The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for Anal Squamous Cell Cancers (Revised 2018)

David B. Stewart, M.D.[1] • Wolfgang B. Gaertner, M.D., M.Sc.[2] • Sean C. Glasgow, M.D.[3]
Daniel O. Herzig, M.D.[4] • Daniel Feingold, M.D.[5] • Scott R. Steele, M.D.[5]

Prepared on Behalf of the Clinical Practice Guidelines Committee of the American Society of Colon and Rectal Surgeons
1 Department of Surgery, University of Arizona, Tucson, Arizona
2 Division of Colorectal Surgery, University of Minnesota, Minneapolis, Minnesota
3 Division of Colorectal Surgery, Washington University School of Medicine, St. Louis, Missouri
4 Division of Colorectal Surgery, Columbia University, New York, New York
5 Division of Colorectal Surgery, Cleveland Clinic, Cleveland, Ohio

CME

Earn Continuing Education (CME) credit online at cme.lww.com.

Links to search strategies: See search strategies for anal dysplasia, HPV vaccination, chemoradiation for squamous cell cancer of the anus, salvage APR, and metastatic disease in supplemental digital content at http://links.lww.com/DCR/A639.

Funding/Support: None reported.

Financial Disclosure: None reported.

Correspondence: Scott R. Steele, M.D., Department of Colorectal Surgery, Cleveland Clinic, 9500 Euclid Ave, A30, Cleveland, OH 44915. E-mail: steeles3@ccf.org

Dis Colon Rectum 2018; 61: 755–774
DOI: 10.1097/DCR.0000000000001114

The American Society of Colon and Rectal Surgeons is dedicated to ensuring high-quality patient care by advancing the science, prevention, and management of disorders and diseases of the colon, rectum, and anus. The Clinical Practice Guidelines Committee is composed of society members who are chosen because they have demonstrated expertise in the specialty of colon and rectal surgery. This committee was created to lead international efforts in defining quality care for conditions related to the colon, rectum, and anus. This is accompanied by developing clinical practice guidelines based on the best available evidence. These guidelines are inclusive and not prescriptive. The purpose of this guideline is to provide information on which decisions can be made rather than to dictate a specific form of treatment. These guidelines are intended for use by all practitioners and healthcare workers, as well as by patients who desire information about the management of the conditions addressed by the topics covered in these guidelines. It should be recognized that these guidelines should not be deemed inclusive of all proper methods of care or exclusive of methods of care reasonably directed toward obtaining the same results. The ultimate judgment regarding the appropriateness of any specific management decision must be made by the treating physician in light of all of the circumstances present in the care of the patient in question.

STATEMENT OF THE PROBLEM

Squamous cell cancers of the anal canal and perianal region remain one of the least common malignancies arising from the alimentary tract. As of 2016, it is estimated that 8200 new cases of squamous cell cancers of the anus were diagnosed in the United States, with 1.7 times as many women as men affected.[1] Within this same time period, ≈1100 patients were estimated to have died of anal cancer, with cancer deaths among women being 1.4 times the number observed among men. Although squamous cancers of the anus remain relatively rare GI malignancies, 2 factors have nonetheless focused greater attention toward this disease. The first is the observation that the frequency of squamous cancers of the anus has increased in the United States from the 1970s through the 2000s,[2] with a notable increase in incidence among men, and, in particular, black men.[3] In addition, given the inverse relationship between stage of disease and survival,[4] studies using population-level data suggest that earlier detection may improve survival from anal cancer, which makes anal cancer an important and treatable public health concern.

The second factor that has resulted in a paradigm shift in understanding the etiology of anal cancer is the discovery that the human papilloma virus (HPV), especially HPV serotypes 16 and 18,[5] is the primary cause of squamous cancers of the anus,[6,7] making anal cancer a sequela of a sexually transmitted disease. This aspect of anal carcinogenesis reinforces the concept that it is a potentially preventable disease and that if evidence-based screening and preventative measures were developed and consistently applied, decreases in cancer-related deaths would follow. The modifiable risk of death from anal cancer is further underscored by large studies that have documented that ≈50% of patients with anal cancer present with localized, node-negative disease, which is associated with high cure rates; one third of patients will present with node-positive disease, whereas only 10% to 15% will present with distant metastases.[8] Thus, even without effective preventative measures, the majority of patients with anal cancer are potentially curable at the time of diagnosis and treatment.

The multiple risk factors associated with developing squamous cancers of the anus are well documented and can be grouped into the 2 broad categories of HPV and immunosuppression, although there is also an association between these categories as well. Among the HPV-related risk factors include lifetime number of sexual partners,[9] a history of previous sexually transmitted diseases of any kind,[10] a history of anogenital warts,[11] anoreceptive intercourse,[12] and a history of cervical, vaginal, or vulvar cancer.[13] Risk factors related to immunity include a diagnosis of HIV,[14] autoimmune disorders such as lupus and sarcoidosis,[15] and being the recipient of a solid organ transplant.[16] Female sex[3] and cigarette smoking[17] are also associated with developing anal malignancies.

ANATOMIC CONSIDERATIONS AND TERMINOLOGY

The management of anal cancers requires a multidisciplinary approach, and the unfamiliarity of nonsurgical disciplines with anorectal anatomy can create ambiguity in describing the location and the clinical stage of anal cancers across disciplines. The anal canal, as viewed by colorectal surgeons, is ≈4 to 5 cm in length beginning at the distal rectum, where the mucosa blends into the anal transitional zone (ATZ) epithelium, which then transitions to nonkeratinized squamous epithelium as it further transitions into keratinized perianal skin at the anal verge. An ATZ, located several millimeters proximal to the dentate line and extending for 0.5 to 1.5 cm in length, represents a region of naturally occurring intestinal metaplasia, representing a transition from the columnar epithelium of the distal rectum to the modified squamous epithelium of the anal canal, referred to as *anoderm*. Because of the presence of metaplasia in the ATZ, this region is particularly susceptible to HPV infection.[18] In addition, the variety of tissue types in the ATZ have been associated with a number of subtypes of squamous cancers of the anus of both keratinizing and nonkeratinizing histologies. Although there were previous efforts to distinguish between histological subtypes of anal cancer, all of these subtypes are now grouped together, because multiple histological variants can exist within the same malignancy,[19] and because the natural history and survival of these subtypes are similar when stratified by treatment and cancer stage.[20]

Because the anatomic landmarks of the anus will not be easily identifiable by nonsurgical providers who are also untrained in techniques such as anoscopy and proctoscopy, a simplified taxonomy[21] has been suggested. An anal canal cancer would be any lesion that cannot be completely visualized with distraction of the gluteal cheeks, whereas a perianal (which replaces the term *anal margin*) lesion can be completely visualized with distraction of the gluteal cheeks, and that is still within 5 cm of the anal orifice. Any lesion >5 cm from the anal orifice would be classified as a skin lesion and would not be considered related to the GI tract.

Confusion often arises over the various pathology terms commonly used to describe lesions involving the anus and perianal skin. The Lower Anogenital Squamous Terminology project unified terminology for all HPV-related squamous precursor lesions with a 2-tiered nomenclature system.[22,23] This system simply designates noninvasive pathology as either low-grade or high-grade squamous intraepithelial lesions (LSILs and HSILs) based on histological findings such as mitotic activity, depth of dermal involvement, and abnormalities in squamous cell differentiation. LSILs include anal intraepithelial neoplasia (AIN) 1, whereas HSILs encompass AIN-2 and AIN-3 designations. The distinction between condylomas and LSILs is somewhat arbitrary; condylomas generally appear as bland exophytic, papillary proliferations with viral cytopathic changes, whereas LSILs tend to be flat lesions.[23] Older terms such as Bowen's disease should no longer be used. Throughout this Clinical Practice Guideline, the terms *LSIL* and *HSIL* will be used, although reference to AIN may appear when directly quoting published research findings.

This guideline only discusses the management of premalignant and malignant squamous neoplasms of the anus and perianal region, excluding other, rarer malignancies. The abbreviation *SCC* will be used to refer to squamous cell cancers.

METHODS

These guidelines were built on the most recent American Society of Colon and Rectal Surgeons Practice Parameters for Anal Squamous Neoplasms, published in 2012.[24] An organized search of MEDLINE, PubMed,

Embase, and the Cochrane Database of Collected Reviews was queried June 2015 through January 2018, searching for relevant publications with no limitations regarding date of publication. Retrieved publications were limited to the English language, but no limits on year of publication were applied. The search strategies were based on the key words *anal cancer* and *anal squamous cancer* as primary search terms, with additional, key-word searches including *AIN*, *anal intraepithelial neoplasia*, *Nigro protocol*, *anal HPV*, *LSIL*, and *HSIL*. Searches were also performed based on various treatments for anal cancers, including "anal cancer AND radiation," "anal cancer AND chemoradiotherapy," "anal cancer AND surgery," "anal cancer AND abdominoperineal resection," "anal cancer AND anal dysplasia," and "anal cancer and lymphadenectomy." Directed searches of the embedded references from the primary articles were also performed in certain circumstances. Prospective randomized controlled trials (RCTs) and meta-analyses were given preference in developing these guidelines. The final grade of recommendation was performed using the Grades of Recommendation, Assessment, Development, and Evaluation system (Table 1).[25]

Premalignant Neoplasms of the Anal Canal and Perianal Region

Patients at increased risk for anal squamous neoplasms should be identified by history, physical examination, and laboratory testing, noting that the risk is higher in HIV-positive individuals, men who have sex with men (MSM), and women with a history of cervical dysplasia. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.

Multiple large (300- to 1200-patient) cohort studies have identified risk factors for anal dysplasia and cancer.[26,27] A systematic review and meta-analysis noted that the pooled prevalence of HPV-16 in HIV-positive MSM was 35.4%.[28] The prevalence of AIN was 29.1%, and the incidence of anal cancer was 45.9 per 100,000 men. For HIV-negative MSM, the prevalence of HPV-16 was 11.8%, the prevalence of AIN was 21.5%, and the incidence of anal cancer was 5.1 per 100,000 men. A cohort of 171 HIV-positive women noted that 12.9% had HSILs.[29] Cervical dysplasia can also guide risk assessment in women; a population-based study of 89,018 women with cervical HSILs matched with control subjects without cervical dysplasia demonstrated an increased rate of anal cancer

TABLE 1. Grade scoring system

	Description	*Benefit vs risk and burdens*	*Methodologic quality of supporting evidence*	*Implications*
1A	Strong recommendation, High-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B	Strong recommendation, Moderate-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C	Strong recommendation, Low- or very-low–quality evidence	Benefits clearly outweigh risk and burdens or vice versa	Observational studies or case series	Strong recommendation but may change when higher-quality evidence becomes available
2A	Weak recommendation, High-quality evidence	Benefits closely balanced with risks and burdens	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patient or societal values
2B	Weak recommendations, Moderate-quality evidence	Benefits closely balanced with risks and burdens	RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patient or societal values
2C	Weak recommendation, Low- or very-low–quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits, risks, and burdens may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

Adapted with permission from Chest 2006;129:174–181.[25]
RCT = randomized controlled trial.

(relative risk = 6.68 (95% CI, 3.64–12.25)) and HSILs (relative risk = 4.97 (95% CI, 3.26–7.57)).[30]

Standardized nomenclature with a 2-tiered system should be used. Biomarkers, including p16, should be used selectively to clarify equivocal high-grade lesions. Grade of Recommendation: Strong recommendation based on low- or very-low–quality evidence, 1C.

There are advantages in standardizing terminology in defining the disease and treatments. The 2-tiered system[22,23] defined in 2012 provides the most appropriate system for standardizing definitions. Two retrospective studies have shown that there can be inconsistent interrater reliability when examining histology specimens.[31] Evidence supporting this 2-tiered system is based in part on 1 prospective blinded study that reported that interrater reliability for cytology using a 2-tiered system was 85% and that p16 staining and HPV oncogene messenger RNA analysis improved the ability to come to a diagnostic consensus.[32]

Individuals with anal dysplasia should be followed at regular intervals with a history, physical examination, and a discussion of screening options. Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.

Prevention of cervical cancer with screening for precancerous lesions has been proven effective.[31] Whether a similar program of screening and destruction of precancerous anal lesions will lead to reductions in anal cancer is a matter of considerable debate. A 2012 systematic review and meta-analysis suggested that, as part of their natural history, rates of progression to anal cancer are substantially lower than those observed for cervical cancer.[28] Regardless of which, if any, intensive screening program is selected, individuals with anal dysplasia should have a periodic office visit to assess for any new or modifiable risk factors, including a digital anorectal examination. Even in an intensive screening program, nearly all the cancers that developed were detectable on digital examination.[33]

It is not clear that screening will prevent a cancer from occurring, but there is evidence that cancers detected during a screening program are identified at an early stage.[33] Multiple cohort studies have shown progression from low-grade to high-grade dysplasia and from dysplasia to cancer even under regimented surveillance. A cohort of 91 HIV-positive patients treated for anal dysplasia followed for >1 year showed that 75.8% had recurrent dysplasia, 46.0% progressed to high-grade dysplasia, and 2.3% developed anal cancer.[34] Studies of 4 cohorts of patients in intensive treatment programs have separately estimated the development of cancer despite treatment, although all recorded the risk differently. One estimated the rate of progression to cancer at 6.9 cases per 100 person-years of follow up,[35] another estimated the Kaplan–Meier probability of SCC at 3 years at 1.97%,[36] a third estimated the duration to development of SCC at 57 to 62 months,[33] and a fourth estimated the 5-year cumulative incidence of SCC at 1.70%.[37] There is consensus among experts that an HSIL is the precursor to invasive cancer.[33,38] What remains unclear is whether screening to identify and ablate premalignant lesions will decrease the incidence of SCC. Nevertheless, even if the progression to cancer cannot be halted, early diagnosis of a cancer justifies follow-up, and a history and examination to identify and treat visible and palpable lesions and/or a discussion of screening options is justified.

Screening with anal cytology (or anal Papanicolaou (Pap) tests) may be considered in high-risk populations as part of a comprehensive screening program, but the sensitivity and specificity of the test do not support its use for universal screening. Grade of Recommendation: Weak recommendations based on moderate-quality evidence, 2B.

Similar to cervical Pap smear cytology, a swab or brush sample from the anal canal to include the ATZ can be evaluated for cytological evidence of dysplasia. Although the data demonstrating effectiveness for cervical cancer screening and prevention are well founded, substantial efforts to prove its role in anal cancer screening have not been conclusive. Because screening tests perform better as the prevalence of a condition is higher, screening a higher-risk population will be more effective. Most studies screen high-risk individuals, including MSM, HIV-positive persons, and/or women with a history of cervical dysplasia. Results from studies that have performed both anal cytology and histologic evaluation are shown in Table 2.[12,29,39–52] The sensitivity and specificity are limited, because the gold standard is the finding of HSILs on biopsies. Currently the ability of anal cytology to identify patients at risk for dysplasia is inconclusive, and an association between anal cytology and reduced rates of anal cancer has not been demonstrated. The decision to perform anal Pap tests should be a shared decision with the patient, including a discussion about how abnormal tests will be further evaluated.

HPV testing may be used as an adjunct to screening for anal cancer. Grade of Recommendation: Weak recommendations based on moderate-quality evidence, 2B.

The presence of HPV, especially subtypes 16 and 18, is associated with the majority of anal cancers. Biomarkers screen for the presence of high-risk HPV to estimate the risk of dysplasia. The main limitation to this strategy is the high prevalence of HPV in the high-risk population. Currently available options include HPV DNA testing, HPV DNA genotyping for HPV-16 and HPV-18, HPV-E6/E7 mRNA testing, and p16/Ki-67 immunostaining based on either anal cytology or biopsy. P16 is a tumor suppressor gene product that indicates HPV integration into the host genome. The Lower Anogenital Squamous Terminology guidelines recommend the use of p16 in borderline HSIL/LSIL cases, with strong positive staining leading to

Table 2. Studies of anal cytology and histologic evaluation for squamous intraepithelial lesions

Study	*Location*	*No./type of patient*	*Anal cytology findings*	*Anal biopsy findings*	*Sensitivity/specificity for cytology detecting HSIL*
Jin et al,[39] 2017	Sydney, NSW, Australia	617 MSM	Negative 41.0% ASC-US 17.5 LSIL 8.0% ASC-H 15.0% HSIL 18.5%	Negative 29.6% LSIL 31.0% HSIL 39.0% SCC 0.2%	Sensitivity 83.2% Specificity 52.4% PPV 45.8% NPV 86.6%
Schofield et al,[12] 2016	Manchester, United Kingdom	284 MSM	Negative 56% Inadequate 2.1% LSIL 31.4% HSIL 10.5%	Normal 4.5% AIN-1 54.9% AIN-2 31.7% AIN-3 7.6% SCC 1.3%	Sensitivity 76.5% Specificity 54.6% PPV 45.8% NPV 86.6%
Heard et al,[29] 2015	Multicenter	171 HIV-positive women	Negative 70.7% ASC-US or LSIL 18.7% ASC-H or HSIL 10.0% SCC 0.6%	Normal 59.2% Benign 20.7% LG-AIN 10.7% HG-AIN 5.9% SCC 0.6%	
Cheng et al,[40] 2015	Taiwan	196 HIV-positive men	Negative 63.8% ASC-US 16.8% LSIL 14.8% HSIL 4.6%	HG-AIN 7.1%	Sensitivity 64.0% Specificity 66.0% PPV 12.7% NPV 96.0%
Sendagorta et al,[41] 2014	Spain	298 HIV-positive MSM	Negative 60.2% ASC-US 5.7% LSIL 24.1% HSIL 10%	Normal 19.3% Benign 10.9% AIN-1 14.3% AIN-2 35.3% AIN-3 20.2%	Incomplete data
Botes et al,[42] 2013	Australia	262 HIV-positive MSM	Negative 23.0% ASC-US 15.8% ASC-H 9.6% LSIL 39.9% HSIL 4.5	No biopsy 11.9% Benign 19.7% LG-AIN 13.9% HG-AIN 54.5%	Incomplete data
Wentzensen et al,[43] 2012	San Francisco, California	363 HIV-positive patients	Negative 30.8% ASC-US 20.1%% ASC-H 7.4% LSIL 18.5% HSIL 16.5%	No biopsy 19.3% Benign 23.4% AIN-1 34.7% AIN-2 15.2% AIN-3 6.9%	
Williams et al,[44] 2010	Australia	154 patients	Negative 5.4% ASC-US 18.7% ASC-H 1.2% LSIL 47.3% HSIL 27.4%	Benign 11.6% LSIL 50.0% HSIL 38.6	Sensitivity 96.0% Specificity 14.0% PPV 89.0% NPV 31.0%
Salit et al,[45] 2010	Toronto, Ontario, Canada	401 HIV-positive MSM	Negative 33.0% ASC-US 12.0% LSIL 43.0% HSIL 12.0%	Normal 59.2% Benign 32.0% LG-AIN 43.0% HG-AIN 25.0%	Sensitivity 84.0% Specificity 39.0% NPV 88.0% PPV 31.0%
Nathan et al,[46] 2010	London, United Kingdom	395 patients	Negative 32.6% ASC-US 26.7% LSIL 32.6% HSIL 8.0%	Normal 24.2% LG-AIN 50.2% HG-AIN 25.6%	Sensitivity 81.0% Specificity 37.0% NPV 85.0% PPV 30.0%
Fox et al,[47] 2005	London, United Kingdom	99 MSM	Negative 26.0% LSIL 59.0% HSIL 15.0%	Normal 16.0% AIN-1 18.0% AIN-2 37.0% AIN-3 26.0%	Sensitivity 83.0% Specificity 38.0% NPV 86.0% PPV 33.0%
Arain et al,[48] 2005	Los Angeles, California	198 patients	Negative 31.7% ASC-US or LSIL 55.2% ASC-H or HSIL 13.1%	Normal 18.3% AIN-1 21.1% AIN-2 35.2% AIN-3 25.4%	Sensitivity 98.0% Specificity 50.0%

(*Continued*)

Table 2. Continued

Study	*Location*	*No./type of patient*	*Anal cytology findings*	*Anal biopsy findings*	*Sensitivity/specificity for cytology detecting HSIL*
Papaconstantinou et al,[49] 2005	Dallas, Texas	47 patients	Negative 23.4% ASC-US or LSIL 57.4% ASC-H or HSIL 14.9% SCC 4.3%	Normal 42.6% AIN-1 17.0% AIN-2 12.8% AIN-3 21.3% SCC 6.4%	Sensitivity 42.0% Specificity 96.0%
Mathews et al,[50] 2004	San Diego, California	1732 patients	Negative 43.2% ASC-US 34.1 LSIL 15.3% HSIL 7.5%	Incomplete data	Sensitivity 85.0% Specificity 56.0%
Panther et al,[51] 2004	Boston, Massachusetts	153 MSM	Negative 12.4% ASC-US 19.6% LSIL 47.1% HSIL 20.9%	Normal 21.6% AIN-1 37.3% AIN-2 14.4% AIN-3 25.5% SCC 1.3%	Sensitivity 47.0% Specificity 90.0%
Palefsky et al,[52] 1997	San Francisco, California	407 patients	Negative 72.4% ASC-US 15.1% LSIL 12.1% HSIL 0.4%	Normal 11.9% LG-AIN 79.3% HG-AIN 8.9%	Sensitivity 69.0% Specificity 59.0%

MSM = men who have sex with men; ASC-US = atypical squamous cells of undetermined significance; ASC-H = atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion; SCC = squamous cell cancers; AIN = anal intraepithelial neoplasia; LG = low-grade; HG = high-grade; PPV = positive predictive value; NPV = negative predictive value.

an HSIL diagnosis and weak or absent staining supporting an LSIL diagnosis. The use of p16 staining, or any of the biomarkers, in a screening setting is less clear.

Two prospective studies have compared anal cytology with HPV testing, as have multiple retrospective cohorts. The ANALOGY trial prospectively evaluated screening with cytology, high-risk HPV typing, and high-resolution anoscopy (HRA). With HPV testing only 59% of HSILs would have been detected.[12] The Australian study used high-risk HPV viral load and high-risk HPV-E6/E7 mRNA, as well as cytology and HRA.[39] Compared with cytology for the detection of HSIL, HPV testing showed similar sensitivity and improved specificity for the detection of HSILs, especially in the HIV-negative group.

HRA may be considered as a screening option for patients at high risk for cancer when performed by clinicians with appropriate training in the procedure. Recommendation: Weak recommendation based on moderate-quality evidence, 2B.

HRA is a procedure performed in the office or in the operating room using magnification and topical agents such as acetic acid and Lugol's solution to identify, biopsy, and ablate lesions not visible by conventional examination or anoscopy. The procedure can be more cost-effective if performed in the office. In addition, because it is superior to cytology or HPV testing in identifying HSILs, HRA may be more cost-effective than other strategies; the cost per HSIL found has been estimated to be $809.39. A prospective screening study of high-risk MSM evaluated all 3 modalities of HPV testing, cytology, and HRA.[12] In a cohort of 284 MSM, AIN-3 was detected in 17 patients, with screening HRA finding 16, HPV-16/18 testing finding 10, any HPV testing finding 16, high-grade cytology detecting 3, and any abnormal cytology detecting 12 subjects. However, only 15% of the cohort tested negative for HPV, representing a methodologic weakness in this study. Cytology missed nearly one third of high-risk lesions, suggesting that HRA would have the most clinical use for screening.

The effectiveness of HRA to prevent the progression of dysplasia or development of cancer has been evaluated in retrospective cohort studies. A retrospective review of 246 patients treated with HRA-targeted destruction of HSIL/LSIL over a 10-year period was published in 2008.[53] A recurrent HSIL was seen in 57% of patients at an average of 19 months. Despite treatment, 1.2% progressed to invasive cancer.

A cohort of 727 MSM followed for a median of 2.2 years was published in 2014. With ablation of all HRA-identified lesions and with regular follow-up, the rate of recurrence at 1 year was 53% in HIV-positive patients and 49% in HIV-negative patients. Over the follow-up period, 5 patients developed cancer, with the probability of cancer 1.97% at 3 years.[36]

There are few comparisons of HRA with other treatment strategies. A retrospective review of 424 patients compared HRA with expectant management in 2 cohorts, one treated by 3 clinicians who followed patients with expectant management and the other treated by 2 clinicians who followed patients with HRA.[54] Anal cancer occurred in 1 of the HRA patients and 2 of the expectant management patients. The 5-year progression rate was similar in the 2 cohorts. Selection bias and the possibility for type II error limit these findings.

Performing HRA requires specialized training and ongoing practice to perform good-quality examinations.[55,56] In addition, patient compliance, patient tolerance, and the risk of over treatment have led some clinicians to wait to start performing HRA until additional data are available. Although HRA effectively identifies HSIL, whether HRA with ablation of HSIL can reduce the incidence of cancer or whether it can do so more consistently than conventional anoscopy remains unclear.

Topical imiquimod, fluorouracil, trichloroacetic acid and cidofovir with close long-term follow-up are each options for the treatment of LSIL or HSIL. Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.

Two randomized trials and 1 prospective cohort study have evaluated imiquimod. A placebo-controlled RCT of 64 HIV-positive patients with HSILs who were followed with HRA suggested superior clearance of HSILs with imiquimod (42.9% vs 4.0%).[57] With a median follow-up of 33 months, 61% showed a sustained absence of HSILs. An RCT comparing imiquimod with topical fluorouracil and electrocautery found that 24% of HSILs had resolved and 11% had a partial response with imiquimod.[58] Although electrocautery had a statistically significant improvement in response when the *p* value was calculated for the 3 treatment options, the difference was not significant if imiquimod and electrocautery were compared head to head. A third prospective cohort study evaluated imiquimod 5 days per week and found that the overall response rate for HSILs was 66%.[59]

Two retrospective studies have evaluated topical fluorouracil. A retrospective review of 46 patients with HSILs or LSILs showed that 57% responded to topical fluorouracil, with 39% having a complete response.[60] A second review of 11 patients with dysplasia (although only 5 had HSILs) showed a decrease in dysplasia in 6 (55%) of 11 patients.[61]

Two retrospective cohort studies have examined the use of trichloroacetic acid. A review of 98 HSILs from 72 patients demonstrated that 28.7% of lesions had resolution or downgrading to LSILs on follow-up, although recurrence occurred in 20.8% of the lesions.[62] A review of 54 men showed that, on a per-lesion basis, 72% of HSILs cleared to LSIL or less.[63]

Cidofovir has been evaluated in 1 prospective pilot study and 1 retrospective cohort study. The pilot study included 16 HIV-positive patients with HSILs and revealed a complete response rate of 10 (62.5%) of 16, although 2 (20.0%) of 10 had recurrent HSILs at the 24-week end point of the study.[64] A small cohort of 24 patients with HSILs demonstrated that 51% had responsive disease, with a complete response observed in 15% of patients.[65]

Ablative treatments with conventional anoscopy or HRA are appropriate therapies for HSILs. Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.

If HRA is used as the primary screening modality, ablative therapies can be used as first-line treatment for dysplasia. A prospective cohort of 98 patients with HSILs treated with infrared coagulation (IRC) showed that 74% had no additional evidence of HSILs on short-term follow-up.[66] There was a comparison to expectant management in that study, but the control group was derived from patients who delayed or declined treatment, and patients who missed follow-up were excluded. In light of these limitations, the findings in this study are best viewed as a cohort treated with IRC. Three reviews have been published from a single center, and it is unclear how much overlap exists.[67–69] Findings from the most recent review, a retrospective review of 96 MSM with HSILs treated with ≥1 IRC showed that 82% of HIV-positive and 90% of HIV-negative individuals were free from HSILs, but recurrence rates were high in the study, and nearly one third of patients were lost to follow-up.[69] A retrospective review of 78 HSILs in 68 HIV-positive MSM showed 64% efficacy per treated lesion.[70] A retrospective review of 66 patients with HSILs treated with IRC reported that only 13% had recurrent HSILs at 1 year of follow-up.[71]

Electrocautery ablation was reviewed in a cohort of 232 MSM with HSIL.[72] Initial clearance rates were high (75%–80%), but recurrences were common (53%–61%), and 1 patient in the cohort developed cancer despite treatment. A cohort of 83 patients treated for HSIL with electrocautery found a complete or partial response in 66.2%.[73] With a mean follow-up of 12.1 months, 25.4% of patients had a high-grade recurrence. A single-center review of 3 ablative techniques, electrocautery, IRC, or laser treatments, showed no differences in the rate of recurrence.[36]

One prospective RCT compared imiquimod, topical fluorouracil, and electrocautery in HIV-positive MSM with confirmed AIN.[58] Resolution of AIN was achieved in 24% of patients in the imiquimod group, 17% of the topical fluorouracil group, and 39% of the electrocautery group ($p = 0.008$ for electrocautery vs fluorouracil; $p = 0.10$ for electrocautery vs imiquimod).

Vaccination against HPV in men and women under age 26 years for primary prevention is typically recommended. Vaccination of individuals with anal dysplasia for secondary prevention of dysplasia and cancer is not recommended. Grade of Recommendation: Weak recommendation based on high-quality evidence, 2A.

The availability of bivalent, quadrivalent, and now nonavalent vaccines has created considerable promise that the next generation of individuals will be largely exempt from HPV-related neoplasms. Although there are convincing data for use of the vaccine in pre-exposure young individuals, the off-label use of the vaccine in those with anal dysplasia is of considerable interest. A systematic review and meta-analysis of the efficacy of the vaccine in cervical dysplasia showed that it had no effect.[74] A systematic review

including all of the sites reported that 9 of 12 studies performed in patients with active disease showed decreased disease recurrence, but no study reported improved outcomes without clinical disease.[75] However, enthusiasm for the vaccine for secondary prevention or regression of dysplasia gained attention after a study of 602 MSM who were randomly assigned to receive either the quadrivalent HPV vaccine or placebo. Those who received the vaccine had a lower rate of intraepithelial neoplasia, and the rate of HSILs was reduced by 54%.[5] A comparative cohort study of 202 patients with previous HSILs treated with or without the quadrivalent vaccine demonstrated that vaccine treatment was associated with decreased risk of recurrent HSILs.[76] A prospective, randomized, National Institutes of Health–funded trial including 574 patients has been completed and presented in abstract form, and the results are available at clinicaltrials.gov (NCT01461096). The number of participants with biopsy-proven HSIL occurrences and recurrences at 1 year or abnormal cytology at 1, 2, or 3 years was the same.

Patients who have been treated for anal dysplasia may be observed without regular cytology, HPV testing, or HRA; however, treatment of visible or palpable disease should be offered. Grade of Recommendation: Weak recommendation based on low or very low-quality evidence, 2C.

Although it is generally accepted that HSIL is a precursor to invasive cancer, there remain no studies that compare more intensive screening and/or HRA protocols with office examinations, conventional anoscopy, and treatment of visible or palpable disease. A review of 574 patients in an HRA program showed that 24% of patients with HSIL had spontaneous regression to LSIL.[77] The progression to cancer is often multifactorial, including contributions from medication compliance, immunosuppression, HIV viral load, ongoing exposure to HPV, smoking, and a variety of other factors.

In the largest prospective randomized US trial, which is currently enrolling, the control arm of the study includes no treatment of HRA-identified HSILs. The Topical or Ablative Treatment in Preventing Anal Cancer in Patients With HIV and Anal High-Grade Squamous Intraepithelial Lesions trial (NCT02135419) will screen HIV-positive patients with HRA and targeted biopsies. Previously untreated individuals who have HSILs identified will be randomly assigned to treatment or monitoring. For patients who are treated, the clinician decides whether the patient should have topical treatment or ablative treatment. Patients with topical treatment may receive imiquimod, fluorouracil, or trichloroacetic acid. Patients with ablative treatment may have IRC, electrocautery, or laser ablation. In the study, number and frequency of the treatments is left to the discretion of the treating physician. For patients who are observed, examinations and cytology are performed every 6 months, with biopsies of any visible lesions. Therefore, although screening and preventative treatment remain controversial, expectant management with treatment of visible or palpable disease remains an option unless or until emerging evidence suggests that screening and ablation of subclinical lesions are beneficial to reduce the incidence of anal cancer.

MALIGNANT NEOPLASMS OF THE ANAL CANAL AND PERIANAL REGION

Pretreatment Evaluation

A disease-specific history and physical examination should be performed, emphasizing symptoms, risk factors, and signs of advanced disease. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.

Most patients present with a slow-growing mass involving either the anal canal or the perianal skin.[78] Pain and bleeding are common, occurring in approximately half of patients, although <20% of patients may be asymptomatic.[10,79] Diagnosis of anal SCC may often be delayed, mainly because of nonspecific anorectal symptoms, which are frequently attributed to benign anorectal pathology, such as hemorrhoids, in <70% to 80% of patients.[78,80] Patients with locally advanced anal cancers may also present with foreign body sensation, symptoms related to anal stenosis, and inguinal pain (commonly representing inguinal lymph node metastases). Risk factors associated with anal SCC include HPV infection; HIV seropositivity; a history of other HPV-related genital neoplasias, such as cervical cancer; cervical intraepithelial neoplasia; vulvar cancer; vulvar intraepithelial neoplasia; previous sexually acquired diseases; cigarette smoking; anoreceptive intercourse; multiple sexual partners; a history of solid-organ transplant; and other forms of immunosuppression.[9,11,81–86] Because the incidence of anal cancer is higher among men practicing anoreceptive intercourse, as well as among patients positive for HIV, a high index of suspicion should be maintained in these patients who present with anorectal complaints.[87] Additional historical factors such as previous radiation and inadequately controlled HIV may limit chemoradiotherapy (CRT) and radical surgery and are important variables to investigate at the time of diagnosis.

Physical examination should focus primarily on anorectal examination and evaluation of the inguinofemoral nodes.[88] Digital anorectal examination should be performed to identify the lesion location and to evaluate for fixation and/or the presence of invasion of local structures, such as the vagina or the anal sphincter mechanism. Anoscopy or proctoscopy with biopsy is essential to establish the size of the lesion, to determine its location within the anal canal, and to confirm diagnosis. The presence of palpable inguinal lymphadenopathy can suggest the need for fine-needle aspiration or core biopsy to confirm malignant involvement and

to help guide radiation planning. In general, metastatic disease is difficult to detect on physical examination, although a complete physical examination should be performed to help identify any potential sites of distant spread that may warrant additional evaluation. All patients with a new diagnosis of anal SCC should undergo basic laboratory studies, including a complete blood count, renal and hepatic function tests, and an assessment of their HIV status if not already known. Women should undergo a cervical Pap test, and men should undergo penile examination to exclude premalignant or malignant lesions. Although the immunohistochemical expression of p16 and Ki-67 has been shown to correlate with the degree of anal intraepithelial neoplasia,[89] their role in the evaluation of anal SCC is still being defined.

Endoscopic and radiologic evaluation should be performed to help determine tumor extension and assess for metastatic disease. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.

Biopsy should be performed under direct vision or with anoscopy. Although anal cancer is not a risk factor for the development of colon cancer, colorectal neoplasms have been demonstrated in <15% of patients with anal cancer; therefore, colonoscopy should be performed to rule out synchronous colorectal neoplasms.[88,89] A CT of the chest, abdomen, and pelvis with intravenous contrast enhancement should be performed to evaluate for distant metastatic disease and lymphadenopathy, including evaluating the inguinal lymph nodes, which may warrant biopsy in the setting of clinical or radiographic abnormalities.[90] Because SCC can metastasize to the brain, a CT of the head may be performed if the patient has symptoms or signs of central nervous system involvement. With CRT being the mainstay of treatment for anal SCC, accurate anatomic imaging of the primary tumor is highly recommended, because it enables optimal radiotherapy planning and allows for posttreatment comparisons. Endoanal ultrasound (EAUS) and MRI are at present the 2 most accepted modalities for determining primary tumor depth, anal sphincter involvement, and perirectal lymph node involvement.[91,92] There is only 1 study to date[93] that directly compares EAUS (using 2-dimensional imaging) with MRI in the primary staging of anal SCC, with comparable results in assessing primary tumor size and perirectal lymph node status. Although EAUS is traditionally considered to be superior to MRI for small superficial tumors, this has not been reported in the current literature. Additional considerations with EAUS include that it is operator dependent and may cause significant discomfort in patients with anal stenosis.

2-[^{18}F] Fluoro-2-deoxy-D-glucose positron emission tomography (PET)/CT may be considered as an adjunct radiologic study in the staging of anal SCC, although it does not replace CT scanning for clinical staging. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.

Staging for SCC of the anal canal focuses on size of the primary lesion and locoregional lymph node involvement. As such, clinical evaluation including size is critically important to determine proper staging. The most widely used clinical staging system is the American Joint Committee on Cancer and International Union Against Cancer TNM classification (Table 3), which defines T stage by maximum tumor diameter. This staging system does not take into account sphincter muscle and perianal skin involvement or the presence of a perianal or anovaginal fistula, which are important prognostic factors that have not been well studied in the era of modern CRT.[94–96]

Although not typically a part of the routine evaluation, 2-[^{18}F] fluoro-2-deoxy-D-glucose PET/CT has been shown to identify distant metastases that are not detected by physical examination or other imaging modalities in 17% to 25% of patients,[97,98] resulting in a reported change in treatment (ie, radiotherapy) in <19% of cases.[99–101] In addition, retrospective studies evaluating the role and impact of PET/CT in anal SCC have shown that metabolic tumor volume at the primary tumor site, as well as hypermetabolic inguinal lymphadenopathy, correlates with overall survival.[102–104] The measurement of metabolic tumor volume at the primary cancer site, as well as with potential pelvic and inguinal lymph node metastases, also influences preradiation planning by radiation oncologists.

The primary treatment for all squamous cell cancers of the anal canal, and for most perianal squamous cell cancers, is CRT. Grade of Recommendation: Strong recommendation based on high-quality evidence, IA.

Before the initial case series by Nigro et al[105] describing patients with squamous anal cancers treated with multimodal neoadjuvant therapy, patients with these malignancies were treated with abdominoperineal resection (APR). The outcomes associated with primary APR were dismal,[106,107] with locoregional recurrence rates as high as 50% and 5-year survival rates ranging from 40% to 70%.[108,109] In addition, the morbidity of an APR during this time period was significant. By contrast, even with the limitations of delivering radiotherapy in his day, Nigro and colleagues provided follow-up data to his original series,[110,111] culminating in an evaluation of 104 patients with squamous cancers of the anus who were treated with 30 Gy of radiotherapy combined with 5-fluorouracil (5-FU) and mitomycin-C (MMC). In 97 patients, no gross tumor remained. In this same series there were 31 patients who underwent an APR regardless of whether there was clinical evidence of tumor persistence, and 22 of these patients were completely free of any histological evidence of cancer.

Currently, CRT is the standard of care for the treatment of all anal canal squamous cell cancers and for all perianal squamous cell cancers that are not well-differentiated, node-negative, T1 lesions amenable to wide local

TABLE 3. American Joint Committee on Cancer and International Union Against Cancer TNM classification of anal cancer

Primary tumor (T)	
TX	Primary tumor cannot be 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
T2	Tumor >2 cm but ≤5 cm
T3	Tumor >5 cm
T4	Tumor of any size invading adjacent organ(s), such as the vagina, urethra, or bladder
Regional lymph nodes (N)	
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
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

When T is...	*And N is...*	*And M is...*	*Then the stage group is...*
Tis	N0	M0	0
T1	N0	M0	I
T1	N1	M0	IIIA
T2	N0	M0	IIA
T2	N1	M0	IIIA
T3	N0	M0	IIB
T3	N1	M0	IIIC
T4	N0	M0	IIIB
T4	N1	M0	IIIC
Any T	Any N	M1	IV

excision. Although there are slight variations in how radiation is administered, there are certain principles that should be followed for every patient.[112,113] A multifield technique should be used to deliver a minimum radiation dose of 45.0 Gy, which is typically delivered to the primary cancer in 25 fractions, each of 1.8 Gy over an ≈5-week time interval. The radiation field should initially extend from the border of L5 to S1, spreading distally to incorporate the entire pelvis, including the anus and the inguinofemoral nodes, terminating onto the perianal skin 2.5 cm distal to the anus. Radiation oncologists should also make efforts to reduce radiation exposure to the femoral heads because of the risk of avascular necrosis.[114] After the first 30.6 Gy is administered, the additional 14.4 Gy of scheduled radiation should be delivered with the cephalad aspect of the radiation field lowered to the distal aspect of the sacroiliac joints while also sparing the inguinal nodes from additional treatment for those patients with no inguinal nodal disease. In addition, for any lesions larger than a T1 cancer or for those that are node positive, a boost of 9 to 14 Gy to the primary tumor and to the involved nodes is recommended. In this setting, the total dose of radiation delivered would be 54 to 59 Gy.

The selection and doses of chemotherapeutic agents for CRT can vary from among several options. Classically, 5-FU is infused at 1000 mg/m^2 on days 1 to 4 and days 29 to 32, with MMC administered in bolus form at 10 mg/m^2 on days 1 and 29.[112] Alternatively, capecitabine, an oral fluoropyrimidine prodrug, can be substituted for 5-FU at a dose of 825 mg/m^2 twice daily.[115,116] When capecitabine is selected, the dose of MMC is often increased to 12 mg/m^2 at the discretion of the treating medical oncologist.

CRT is associated with significant rates of acute toxicity. In the Radiation Therapy Oncology Group (RTOG) 9811 study,[112] a total of 90% of patients treated with MMC-based CRT experienced some form of GI toxicity, ranging from nausea to vomiting and diarrhea. The incidence of grade III or IV nonhematologic toxicity was 74% in this group, whereas the incidence of severe long-term toxic effects was 11%. This high incidence of significant toxicities has prompted investigations into alternative CRT regimens, as discussed below.

Patients preparing for CRT need to be counseled regarding sexual and reproductive health choices. Both men and women of child-producing ages should be counseled regarding sperm and ova banking before the onset of therapy. Women should be asked if they have undergone a recent gynecologic examination with screening for cervical HPV, given the frequent association between anorectal HPV and HPV of the cervix. Female patients who are planning on sexual activity at any point after CRT should be counseled regarding the use of vaginal dilators to prevent vaginal stenosis resulting in the inability for coitus. These issues are easily and frequently overlooked and should typically be included in pretherapy counseling to preserve quality of life for long-term survivors of anal cancer.

Multimodal therapy involving chemotherapy combined with radiotherapy provides superior locoregional control compared with treatment with radiotherapy alone. Grade of Recommendation: Strong recommendation based on high-quality evidence, IA.

Cancers with squamous histology are typically radiosensitive, and with the initial implementation of radiation as monotherapy for squamous cancers of the anus, a high rate of locoregional disease control and avoidance of surgery was documented with smaller, earlier-stage cancers.[117,118] With larger, bulkier cancers, however, persistence and recurrence rates were frequently encountered, and this raised questions regarding a possible role for chemotherapy in combination with radiotherapy. The first large study to evaluate the role of multimodality therapy in anal can-

cer was the United Kingdom Coordinating Committee on Cancer Research Anal Cancer Trial (ACT I) Working Party.[119] In this trial, 585 patients were randomly assigned to receive either 45 Gy of radiation in 20 to 25 fractions over 4 to 5 weeks or to receive the same form of radiotherapy but with the addition of 5-FU and MMC. With a median follow-up time of 42 months, 59% of the radiotherapy patients had experienced a local failure compared with 36% of the CRT group, amounting to a 46% reduction in local failure associated with the use of CRT. Similar rates of tumor response were observed in both treatment groups at 6 weeks. Although the risk of death in the CRT arm was lower, there was no difference in overall survival between the 2 arms at 3 years after treatment. Not unexpectedly, the CRT cohort was associated with a higher incidence of early morbidity, whereas late adverse events related to treatment occurred with similar frequency. This study was instrumental in establishing CRT as the first-line therapy for squamous cancers of the anal canal. A recent analysis of this original study population[120] has provided 13-year follow-up, demonstrating that CRT is associated with 25.3 fewer locoregional recurrences and 12.5 fewer anal cancer–related deaths for every 100 patients treated with CRT compared with every 100 patients treated with radiation alone. In addition, although there was a 9.1% increase in deaths unrelated to anal cancer during the first 5 years after CRT, this increased risk of noncancer-related mortality disappeared after 10 years. Local failure rates favored CRT (57% vs 32%) at 5 years, as did colostomy-free survival at 5 years (37% vs 47%).

The year following ACT I, the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups published a study (22861)[121] evaluating the role of multimodality therapy as compared with radiation alone for anal cancer. In this randomized study, 110 patients were assigned to either 45 Gy followed by a boost of variable dosing depending on tumor response versus the same radiation regimen combined with 5-FU and MMC, the latter of which was provided as a bolus only on the first treatment day. Patients in the CRT arm experienced a complete response rate of 80% compared with 54% in the radiation arm, with improved locoregional control and with superior progression-free and colostomy-free survival rates. As with the United Kingdom Coordinating Committee on Cancer Research study, there were no differences in overall survival rates at 3 years after treatment.

The combination of 5-FU and MMC in conjunction with radiotherapy remains as first-line multimodal therapy for the treatment of squamous cancers of the anus. Grade of Recommendation: Strong recommendation based on high-quality evidence, IA.

MMC has a significant toxicity profile, including hematologic toxicity in the form of bone marrow suppression with neutropenia and thrombocytopenia, pulmonary toxicity, and acute kidney injuries.[122] Because of earlier, albeit small, studies suggesting comparable oncologic outcomes and lower rates of toxicity associated with omission of MMC, the RTOG 8704 trial[123] was performed by the RTOG and the Eastern Cooperative Oncology Group to evaluate whether MMC could be removed from CRT while maintaining the same disease control and cure rates. During this trial, 310 patients were randomly assigned to receive either radiotherapy (ranging from 45.0 to 50.4 Gy) with 5-FU infused for 4 days versus the same radiotherapy regimen combined with 5-FU and MMC at 10 mg/m^2 as a bolus over 2 days. After treatment, biopsies yielding histology positive for cancer did not differ to a statistically significant degree between either treatment arm (15.0% vs 7.7%; $p = 0.135$). At 4 years after treatment, colostomy rates (9% vs 22%; $p = 0.002$), colostomy free-survival (71% vs 59%; $p = 0.14$), and disease-free survival (73% vs 51%; $p = 0.0003$) favored the cohort that received MMC. There was no difference in overall survival, whereas toxicity was significantly higher in the MMC cohort (23% vs 7% for grade 4 and 5 toxicity; $p < 0.001$). Although toxicity with MMC was higher, the results of the study nonetheless supported the inclusion of MMC in CRT compared with the use of 5-FU and radiation alone.

Although the net benefit of including MMC with 5-FU and radiation was established early in the evolution of multimodality anal cancer therapy, lingering concerns regarding MMC-related toxicity lead to attempts to substitute MMC with other agents. Several important clinical trials have evaluated whether cisplatin might offer improved toxicity rates while providing comparable, or superior, disease control. The ACT II trial,[124] which remains the largest clinical trial on anal cancer to date, enrolled patients with squamous cancers of the anus from a total of 59 centers across the United Kingdom. Patients were randomly assigned to 1 of 4 groups, receiving either MMC or cisplatin, with 5-FU and radiotherapy (50.4 Gy) with or without 2 infusions of maintenance chemotherapy consisting of 5-FU and cisplatin provided at weeks 11 and 14. A total of 940 patients were enrolled, with a median follow-up of 5.1 years. Complete response rates were similar in both MMC and cisplatin treatment groups at 26 weeks after therapy, with similar incidences of treatment-related toxicities. There was no significant difference in 3-year progression-free survival between the MMC and cisplatin cohorts, and colostomy rates were similar between MMC- and cisplatin-treated patients. Because of similar rates of grade 3 and 4 adverse events, with no significant difference in complete response rates or progression-free survival, this study concluded that first-line therapy for squamous cancers of the anus should continue as 5-FU and MMC combined with radiotherapy.

A second major study investigating the benefit of MMC versus cisplatin was published by Ajani et al[112] in the RTOG 9811 study, a multicenter RCT. Study patients were randomly assigned to receive 5-FU and MMC with 45 to 59 Gy of radiotherapy or to receive induction 5-FU with cisplatin followed by CRT with 5-FU and cisplatin. A total of 644 patients were evaluated with a median follow-up time of 2.5 years. There was no significant difference between the treatment arms in terms of 5-year disease-free survival or 5-year overall survival; 5-year locoregional recurrence rates and distant metastasis rates were also similar between the groups. A significantly higher colostomy rate was associated with the cisplatin treatment arm (10% vs 19%; $p = 0.02$), whereas the MMC arm experienced a higher incidence of hematologic toxicity. This study concluded that the routine use of cisplatin in place of MMC is not recommended. A subsequent analysis of this same study population was undertaken by Gunderson et al,[125] published in 2012, to determine the long-term effects of MMC versus cisplatin on recurrence and survival. In this analysis, both disease-free and overall survival were actually improved in the MMC-treated group compared with the cisplatin group, with a trend toward improved colostomy-free survival and locoregional control. These results strengthened the recommendations to include MMC in first-line multimodality therapy for anal squamous cancers.

The European Organization for Research and Treatment of Cancer 22011-40014 trial[126] evaluated the role of cisplatin not as a replacement for MMC but as a substitute for 5-FU. In this study, 88 patients with either node-negative cancers >4 cm in diameter or those with node-positive disease were randomly assigned to radiotherapy totaling 59.4 Gy, with a 2-week gap in radiotherapy deliberately introduced in the middle of the therapy period, combined with either MMC/cisplatin or MMC/5-FU. The cisplatin-treated patients demonstrated a trend toward lower compliance with receipt of CRT. Toxicity rates were similar between the groups, with the exception of a higher incidence of grade 3 hematologic toxicity in the cisplatin group. Survival analyses with this trial were made difficult because of median event-free, overall, and progression-free survivals not being reached. Despite this study concluding that the combination of MMC and cisplatin is promising, additional data regarding this form of CRT are required before its role can be determined.

The use of induction chemotherapy before CRT has also been evaluated, with disappointing results. The UNICANCER ACCORD 03 study[127] was a 4-arm, prospective randomized trial designed to assess both the role of induction chemotherapy consisting of 5-FU on days 1 through 4 and days 29 through 32, and cisplatin on days 1 and 29, before CRT, as well as to test the effect of a higher dose applied to a radiation boost. Patients were randomly assigned to the following: 1) receive 2 cycles of induction chemotherapy, CRT, and a standard-dose boost (15 Gy); 2) receive 2 cycles of induction chemotherapy, CRT, and a high-dose boost (20–25 Gy); 3) receive CRT and a standard-dose boost; or 4) receive CRT and a high-dose boost. Of the 307 patients enrolled, 283 received a complete treatment course, with a median follow-up of 50 months. No benefit to either induction chemotherapy or high-dose boost radiation was observed, with comparable partial and complete tumor response rates, locoregional failure rates, and 3-year colostomy-free, event-free, and overall survival. A recent small retrospective study (n = 38)[128] of patients with T4 anal cancers treated with 45 Gy of radiotherapy with concurrent 5-FU and cisplatin (n = 27) versus patients treated with induction chemotherapy with 5-FU and cisplatin followed by CRT (n = 11) was conducted. There was no statistically significant difference between the 2 groups based on 5-year overall, disease-free, or relapse-free survival, although 5-year colostomy-free survival was much higher in the group receiving induction chemotherapy (100% vs 38%; $p = 0.0006$), leading the authors to suggest that induction chemotherapy has a role in the management of T4 anal cancers. At this time, there is insufficient high-quality data to support the use of induction chemotherapy outside of a clinical trial.

No oncologic benefit exists for providing radiation doses >59 Gy. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, IB.

Once doses of radiotherapy exceed 40 Gy, the incidence of radiation-related toxicities increases. There is good evidence that the minimum dose of radiation for anal squamous cancers should be 45 Gy, although the optimal dose is a matter of debate, in large part because of different radiation delivery techniques and different tumor stages included in the studies on this subject, all of which influence toxicity and response rates. The data on optimal radiation dosing have either been the subject of smaller and nonrandomized studies or have been evaluated in randomized studies looking at such issues as adjusting the dose of boost radiation to the total dosage. The number of studies dedicated to the subject are few, although 1 such study[129] consisted of a small number (n = 69) of early stage Tis and T1 cancers. The study population was extremely heterogeneous, with 26 subjects undergoing local excision before radiotherapy and with varying doses of external beam radiotherapy, with or without brachytherapy, with 8 patients treated with brachytherapy alone. The study concluded, on the basis of local control and toxicity rates, that for T1 cancers a radiation dosing range of 50 to 60 Gy was optimal. One of the only other ret-

rospective studies on this subject[130] included patients with stage I to III disease, although with a study population of only 43 subjects and with a median follow-up of only 42 months. Locoregional control was improved for patients who received >50 Gy (86.5% vs 34.0%; $p = 0.012$), although no dosage ceiling was suggested from these data.

An older study, the RTOG 9208 trial,[131] was a clinical trial that enrolled only 47 patients with at least T1 squamous anal cancers who received CRT with 5-FU and MMC with 59.6 Gy of radiation, which included a 2-week rest period during CRT. The study patients were compared with patients enrolled in the previous RTOG 8704 trial who had received 40.0 to 50.4 Gy of radiation. Despite a higher dose of radiation, patients in the 9208 trial actually had a higher colostomy rate at 1 and 2 years after treatment, without an improvement in locoregional control. No benefit to higher doses exceeding 59 Gy was noted, although concerns for escalating incidences in toxicity were raised. The lack of efficacy with higher doses of radiation is also echoed in the results of the previously mentioned ACCORD 03 trial, which found no benefit to increasing radiation dosing by using high-dose boost treatments.

Missed treatments should be avoided, because they are strongly associated with inferior disease control. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, IB.

The ACT II trial primarily evaluated the role of cisplatin with CRT, and the use of maintenance chemotherapy with 5-FU and cisplatin in addition to CRT, finding no advantage to either of these alternative approaches. This study touted a high rate of complete response (90%), with similar 3-year progression-free survival in the MMC and cisplatin groups, and with an overall 3-year colostomy-free survival of 74%, with 75% of patients having locoregional control with organ preservation. The authors of this study attributed these excellent results in part to high compliance rates with the 50.4 Gy of planned radiation and in part because of the ability to provide CRT in a shorter time interval by avoiding a planned treatment gap, which was a common feature of CRT before this study. A similar observation can be gleaned from the Eastern Cooperative Oncology Group E4292 trial,[132] a study of 33 patients designed to evaluate whether cisplatin could replace MMC as part of CRT. This study accrued a total of 13 patients who did not receive a planned 2-week treatment break, which the larger number of study patients did receive. Complete response rates of 78% were noted in patients without a treatment break, which was higher than in subjects who did receive a break in therapy. The RTOG 9208 trial[131] included a 2-week treatment break, which was associated with increased locoregional failure rates and lower colostomy-free survival rates. Treatment breaks and interruptions to CRT should be avoided if possible, although they occur as frequently as in 80% of patients with anal cancer,[133] making treatment compliance a major and potentially modifiable factor associated with survival.

Surveillance

Disease surveillance should typically start 8 to 12 weeks from the completion of CRT. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.

Slow tumor regression after completion of CRT is based on evidence from trials, such ACT II, in which randomly assigned patients had clinical complete response documented at 11 and 26 weeks postcompletion of CRT. Data from this trial indicate that 29% of patients who did not demonstrate a complete remission at 11 weeks had achieved a complete response by 26 weeks, with durable response.[124]

Most patients are reasonably comfortable with anal examination by the eighth week after completion of CRT, although earlier evaluation to ensure symptom control should be tailored to the individual. The National Comprehensive Cancer Network guidelines[134] recommend evaluation at 8 to 12 weeks after completion of CRT. Clinical assessment should include digital rectal examination, anoscopy, and palpation of the inguinal lymph nodes. Because of slow tumor regression, biopsies for persistent disease are typically avoided at 8 to 12 weeks and <6 months post-CRT.

Posttreatment imaging is most frequently undertaken 3 months from the completion of CRT, when treatment-related fibrosis and residual tumor could be distinguished.[135] Imaging recommendations from the National Comprehensive Cancer Network guidelines include CT of the chest, abdomen, and pelvis annually for 3 years (if T3–T4 or inguinal node positive).

Surveillance involving digital rectal examination, anoscopy, and imaging should be continued for 5 years after completion of CRT. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.

After the first evaluation post-CRT, additional surveillance including digital anorectal examination, anoscopy, and palpation of inguinal lymph nodes every 3 to 6 months for those in complete remission or every 4 weeks until remission <6 months is recommended in patients with evidence of persistent disease.[134] Patients with residual changes require close follow-up and documentation of any changes identified. New tissue thickening, growth, or ulceration should be evaluated. Examination under anesthesia and potential targeted biopsy should be considered in patients with persistent abnormalities 5 to 6 months after CRT, stenosis, pain, or scarring pre-

venting adequate surveillance examinations. The majority of relapses and thus the most efficient time for more frequent surveillance are within the first 3 years of completion of CRT. The ACT II trial with long-term follow-up demonstrated <1% of relapses occurring beyond 3 years.[124] Other trials suggest that this may be closer to 5%; thus, there seems to be some rationale to continue surveillance out to 5 years.[125,136]

CT scans of the chest, abdomen, and pelvis annually for 3 years for patients with T3 to T4 tumors or positive inguinal lymph nodes are also recommended. There are no formal recommendations with regard to post-CRT EAUS, MRI, or PET/CT. One retrospective study evaluating the impact of PET/CT on assessing for residual tumor in 52 patients after CRT showed negative predictive and positive predictive values of 100% and 71%.[137] Vercellino et al[138] showed a sensitivity for the detection of persistent or recurrent disease of 93% and specificity of 81% with PET/CT, leading to changes in management in 20% of patients. The role of post-CRT imaging with MRI and PET/CT to detect locoregional persistent or recurrent tumor seems to be evolving; however, its true ability to impact earlier salvage compared with clinical evaluation remains inconclusive.

Treatment of Recurrent or Persistent Disease

APR is effective salvage therapy for persistent or recurrent disease. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.

Approximately 20% to 30% of patients will have persistent or recurrent disease after primary CRT.[133] Predictors of recurrent and persistent locoregional disease after definitive CRT include higher T and N stages at original presentation, HIV-positive status, and the inability to complete CRT.[133,139] Although patients with persistent disease who present within 6 months of completing CRT have been reported to have worse prognosis,[140–142] recent data suggest that persistent and recurrent disease does not show any significant difference in survival, and patients with late recurrence (>24 mo) may have a better prognosis.[143]

APR is recommended for persistent or recurrent disease for salvage therapy, with reported 5-year locoregional control in 30% to 77% of patients[144–148] and 5-year overall survival rates of 24% to 69%.[141,142,145–149] Positive surgical margins (microscopic or macroscopic), male sex, and higher Charlson comorbidity index portend a worse prognosis, whereas younger age (<55 y), as well as T1 to T2 and N0 to N1 disease have been associated with higher overall survival after APR.[145,150]

Major wound complications are common, reported in 36% to 80%.[145] Muscle flap reconstruction has been associated with significantly lower rates of such complications without major donor-site morbidity.[148,151,152] Pedicled muscle flaps have shown a significantly lower rate of recipient site complications than V–Y advancement flaps, with the vertical rectus abdominis myocutaneous flap showing superior results compared with the gracilis flap in terms of the overall reduction of complications.[153]

Patients with HIV or AIDS who present with anal cancer as the first manifestation of their immunosuppression, and who are not medically deconditioned, can be safely treated according to the same regimens as immunocompetent patients. Grade of Recommendation: Strong recommendation based on medium-quality evidence, IC.

As the medical management of HIV has improved and as the life expectancy of patients with HIV has increased, older and smaller retrospective studies that suggested poorer outcomes for HIV-positive patients treated for anal cancer have been questioned in terms of their generalizability to the management of current HIV patients with anal cancer. One of these earlier retrospective studies suggesting that well-compensated HIV patients could be treated similarly to HIV-negative patients was published in 1999 by Hoffman et al.[154] In this small retrospective analysis of 17 HIV-positive patients with anal cancer treated with either CRT or radiation alone, patients with CD4 counts ≥200 cells per cubic millimeter had excellent disease control with an incidence of treatment toxicities similar to what has been described in the literature for immunocompetent patients. Patients with a CD4 count <200 cells per cubic millimeter (n = 8) had a significantly higher incidence of treatment toxicities, although with 7 of these 8 patients achieving disease control. A more recent publication from 2010[155] evaluated 21 HIV-positive patients receiving CRT. Completion of treatment was achieved in all 21 patients, with a complete response of 81% and 6 patients (29%) dying of disease. The authors noted that the 5-year local control, cancer-specific, and overall survival rates were 59%, 75%, and 67%. Because the majority of the patients were able to complete CRT without dose reductions in either radiation or chemotherapy, this study also supported the concept that HIV-positive patients could be treated according to standard regimens with the expectation of good tolerance to therapy. Another recent retrospective study[156] of 36 HIV-positive patients treated with standard regimens of CRT again demonstrated completion of treatment in all of the patients, with complete response rates of 86% and with 5-year local control, colostomy-free, cancer-specific, and overall survival rates of 72%, 87%, 77%, and 74%. This study noted a CRT-related decline in CD4 counts for <6 years after treatment, although this decrease in CD4 counts was not associated with increased HIV-related morbidity, with oncologic outcomes comparable to descriptions of the HIV-negative population in the literature.

One of the largest retrospective studies on this subject to date was a review of patient data from the Veteran's Affairs system,[157] analyzing 1184 individuals treated for squamous cancers of the anus, of whom 175 were documented to be HIV positive. As with previous studies, this study reported no difference in the receipt of treatment based on HIV status, with 2-year observed survival rates of 77% and 75% among HIV-positive and HIV-negative individuals. Based on multivariate analysis, HIV status was not associated with differences in survival.

There are insufficient data to comment on whether highly active antiretroviral therapy is associated with improved outcomes after CRT. Patients with ongoing HIV/AIDS disease–related complications present before their diagnosis of anal cancer may not tolerate standard CRT and may require dose reductions; this subpopulation of patients with HIV is therefore at risk for higher CRT toxicity rates and worse oncologic outcomes.

Perianal squamous cancers, which are well-differentiated, node-negative, T1 lesions, can be adequately treated with wide-local excision with 1-cm margins of resection. All other anal margin cancers are preferentially treated with CRT. Grade of Recommendation: Strong recommendation based on low-quality evidence, IC.

Patients with well-differentiated, node-negative T1 lesions involving the perianal skin are preferentially treated with wide-local excision provided that 1-cm margins of resection can be obtained without compromising the patient's sphincter mechanism, which would compromise the functional outcome of a local excision. The data in support of wide-local excision are from small retrospective studies, although the outcomes of these studies are consistently excellent, with 5-year survival rates of 100%.[158] In addition, wide-local excision avoids the toxicity associated with radiotherapy. Any perianal squamous cancers that do not meet the above-mentioned favorable criteria should be treated with CRT, because there is a well-documented history of locoregional recurrence and decreased survival when such cancers are treated with wide-local excision.[106,159]

Treatment of Distant Disease

Systemic chemotherapy should be considered for patients with distant metastatic disease. Metastasectomy, radiation, and radiofrequency ablation can be considered in selected cases. Grade of Recommendation: Weak recommendation based on low- or very-low–quality evidence, 2C.

Because of high response rates with chemoradiation, reports comparing treatment of patients with metastatic disease are limited. The most extensive published experience is a retrospective review of a 14-year experience at a single center in France.[160] A total of 50 patients, 10 with synchronous disease at the time of diagnosis and 40 with distant failure after chemoradiation, were treated with multimodal therapy. Patients received ≥1 chemotherapy regimen, 13 had surgical metastasectomy, 11 had radiotherapy, and 6 had radiofrequency ablation. Median overall survival was 20 months. Overall response rate was 56%. There was no clear advantage of any chemotherapy regimen, but patients who could also have resection, radiation, or ablation had an overall survival of 22 months compared with 13 months with chemotherapy alone ($p = 0.002$). A similar-sized cohort has been published in abstract form, including 53 patients treated with chemotherapy, with a median overall survival of 38 months.[161,162] A small single-center study reported in 1999 that included 19 patients with metastatic anal cancer treated with 5-FU and cisplatin described a response rate of 66%, with 1 patient achieving a complete response.[163] A single-center report described the combination of carboplatin and paclitaxel in 13 patients with a response rate of 62%, with 2 patients achieving a complete response.[164]

Targeted therapy to the epidermal growth factor receptor (EGFR) has been considered because of the high expression of EGFR in anal cancers.[165] The use of cetuximab in the setting of localized disease has been limited by toxicity when combined with traditional chemoradiation.[166,167] However, response rate was high, and it is possible that, in the metastatic setting, without concurrent radiation, there is a role for the addition of an EGFR inhibitor to cytotoxic chemotherapy regimens. Because of the lack of uniform treatment, there are also active clinical trials in this area available at clinicaltrials.gov, examining novel approaches including pembrolizumab and nivolumab.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66:7–30.
2. Nelson RA, Levine AM, Bernstein L, Smith DD, Lai LL. Changing patterns of anal canal carcinoma in the United States. *J Clin Oncol*. 2013;31:1569–1575.
3. Johnson LG, Madeleine MM, Newcomer LM, Schwartz SM, Daling JR. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973-2000. *Cancer*. 2004;101:281–288.
4. Nielsen A, Munk C, Kjaer SK. Trends in incidence of anal cancer and high-grade anal intraepithelial neoplasia in Denmark, 1978-2008. *Int J Cancer*. 2012;130:1168–1173.
5. 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.
6. Palefsky JM, Holly EA, Gonzales J, Berline J, Ahn DK, Greenspan JS. Detection of human papillomavirus DNA in anal intraepithelial neoplasia and anal cancer. *Cancer Res*. 1991;51:1014–1019.
7. Holly EA, Ralston ML, Darragh TM, Greenblatt RM, Jay N, Palefsky JM. Prevalence and risk factors for anal squamous intraepithelial lesions in women. *J Natl Cancer Inst*. 2001;93:843–849.

8. Abbas A, Yang G, Fakih M. Management of anal cancer in 2010: part 1–overview, screening, and diagnosis. *Oncology (Williston Park)*. 2010;24:364–369.
9. 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.
10. Ryan DP, Compton CC, Mayer RJ. Carcinoma of the anal canal. *N Engl J Med*. 2000;342:792–800.
11. Daling JR, Weiss NS, Hislop TG, et al. Sexual practices, sexually transmitted diseases, and the incidence of anal cancer. *N Engl J Med*. 1987;317:973–977.
12. Schofield AM, Sadler L, Nelson L, et al. A prospective study of anal cancer screening in HIV-positive and negative MSM. *AIDS*. 2016;30:1375–1383.
13. Radecki Breitkopf C, Finney Rutten LJ, Findley V, et al. Awareness and knowledge of human papillomavirus (HPV), HPV-related cancers, and HPV vaccines in an uninsured adult clinic population. *Cancer Med*. 2016;5:3346–3352.
14. Abramowitz L, Benabderrahmane D, Walker F, et al. Determinants of macroscopic anal cancer and precancerous lesions in 1206 HIV-infected screened patients. *Colorectal Dis*. 2016;18:997–1004.
15. Hemminki K, Liu X, Ji J, Sundquist J, Sundquist K. Autoimmune disease and subsequent digestive tract cancer by histology. *Ann Oncol*. 2012;23:927–933.
16. Patel HS, Silver AR, Northover JM. Anal cancer in renal transplant patients. *Int J Colorectal Dis*. 2007;22:1–5.
17. Brickman C, Palefsky JM. Cancer in the HIV-infected host: epidemiology and pathogenesis in the antiretroviral era. *Curr HIV/AIDS Rep*. 2015;12:388–396.
18. Pirog EC, Quint KD, Yantiss RK. P16/CDKN2A and Ki-67 enhance the detection of anal intraepithelial neoplasia and condyloma and correlate with human papillomavirus detection by polymerase chain reaction. *Am J Surg Pathol*. 2010;34:1449–1455.
19. Fenger C. Prognostic factors in anal carcinoma. *Pathology*. 2002;34:573–578.
20. Das P, Crane CH, Eng C, Ajani JA. Prognostic factors for squamous cell cancer of the anal canal. *Gastrointest Cancer Res*. 2008;2:10–14.
21. Pineda CE, Welton ML. Management of anal squamous intraepithelial lesions. *Clin Colon Rectal Surg*. 2009;22:94–101.
22. Darragh TM, Colgan TJ, Cox JT, et al.; Members of LAST Project Work Groups. 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.
23. Yang EJ, Kong CS, Longacre TA. Vulvar and anal intraepithelial neoplasia: terminology, diagnosis, and ancillary studies. *Adv Anat Pathol*. 2017;24:136–150.
24. Steele SR, Varma MG, Melton GB, Ross HM, Rafferty JF, Buie WD; Standards Practice Task Force of the American Society of Colon and Rectal Surgeons. Practice parameters for anal squamous neoplasms. *Dis Colon Rectum*. 2012;55:735–749.
25. Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. *Chest*. 2006;129:174–181.
26. Palefsky JM, Holly EA, Ralston ML, et al. Anal squamous intraepithelial lesions in HIV-positive and HIV-negative homosexual and bisexual men: prevalence and risk factors. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;17:320–326.
27. Chin-Hong PV, Vittinghoff E, Cranston RD, et al. Age-related prevalence of anal cancer precursors in homosexual men: the EXPLORE study. *J Natl Cancer Inst*. 2005;97:896–905.
28. 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.
29. Heard I, Etienney I, Potard V, et al.; ANRS-C017 VIHGY Study Group. High prevalence of anal human papillomavirus-associated cancer precursors in a contemporary cohort of asymptomatic HIV-infected women. *Clin Infect Dis*. 2015;60:1559–1568.
30. Ebisch RMF, Rutten DWE, IntHout J, et al. Long-lasting increased risk of human papillomavirus-related carcinomas and premalignancies after cervical intraepithelial neoplasia grade 3: a population-based cohort study. *J Clin Oncol*. 2017;35:2542–2550.
31. Schiffman M, Wentzensen N, Wacholder S, Kinney W, Gage JC, Castle PE. Human papillomavirus testing in the prevention of cervical cancer. *J Natl Cancer Inst*. 2011;103:368–383.
32. Darragh TM, Tokugawa D, Castle PE, et al. Interrater agreement of anal cytology. *Cancer Cytopathol*. 2013;121:72–78.
33. 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.
34. Fazendin EA, Crean AJ, Fazendin JM, et al. Condyloma acuminatum, anal intraepithelial neoplasia, and anal cancer in the setting of HIV: do we really understand the risk? *Dis Colon Rectum*. 2017;60:1078–1082.
35. 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.
36. 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.
37. Cachay E, Agmas W, Mathews C. Five-year cumulative incidence of invasive anal cancer among HIV-infected patients according to baseline anal cytology results: an inception cohort analysis. *HIV Med*. 2015;16:191–195.
38. Goldstone SE. Introduction. *Semin Colon Rectal Surg*. 2017;28:55–56.
39. Jin F, Roberts JM, Grulich AE, et al.; SPANC Research Team. The performance of human papillomavirus biomarkers in predicting anal high-grade squamous intraepithelial lesions in gay and bisexual men. *AIDS*. 2017;31:1303–1311.
40. Cheng SH, Wang CC, Chang SL, Chu FY, Hsueh YM. Oncogenic human papillomavirus is not helpful for cytology screening of the precursor lesions of anal cancers in Taiwanese men who are infected with human immunodeficiency virus. *Int J Clin Oncol*. 2015;20:943–951.
41. Sendagorta E, Herranz P, Guadalajara H, et al. Prevalence of abnormal anal cytology and high-grade squamous intraepithelial lesions among a cohort of HIV-infected men who have sex with men. *Dis Colon Rectum*. 2014;57:475–481.

42. Botes LP, Pett S, Carr A, et al. Anal cytological abnormalities are poor predictors of high-grade intraepithelial neoplasia amongst HIV-positive men who have sex with men. *Sex Health*. 2013;10:9–17.
43. Wentzensen N, Follansbee S, Borgonovo S, et al. Human papillomavirus genotyping, human papillomavirus mRNA expression, and p16/Ki-67 cytology to detect anal cancer precursors in HIV-infected MSM. *AIDS*. 2012;26:2185–2192.
44. Williams VM, Metcalf C, French MA, McCloskey JC. Audit of paired anal cytology and histopathology outcomes in patients referred to a public sexual health clinic. *Sex Health*. 2010;7:346–351.
45. Salit IE, Lytwyn A, Raboud J, et al. The role of cytology (Pap tests) and human papillomavirus testing in anal cancer screening. *AIDS*. 2010;24:1307–1313.
46. Nathan M, Singh N, Garrett N, Hickey N, Prevost T, Sheaff M. Performance of anal cytology in a clinical setting when measured against histology and high-resolution anoscopy findings. *AIDS*. 2010;24:373–379.
47. Fox PA, Seet JE, Stebbing J, et al. The value of anal cytology and human papillomavirus typing in the detection of anal intraepithelial neoplasia: a review of cases from an anoscopy clinic. *Sex Transm Infect*. 2005;81:142–146.
48. Arain S, Walts AE, Thomas P, Bose S. The anal pap smear: cytomorphology of squamous intraepithelial lesions. *Cytojournal*. 2005;2:4.
49. Papaconstantinou HT, Lee AJ, Simmang CL, et al. Screening methods for high-grade dysplasia in patients with anal condyloma. *J Surg Res*. 2005;127:8–13.
50. Mathews WC, Sitapati A, Caperna JC, Barber RE, Tugend A, Go U. Measurement characteristics of anal cytology, histopathology, and high-resolution anoscopic visual impression in an anal dysplasia screening program. *J Acquir Immune Defic Syndr*. 2004;37:1610–1615.
51. Panther LA, Wagner K, Proper J, et al. High resolution anoscopy findings for men who have sex with men: inaccuracy of anal cytology as a predictor of histologic high-grade anal intraepithelial neoplasia and the impact of HIV serostatus. *Clin Infect Dis*. 2004;38:1490–1492.
52. Palefsky JM, Holly EA, Hogeboom CJ, Berry JM, Jay N, Darragh TM. Anal cytology as a screening tool for anal squamous intraepithelial lesions. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1997;14:415–422.
53. Pineda CE, Berry JM, Jay N, Palefsky JM, Welton ML. High-resolution anoscopy targeted surgical destruction of anal high-grade squamous intraepithelial lesions: a ten-year experience. *Dis Colon Rectum*. 2008;51:829–835.
54. Crawshaw BP, Russ AJ, Stein SL, et al. High-resolution anoscopy or expectant management for anal intraepithelial neoplasia for the prevention of anal cancer: is there really a difference? *Dis Colon Rectum*. 2015;58:53–59.
55. Mathews WC, Agmas W, Cachay E. Comparative accuracy of anal and cervical cytology in screening for moderate to severe dysplasia by magnification guided punch biopsy: a meta-analysis. *PLoS One*. 2011;6:e24946.
56. Palefsky JM. Practising high-resolution anoscopy. *Sex Health*. 2012;9:580–586.
57. Fox PA, Nathan M, Francis N, et al. A double-blind, randomized controlled trial of the use of imiquimod cream for the treatment of anal canal high-grade anal intraepithelial neoplasia in HIV-positive MSM on HAART, with long-term follow-up data including the use of open-label imiquimod. *AIDS*. 2010;24:2331–2335.
58. Richel O, de Vries HJ, van Noesel CJ, Dijkgraaf MG, Prins JM. 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.
59. van der Snoek EM, den Hollander JC, van der Ende ME. Imiquimod 5% cream for five consecutive days a week in an HIV-infected observational cohort up to 32 weeks in the treatment of high-grade squamous intraepithelial lesions. *Sex Transm Infect*. 2015;91:245–247.
60. Richel O, Wieland U, de Vries HJ, et al. Topical 5-fluorouracil treatment of anal intraepithelial neoplasia in human immunodeficiency virus-positive men. *Br J Dermatol*. 2010;163:1301–1307.
61. Snyder SM, Siekas L, Aboulafia DM. Initial experience with topical fluorouracil for treatment of hiv-associated anal intraepithelial neoplasia. *J Int Assoc Physicians AIDS Care (Chic)*. 2011;10:83–88.
62. Cranston RD, Baker JR, Liu Y, Wang L, Elishaev E, Ho KS. Topical application of trichloroacetic acid is efficacious for the treatment of internal anal high-grade squamous intraepithelial lesions in HIV-positive men. *Sex Transm Dis*. 2014;41:420–426.
63. Singh JC, Kuohung V, Palefsky JM. Efficacy of trichloroacetic acid in the treatment of anal intraepithelial neoplasia in HIV-positive and HIV-negative men who have sex with men. *J Acquir Immune Defic Syndr*. 2009;52:474–479.
64. Sendagorta E, Bernardino JI, Álvarez-Gallego M, et al.; CIDAN127412 GESIDA Study Group. Topical cidofovir to treat high-grade anal intraepithelial neoplasia in HIV-infected patients: a pilot clinical trial. *AIDS*. 2016;30:75–82.
65. Stier EA, Goldstone SE, Einstein MH, et al. Safety and efficacy of topical cidofovir to treat high-grade perianal and vulvar intraepithelial neoplasia in HIV-positive men and women. *AIDS*. 2013;27:545–551.
66. Weis SE, Vecino I, Pogoda JM, Susa JS. Treatment of high-grade anal intraepithelial neoplasia with infrared coagulation in a primary care population of HIV-infected men and women. *Dis Colon Rectum*. 2012;55:1236–1243.
67. Goldstone SE, Kawalek AZ, Huyett JW. Infrared coagulator: a useful tool for treating anal squamous intraepithelial lesions. *Dis Colon Rectum*. 2005;48:1042–1054.
68. Goldstone SE, Hundert JS, Huyett JW. Infrared coagulator ablation of high-grade anal squamous intraepithelial lesions in HIV-negative males who have sex with males. *Dis Colon Rectum*. 2007;50:565–575.
69. Goldstone RN, Goldstone AB, Russ J, Goldstone SE. Long-term follow-up of infrared coagulator ablation of anal high-grade dysplasia in men who have sex with men. *Dis Colon Rectum*. 2011;54:1284–1292.
70. Cranston RD, Hirschowitz SL, Cortina G, Moe AA. A retrospective clinical study of the treatment of high-grade anal dysplasia by infrared coagulation in a population of HIV-positive men who have sex with men. *Int J STD AIDS*. 2008;19:118–120.
71. Sirera G, Videla S, Piñol M, et al.; HIV-HPV Study Group. Long-term effectiveness of infrared coagulation for the treatment of anal intraepithelial neoplasia grades 2 and 3 in HIV-infected men and women. *AIDS*. 2013;27:951–959.

72. Marks DK, Goldstone SE. Electrocautery ablation of high-grade anal squamous intraepithelial lesions in HIV-negative and HIV-positive men who have sex with men. *J Acquir Immune Defic Syndr*. 2012;59:259–265.
73. Burgos J, Curran A, Landolfi S, et al. The effectiveness of electrocautery ablation for the treatment of high-grade anal intraepithelial neoplasia in HIV-infected men who have sex with men. *HIV Med*. 2016;17:524–531.
74. Miltz A, Price H, Shahmanesh M, Copas A, Gilson R. Systematic review and meta-analysis of L1-VLP-based human papillomavirus vaccine efficacy against anogenital pre-cancer in women with evidence of prior HPV exposure. *PLoS One*. 2014;9:e90348.
75. Dion GR, Teng S, Boyd LR, et al. Adjuvant human papillomavirus vaccination for secondary prevention: a systematic review. *JAMA Otolaryngol Head Neck Surg*. 2017;143:614–622.
76. Swedish KA, Factor SH, Goldstone SE. Prevention of recurrent high-grade anal neoplasia with quadrivalent human papillomavirus vaccination of men who have sex with men: a nonconcurrent cohort study. *Clin Infect Dis*. 2012;54:891–898.
77. Tong WW, Jin F, McHugh LC, et al. Progression to and spontaneous regression of high-grade anal squamous intraepithelial lesions in HIV-infected and uninfected men. *AIDS*. 2013;27:2233–2243.
78. Klas JV, Rothenberger DA, Wong WD, Madoff RD. Malignant tumors of the anal canal: the spectrum of disease, treatment, and outcomes. *Cancer*. 1999;85:1686–1693.
79. Robb BW, Mutch MG. Epidermoid carcinoma of the anal canal. *Clin Colon Rectal Surg*. 2006;19:54–60.
80. Tanum G, Tveit K, Karlsen KO. Diagnosis of anal carcinoma: doctor's finger still the best? *Oncology*. 1991;48:383–386.
81. Santoso JT, Long M, Crigger M, Wan JY, Haefner HK. Anal intraepithelial neoplasia in women with genital intraepithelial neoplasia. *Obstet Gynecol*. 2010;116:578–582.
82. Park IU, Ogilvie JW Jr, Anderson KE, et al. Anal human papillomavirus infection and abnormal anal cytology in women with genital neoplasia. *Gynecol Oncol*. 2009;114:399–403.
83. Ogilvie JW Jr, Park IU, Downs LS, Anderson KE, Hansberger J, Madoff RD. Anal dysplasia in kidney transplant recipients. *J Am Coll Surg*. 2008;207:914–921.
84. Welton ML, Sharkey FE, Kahlenberg MS. The etiology and epidemiology of anal cancer. *Surg Oncol Clin N Am*. 2004;13:263–275.
85. Daling JR, Sherman KJ, Hislop TG, et al. Cigarette smoking and the risk of anogenital cancer. *Am J Epidemiol*. 1992;135:180–189.
86. Chiao EY, Krown SE, Stier EA, Schrag D. A population-based analysis of temporal trends in the incidence of squamous anal canal cancer in relation to the HIV epidemic. *J Acquir Immune Defic Syndr*. 2005;40:451–455.
87. Palefsky JM, Holly EA, Ralston ML, Jay N, Berry JM, Darragh TM. High incidence of anal high-grade squamous intra-epithelial lesions among HIV-positive and HIV-negative homosexual and bisexual men. *AIDS*. 1998;12:495–503.
88. Anal canal. In: Greene FL, Page DL, Fleming ID, eds. *AJCC Cancer Staging Manual*. 6th ed. New York, NY: Springer; 2002:125–130.
89. Bean SM, Eltoum I, Horton DK, Whitlow L, Chhieng DC. Immunohistochemical expression of p16 and Ki-67 correlates with degree of anal intraepithelial neoplasia. *Am J Surg Pathol*. 2007;31:555–561.
90. Gordon PH. Current status: perianal and anal canal neoplasms. *Dis Colon Rectum*. 1990;33:799–808.
91. Giovannini M, Bardou VJ, Barclay R, et al. Anal carcinoma: prognostic value of endorectal ultrasound (ERUS)–results of a prospective multicenter study. *Endoscopy*. 2001;33:231–236.
92. Jacopo M. Endoanal ultrasound for anal cancer staging. *Int J Colorectal Dis*. 2011;26:385–386.
93. Otto SD, Lee L, Buhr HJ, Frericks B, Höcht S, Kroesen AJ. Staging anal cancer: prospective comparison of transanal endoscopic ultrasound and magnetic resonance imaging. *J Gastrointest Surg*. 2009;13:1292–1298.
94. Boman BM, Moertel CG, O'Connell MJ, et al. Carcinoma of the anal canal: a clinical and pathologic study of 188 cases. *Cancer*. 1984;54:114–125.
95. Gaertner WB, Hagerman GF, Finne CO, et al. Fistula-associated anal adenocarcinoma: good results with aggressive therapy. *Dis Colon Rectum*. 2008;51:1061–1067.
96. Grabenbauer GG, Kessler H, Matzel KE, Sauer R, Hohenberger W, Schneider IH. Tumor site predicts outcome after radiochemotherapy in squamous-cell carcinoma of the anal region: long-term results of 101 patients. *Dis Colon Rectum*. 2005;48:1742–1751.
97. 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.
98. 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.
99. Krengli M, Milia ME, Turri L, et al. FDG-PET/CT imaging for staging and target volume delineation in conformal radiotherapy of anal carcinoma. *Radiat Oncol*. 2010;5:10.
100. Nguyen BT, Joon DL, Khoo V, et al. Assessing the impact of FDG-PET in the management of anal cancer. *Radiother Oncol*. 2008;87:376–382.
101. Kidd EA, Dehdashti F, Siegel BA, Grigsby PW. Anal cancer maximum F-18 fluorodeoxyglucose uptake on positron emission tomography is correlated with prognosis. *Radiother Oncol*. 2010;95:288–291.
102. Gauthé M, Richard-Molard M, Fayard J, Alberini JL, Cacheux W, Lièvre A. Prognostic impact of tumour burden assessed by metabolic tumour volume on FDG PET/CT in anal canal cancer. *Eur J Nucl Med Mol Imaging*. 2017;44:63–70.
103. Bazan JG, Koong AC, Kapp DS, et al. Metabolic tumor volume predicts disease progression and survival in patients with squamous cell carcinoma of the anal canal. *J Nucl Med*. 2013;54:27–32.
104. Day FL, Link E, Ngan S, et al. FDG-PET metabolic response predicts outcomes in anal cancer managed with chemoradiotherapy. *Br J Cancer*. 2011;105:498–504.
105. Nigro ND, Vaitkevicius VK, Considine B Jr. Combined therapy for cancer of the anal canal: a preliminary report. *Dis Colon Rectum*. 1974;17:354–356.
106. Pintor MP, Northover JM, Nicholls RJ. Squamous cell carcinoma of the anus at one hospital from 1948 to 1984. *Br J Surg*. 1989;76:806–810.
107. Beahrs OH, Wilson SM. Carcinoma of the anus. *Ann Surg*. 1976;184:422–428.
108. Dougherty BG, Evans HL. Carcinoma of the anal canal: a study of 79 cases. *Am J Clin Pathol*. 1985;83:159–164.
109. Fuchshuber PR, Rodriguez-Bigas M, Weber T, Petrelli NJ. Anal canal and perianal epidermoid cancers. *J Am Coll Surg*. 1997;185:494–505.

110. Buroker TR, Nigro N, Bradley G, et al. Combined therapy for cancer of the anal canal: a follow-up report. *Dis Colon Rectum*. 1977;20:677–678.
111. Nigro ND. An evaluation of combined therapy for squamous cell cancer of the anal canal. *Dis Colon Rectum*. 1984;27:763–766.
112. 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.
113. Martenson JA, Lipsitz SR, Wagner H Jr, et al. Initial results of a phase II trial of high dose radiation therapy, 5-fluorouracil, and cisplatin for patients with anal cancer (E4292): an Eastern Cooperative Oncology Group study. *Int J Radiat Oncol Biol Phys*. 1996;35:745–749.
114. Meyer JJ, Willett CG, Czito BG. Emerging role of intensity-modulated radiation therapy in anorectal cancer. *Expert Rev Anticancer Ther*. 2008;8:585–593.
115. 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.
116. 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.
117. Papillon J, Mayer M, Montbarbon JF, Gerard JP, Chassard JL, Bailly C. A new approach to the management of epidermoid carcinoma of the anal canal. *Cancer*. 1983;51:1830–1837.
118. Papillon J, Montbarbon JF. Epidermoid carcinoma of the anal canal: a series of 276 cases. *Dis Colon Rectum*. 1987;30:324–333.
119. UKCCCR Anal Cancer Trial Working Party; UK Co-ordinating Committee on Cancer Research. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. *Lancet*. 1996;348:1049–1054.
120. 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.
121. 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.
122. Vinayan A, Glynne-Jones R. Anal cancer: what is the optimum chemoradiotherapy? *Best Pract Res Clin Gastroenterol*. 2016;30:641–653.
123. 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.
124. 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, 2×2 factorial trial. *Lancet Oncol*. 2013;14:516–524.
125. 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.
126. Matzinger O, Roelofsen F, Mineur L, et al.; EORTC Radiation Oncology and Gastrointestinal Tract Cancer Groups. Mitomycin C with continuous fluorouracil or with cisplatin in combination with radiotherapy for locally advanced anal cancer (European Organisation for Research and Treatment of Cancer phase II study 22011-40014). *Eur J Cancer*. 2009;45:2782–2791.
127. Peiffert D, Tournier-Rangeard L, Gérard 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.
128. 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.
129. 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.
130. Ferrigno R, Nakamura RA, Dos Santos Novaes PE, 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.
131. 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.
132. Chakravarthy AB, Catalano PJ, Martenson JA, et al. Long-term follow-up of a Phase II trial of high-dose radiation with concurrent 5-fluorouracil and cisplatin in patients with anal cancer (ECOG E4292). *Int J Radiat Oncol Biol Phys*. 2011;81:e607–e613.
133. 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.
134. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology anal carcinoma, version 1.2018. https://www.nccn.org/professionals/physician_gls/recently_updated.aspx. Accessed January 10, 2018.
135. Ciombor KK, Ernst RD, Brown G. Diagnosis and diagnostic imaging of anal canal cancer. *Surg Oncol Clin N Am*. 2017;26:45–55.
136. Abunassar M, Reinders J, Jonker DJ, Asmis T. Review of anal cancer patients at the Ottawa hospital. *Eur J Surg Oncol*. 2015;41:653–658.
137. Teagle AR, Gilbert DC, Jones JR, Burkill GJ, McKinna F, Dizdarevic S. Negative 18F-FDG-PET-CT may exclude residual or recurrent disease in anal cancer. *Nucl Med Commun*. 2016;37:1038–1045.
138. Vercellino L, Montravers F, de Parades V, et al. Impact of FDG PET/CT in the staging and the follow-up of anal carcinoma. *Int J Colorectal Dis*. 2011;26:201–210.
139. 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.
140. Ferenschild FT, Vermaas M, Hofer SO, Verhoef C, Eggermont AM, de Wilt JH. Salvage abdominoperineal resection and perineal wound healing in local recurrent or persistent anal cancer. *World J Surg*. 2005;29:1452–1457.

141. Papaconstantinou HT, Bullard KM, Rothenberger DA, Madoff RD. Salvage abdominoperineal resection after failed Nigro protocol: modest success, major morbidity. *Colorectal Dis.* 2006;8:124–129.
142. Stewart D, Yan Y, Kodner IJ, et al. Salvage surgery after failed chemoradiation for anal canal cancer: should the paradigm be changed for high-risk tumors? *J Gastrointest Surg.* 2007;11:1744–1751.
143. Severino NP, Chadi SA, Rosen L, et al. Survival following salvage abdominoperineal resection for persistent and recurrent squamous cell carcinoma of the anus: do these disease categories affect survival? *Colorectal Dis.* 2016;18:959–966.
144. Lefèvre 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.
145. 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.
146. 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.
147. Goéré D, Bonnet S, Pocard M, Deutsch E, Lasser P, Elias D. Oncologic and functional results after abdominoperineal resection plus pseudocontinent perineal colostomy for epidermoid carcinoma of the anus. *Dis Colon Rectum.* 2009;52:958–963.
148. Lefevre JH, Parc Y, Kernéis S, et al. Abdomino-perineal resection for anal cancer: impact of a vertical rectus abdominis myocutaneus flap on survival, recurrence, morbidity, and wound healing. *Ann Surg.* 2009;250:707–711.
149. Vorob'ev GI, Shelygin IuA, Nechushkin MI, Rybakov EG. Results of surgical treatment of residual and recurrent anal tumors [in Russian]. *Khirurgiia (Mosk).* 2008;8:4–9.
150. Mariani P, Ghanneme A, De la Rochefordière A, Girodet J, Falcou MC, Salmon RJ. Abdominoperineal resection for anal cancer. *Dis Colon Rectum.* 2008;51:1495–1501.
151. Hardt J, Mai S, Weiß C, Kienle P, Magdeburg J. Abdominoperineal resection and perineal wound healing in recurrent, persistent, or primary anal carcinoma. *Int J Colorectal Dis.* 2016;31:1197–1203.
152. Sunesen KG, Buntzen S, Tei T, Lindegaard JC, Nørgaard M, Laurberg S. Perineal healing and survival after anal cancer salvage surgery: 10-year experience with primary perineal reconstruction using the vertical rectus abdominis myocutaneous (VRAM) flap. *Ann Surg Oncol.* 2009;16:68–77.
153. Sheckter CC, Shakir A, Vo H, Tsai J, Nazerali R, Lee GK. Reconstruction following abdominoperineal resection (APR): indications and complications from a single institution experience. *J Plast Reconstr Aesthet Surg.* 2016;69:1506–1512.
154. Hoffman R, Welton ML, Klencke B, Weinberg V, Krieg R. The significance of pretreatment CD4 count on the outcome and treatment tolerance of HIV-positive patients with anal cancer. *Int J Radiat Oncol Biol Phys.* 1999;44:127–131.
155. Fraunholz I, Weiss C, Eberlein K, Haberl A, Rödel C. Concurrent chemoradiotherapy with 5-fluorouracil and mitomycin C for invasive anal carcinoma in human immunodeficiency virus-positive patients receiving highly active antiretroviral therapy. *Int J Radiat Oncol Biol Phys.* 2010;76:1425–1432.
156. Fraunholz IB, Haberl A, Klauke S, Gute P, Rödel CM. Long-term effects of chemoradiotherapy for anal cancer in patients with HIV infection: oncological outcomes, immunological status, and the clinical course of the HIV disease. *Dis Colon Rectum.* 2014;57:423–431.
157. 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.
158. Schraut WH, Wang CH, Dawson PJ, Block GE. Depth of invasion, location, and size of cancer of the anus dictate operative treatment. *Cancer.* 1983;51:1291–1296.
159. Jensen SL, Hagen K, Harling H, Shokouh-Amiri MH, Nielsen OV. Long-term prognosis after radical treatment for squamous-cell carcinoma of the anal canal and anal margin. *Dis Colon Rectum.* 1988;31:273–278.
160. Evesque L, Benezery K, Follana P, et al. Multimodal therapy of squamous cell carcinoma of the anus with distant metastasis: a single-institution experience. *Dis Colon Rectum.* 2017;60:785–791.
161. Pathak P, King BT, Ohinata A, et al. The treatment of metastatic squamous cell carcinoma (SCCA) of the anal canal: a single institution experience [abstract]. *Gastroenterol Hepatol (N Y).* 2008;4:.
162. Eng C, Pathak P. Treatment options in metastatic squamous cell carcinoma of the anal canal. *Curr Treat Options Oncol.* 2008;9:400–407.
163. Faivre C, Rougier P, Ducreux M, et al. 5-fluorouracile and cisplatinum combination chemotherapy for metastatic squamous-cell anal cancer [in French]. *Bull Cancer.* 1999;86:861–865.
164. Kim R, Byer J, Fulp WJ, Mahipal A, Dinwoodie W, Shibata D. Carboplatin and paclitaxel treatment is effective in advanced anal cancer. *Oncology.* 2014;87:125–132.
165. Paliga A, Onerheim R, Gologan A, et al. EGFR and K-ras gene mutation status in squamous cell anal carcinoma: a role for concurrent radiation and EGFR inhibitors? *Br J Cancer.* 2012;107:1864–1868.
166. 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.
167. 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.