr Surg 2016;137:1602-1613. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26796372.

236. Lefevre JH, Corte H, Tiret E, et al. Abdominoperineal resection for squamous cell anal carcinoma: survival and risk factors for recurrence. Ann Surg Oncol 2012;19:4186-4192. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22825769.

237. Harris DA, Williamson J, Davies M, et al. Outcome of salvage surgery for anal squamous cell carcinoma. Colorectal Dis 2013;15:968-973. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23522325.

238. Hewitt M, Greenfield S, Stovall E, eds. From Cancer Patient to Cancer Survivor: Lost in Transition. Committee on Cancer Survivorship: Improving Care and Quality of Life, Institute of Medicine and National Research Council: National Academy of Sciences; 2006. Available at: http://www.nap.edu/catalog/11468.html.

239. El-Shami K, Oeffinger KC, Erb NL, et al. American Cancer Society Colorectal Cancer Survivorship Care Guidelines. CA Cancer J Clin 2015;65:428-455. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26348643.

240. Bentzen AG, Guren MG, Vonen B, et al. Faecal incontinence after chemoradiotherapy in anal cancer survivors: long-term results of a national cohort. Radiother Oncol 2013;108:55-60. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23891095.

241. Mirabeau-Beale K, Hong TS, Niemierko A, et al. Clinical and treatment factors associated with vaginal stenosis after definitive chemoradiation for anal canal cancer. Pract Radiat Oncol 2015;5:e113-118. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25424587.

242. Sunesen KG, Norgaard M, Lundby L, et al. Long-term anorectal, urinary and sexual dysfunction causing distress after radiotherapy for anal cancer: a Danish multicentre cross-sectional questionnaire study. Colorectal Dis 2015;17:O230-239. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26218674.

243. Knowles G, Haigh R, McLean C, Phillips H. Late effects and quality of life after chemo-radiation for the treatment of anal cancer. Eur J Oncol Nurs 2015;19:479-485. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25911268.

244. Sterner A, Derwinger K, Staff C, et al. Quality of life in patients treated for anal carcinoma-a systematic literature review. Int J Colorectal Dis 2019;34:1517-1528. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31324957.

245. Jephcott CR, Paltiel C, Hay J. Quality of life after non-surgical treatment of anal carcinoma: a case control study of long-term survivors. Clin Oncol (R Coll Radiol) 2004;16:530-535. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15630846.

246. Badin S, Iqbal A, Sikder M, Chang VT. Persistent pain in anal cancer survivors. J Cancer Surviv 2008;2:79-83. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18648976.