HHS Public Access

Author manuscript

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2024 May 17.

Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2019 November 01; 105(3): 591–605. doi:10.1016/j.ijrobp.2019.06.2544.

Executive Summary of the American Radium Society Appropriate Use Criteria for Treatment of Anal Cancer

Suzanne Russo, MD[*], **Christopher J. Anker, MD**[†], **May Abdel-Wahab, MD, PhD**[‡], **Nilofer Azad, MD**[§], **Nancy Bianchi, MSLIS**[†], **Prajnan Das, MD**[‖], **Jadranka Dragovic, MD**[¶], **Karyn A. Goodman, MD**[#], **William Jones III, MD**[**], **Timothy Kennedy, MD, MBA**[††], **Rachit Kumar, MD**[‡‡], **Percy Lee, MD**[§§], **Navesh Sharma, DO, PhD**[‖‖], **William Small, MD**[¶¶], **W. Warren Suh, MD, MPH**[##], **Salma K. Jabbour, MD**[***]

[*]Case Western Reserve University School of Medicine and University Hospitals, Cleveland Ohio

[†]University of Vermont Cancer Center, Burlington, Vermont

[‡]International Atomic Energy Agency, Division of Human Health, New York City, New York

[§]Johns Hopkins University School of Medicine, Baltimore, Maryland

[‖]The University of Texas MD Anderson Cancer Center, Houston, Texas

[¶]Henry Ford Cancer Institute, Henry Ford Hospital, Detroit Michigan

[#]University of Colorado School of Medicine, Aurora Colorado

[**]UT Health Cancer Center, University of Texas Health Science Center at San Antonio, San Antonio, Texas

[††]Rutgers Cancer Institute of NJ, New Brunswick, New Jersey

[‡‡]Banner MD Anderson Cancer Center, Gilbert, Arizona

[§§]University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, California

[‖‖]Milton S. Hershey Cancer Institute, Hershey, Pennsylvania

[¶¶]Loyola University Medical Center, Maywood, Illinois

Corresponding author: Salma K. Jabbour, MD; jabbousk@cinj.rutgers.edu.

The American Radium Society Appropriate Use Criteria seek and encourage collaboration with other organizations on the development of the criteria through representation on expert panels. Participation by representatives from collaborating organizations on the expert panel does not necessarily imply individual or society endorsement of the final document.

Supporting documents

For additional information on the American Radium Society Appropriate Use Criteria methodology and other supporting documents, go to http://www.americanradiumsociety.org/page/aucmethodology.

Disclosures: All panelists were required to declare all conflicts of interest for the previous 36 months before initiating work on this document. These complete disclosure forms are retained by the American Radium Society in perpetuity. The American Radium Society Appropriate Use Criteria Steering Committee reviewed these disclosures with the chair of this document and approved participation of the panelists before starting development of this work. Disclosures potentially relevant to the content of this guideline are provided. P.D. receives consulting fees and an honorarium for the Data Safety Monitoring Board of Eisai Medical Research. K.A.G. serves on the Advisory Board for RenovoRx. P.L. receives consulting fees and an honorarium from AstraZeneca, Varian, and View-Ray and a research grant from AstraZeneca. N.S. receives consulting fees and an honorarium from Sirtex Medical. W.S. receives consulting fees and an honorarium from Varian and Carl Zeiss. S.K.J. receives research grants from Merck and Nestle and personal fees from Elekta.

[##]Ridley-Tree Cancer Center, Sansum Clinic, Santa Barbara, California

[***]Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey

Introduction

The incidence of anal cancer has increased over the past several decades. Compared with an estimated 5260 cases diagnosed in 2010 in the United States, 8580 cases occurred in 2018, representing 17% of lower gastrointestinal malignancies.[1] The majority of anal cancers are squamous cell carcinoma (SCC) and approximately 90% of SCCs are related to human papillomavirus (HPV).[2] Most of these cancers are caused by HPV types 16 and 18.[3-5] The use of HPV vaccines is expected to decrease the incidence of anal cancer in the future.[6] Approximately half of patients present with localized disease, one-third with regional nodal disease, and 10% to 15% with distant metastases.[1]

Basaloid cancers arise from the functional zone just above the dentate line and are considered to be types of SCC. These and other subtypes are treated like SCC because there is no prognostic significance. Adenocarcinoma of the anus is associated with poor prognosis and high rate of distant metastases. The role of chemoradiation therapy (CRT) for adenocarcinoma is not firmly demonstrated in the literature, but a systematic review concluded that CRT followed by surgery offers the best chance at survival.[7] Small cell carcinoma of the anal region is rare, and experience in treating it is limited. Other rare histologies include melanoma, lymphoma, and sarcoma. Treatments of other histologies are not as well defined in the literature.

The size of the primary tumor and the presence of nodal or distant metastases are determinants of outcome. Patients with de novo tumors >5 cm are at significantly increased risk of requiring a colostomy[8] and inferior disease-free survival (DFS) and overall survival (OS) rates. Improved local control (LC) and OS have been correlated with HPV and p16 positivity.[9-11]

The traditional management of abdominoperineal resection (APR) for tumors of the anal region was progressively replaced by radiation therapy (RT) alone and eventually by CRT. Although there are no randomized trials comparing APR with RT or CRT, CRT has supplanted other forms of therapy primarily because of its superior LC and colostomy-free survival (CFS) rates for most patients with anal cancer. The American Radium Society Appropriate Use Criteria presented in this manuscript are evidence-based guidelines for treatment of anal cancer that have been reviewed by an expert panel. An extensive analysis of current medical literature from peer-reviewed journals was performed with application of consensus methodology to rate the appropriateness of imaging and treatment procedures for the treatment of anal cancer.

Methods and Materials

An extensive analysis of current medical literature from peer-reviewed journals was conducted from January 1, 2008, to October 15, 2018, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[12] guidelines to search the Ovid MEDLINE

without Revisions database to retrieve a comprehensive set of relevant articles. We developed strategies using subject and combinations of keyword search terms (Table 1). We reviewed the bibliographies of full articles for a comprehensive survey, and relevant studies were included. The literature was reviewed for quality of study design, cohort size, selection bias, variability of evaluation of participants in regard to time from exposure, and methods of assessments.

A well-established consensus methodology (modified Delphi)[13] was used by the expert panel to rate the appropriateness of imaging and treatment procedures. The expert panel is a multidisciplinary panel composed of radiation, medical, and surgical oncologists with expertise in the management of anal cancer.

Results and Discussion

Epidermoid tumors of the anal margin

The anal margin is defined generally as the perianal region starting at the anal verge and includes the perianal skin, comprising a 5-cm radius from the squamous mucocutaneous junction. The staging follows that of anal cancer. Owing to tumor location and consequent proclivity for early diagnosis, patients with these tumors tend to have a better prognosis.

Patients with very early-stage (T1N0M0) anal margin cancer are very well managed by local wide excision,[14] similar to treatment for a skin cancer. For well-differentiated T1N0 cancers of the anal margin undergoing local excision, adequate margin has been defined as >1 cm.[15-17] For inadequate margins, re-excision is the preferred treatment if a margin negative resection is believed to be possible. Local RT may be delivered with or without with 5-fluorouracil (5-FU) or capecitabine and with or without mitomycin C (MMC) when surgical margins are inadequate.[18] The recommended RT dose without chemotherapy in these cases is between 50 and 54 Gy over 5 to 6 weeks (Table 2). Definitive local radiation without chemotherapy can provide excellent local control (86%-95% at 10 years) and may be considered for patients with small tumors 4 cm or less in diameter who are unable or unwilling to undergo local excision.[19,20] More advanced stages of anal margin SCC or lesions that involve the anal verge are managed similarly (stage-for-stage) with treatment options similar to those for anal canal cancers owing to an increased risk of nodal failure.[21]

Squamous cell carcinoma of the anal canal

Workup and staging—The TNM classification system is used in the treatment guidelines because it is suitable for a disease treated primarily with nonsurgical means and is staged clinically. It is important to note that there are changes to the new 2016 edition of the American Joint Committee on Cancer staging system.[22] The major change in this eighth edition is a revision of the nodal staging reflecting the results from Radiation Therapy Oncology Group (RTOG) study 9811 that there were no notable outcome differences beyond nodal positivity. Specifically, the location and number of involved lymph nodes were not prognostic.[23]

Because anal cancer is typically treated nonsurgically, optimal treatment and outcomes are dependent on adequate pretreatment staging. Women should have a gynecologic

examination including a Pap smear to rule out concurrent cervical malignancy and men should be screened for penile SCC, and both should be evaluated for other potential sexually transmitted diseases including human immunodeficiency virus (HIV) before initiation of RT. In addition, women of childbearing age should be referred for fertility preservation consultation before treatment. Positron emission tomography (PET) in addition to diagnostic computed tomography (CT) for identifying the primary tumor and involved nodes should be used.[24] A meta-analysis of PET in anal cancer revealed the pooled sensitivity and specificity of nodal detection to be 94% and 76%, respectively. Another meta-analysis demonstrated that when PET/CT was used in initial staging, the rate of nodal upstaging was 21% (95% confidence interval, 13-30), and the TNM stage was altered in 41% of patients.[25] Whenever possible, it is preferable to perform the PET/CT in RT treatment position to assist with tumor localization for treatment planning purposes. These modalities, although quite good, are not perfect, as indicated by a surgical series that showed pelvic nodal disease was often <0.5 cm,[26] and pathologic staging with a sentinel lymph node biopsy may be considered.[27,28] A diffusion-weighted magnetic resonance imaging (MRI) technique can also be helpful in delineating the volume and extent of primary and nodal tumor involvement and appears to provide additional information compared with T_2-weighted images.[29]

Surgical management—APR resulting in permanent colostomies was the standard treatment for anal cancers until the 1970s, yielding 5-year OS and LC of only approximately 50% and 30%, respectively.[30,31] In the seminal follow-up report by Nigro et al, 28 patients received CRT to only 30 Gy in 15 fractions concurrent with 5-FU and MMC, and a complete pathologic response was noted in 7 of 12 patients who underwent APR. A complete clinical response occurred in another cohort of 16 patients. The only patients to die of their disease had tumors >7 cm at initial presentation and were found to have residual disease within their APR specimen. The investigators concluded that definitive CRT should be the new standard of care and that escalation of the RT dose beyond 30 Gy should be considered for more advanced disease. The role of APR for CRT failures is discussed under “Salvage treatment.”

Although wide local excision is not considered standard in the treatment of anal canal cancer, it is sometimes performed in the initial evaluation or management of early-stage small tumors without evidence of anal sphincter or nodal involvement. Even with adequate staging, the risk of recurrence remains high enough after local excision to warrant definitive CRT, which is considered the standard of care for the curative treatment of carcinoma of the anal canal whether or not local excision is performed. The cure rates are markedly lower for local excision: approximately 60% at 5 years, with local recurrences seen in 40%.[31] Reciprocal findings for RT alone note a 5-year OS of 90% to 100% and a local failure rate of 10% to 20%. Local excision alone may not provide long-term control but could be considered for short-term control under special clinical circumstances such as a patient with a poor performance status or significant comorbidities that would compromise tolerance of definitive CRT regimens.

When local excision incidentally demonstrates anal carcinoma, definitive therapy is still warranted. A matched-pair comparison of incidental R0/1 resection with dose-reduced CRT compared with standard definitive doses of CRT for T1-2 N0 anal cancer demonstrated similar treatment results. In this study a total of 20 patients with T1-2 N0 anal carcinoma

who received RT with or without chemotherapy after incidental R0/1 tumor resection were matched with 20 comparable patients who were treated with standard CRT without surgery. Patients treated post-operatively received significantly lower RT doses (median 54.0 Gy vs 59.7 Gy) and less frequent concomitant chemotherapy than those treated definitively. The 5-year LC and OS rates were 97.5% and 90.0%, respectively, with similar toxicity and 95% 5-year colostomy-free survival in both groups,[32] but these results are limited because these were early-stage tumors.

External beam RT alone—The efficacy of RT alone in patients with anal cancer has been well studied. Touboul et al [33] reported on 270 patients with T1-T4 carcinoma of the anal canal treated with RT alone up to 65 Gy with a 4-to-6-week planned break during therapy. Local control for tumors ≤4 cm was 90% at 10 years, whereas it was 65% at 10 years for tumors >4 cm, leading the authors to hypothesize a potential benefit to concurrent chemotherapy. Overall, 57% of patients maintained normal anal function.[33] Newman et al reported similar results with RT alone in a study for which local control was related to T stage. They reported 100% local control for T1 tumors, 86% for T2, 92% for T3, and 63% for T4. Overall, 74% of patients maintained a functional anus.[34] Despite encouraging results of RT alone, concurrent chemotherapy with RT demonstrates superiority to RT alone in patients with anal canal cancer; however radiation alone can be considered to treat older patients or those with or significant comorbid illness and stage I anal cancer.[35]

Interstitial brachytherapy RT alone

Few studies have reported on the efficacy of brachytherapy alone. James et al reported that brachytherapy was relatively effective for patients with small node-negative anal canal cancer. LC for tumors ≤5 cm was 64% and diminished to 23% for tumors >5 cm. Survival was also related to tumor size. The long-term OS rate was 60% for tumors ≤5 cm and only 30% for tumors >5 cm. Eighty-two percent of patients who had no evidence of recurrent cancer retained normal anal function.[36] No direct comparison of brachytherapy to CRT has been made; however, these results appear inferior to those of combined-modality treatment.

RT alone versus CRT

Concurrent chemotherapy and radiation yield results superior to those of radiation alone or radical surgical resection.[37-39] Two major randomized studies have compared the use of RT alone with combined CRT. Bartelink et al reported the results of a study by the European Organization for Research and Treatment of Cancer that compared RT alone to RT plus concurrent chemotherapy for patients with T3-T4 (any N) tumors and patients with T1-T2 node-positive tumors. In that study, LC increased from 55% with RT alone to 73% when combined with CRT. Similarly, CFS increased from 45% with RT alone to 77% with combined-modality therapy. There was no difference in 5-year OS (56% for the entire group) or late toxicity between the 2 arms.[40] The United Kingdom Coordinating Committee on Cancer Research Anal Cancer Working Party reported the results of RT alone versus CRT for patients with T1-T4—any N—tumors. Its findings showed that adding chemotherapy reduced the absolute risk of locoregional relapse by 25.3%, the risk of cancer-related death by 12%, and the colostomy rate by 10%. This group concluded that CRT with surgical

salvage for failure was superior to RT alone[41] (Tables 3-5). There was no significant benefit to induction chemotherapy before concurrent CRT.[42,43]

Use of mitomycin—In a large intergroup study by Flam et al, the addition of MMC to 5-FU and RT was found to be superior to 5-FU and RT alone; however, the addition of MMC increased G4-5 toxicity (26% vs 8%), and the DFS rate increased from 51% with 5-FU and RT compared with 73% with RT combined with 5-FU and MMC.[44] The addition of MMC also improved the CFS rate from 9% to 22% without a significant difference in OS.

Use of cisplatin—Owing to the toxicity associated with MMC, investigators assessed the efficacy of replacing MMC with cisplatin (CDDP) when delivered concurrently with RT and 5-FU.[45-47] The phase 3 Anal Cancer Trial (ACT) 2 trial in the United Kingdom attempted to address whether cisplatin could be substituted for MMC during CRT and whether maintenance chemotherapy with cisplatin would improve progression-free survival (PFS) beyond CRT alone. This randomized study included 940 patients (46% T3-T4 primaries; 32% with involved nodes randomized to either RT with 5-FU and MMC or RT with 5-FU and cisplatin). At a median follow-up of 5.1 years, both arms demonstrated similar rates of clinical complete response (89.6% vs 90.5%). There was no difference in PFS with the addition of maintenance chemotherapy, and MMC had higher rates of nonclinically significant grade 3 or 4 hematologic toxicity.[48]

RTOG 9811 randomized 649 patients to up-front 5-FU, MMC, and RT or induction 5-FU and CDDP followed by 5-FU, CDDP, and RT. In the updated analysis of RTOG 9811,[49] the use of MMC was associated with better DFS (67.8% vs 57.8% at 5 years, $P = .006$) and OS (78.3% vs 70.7% at 5 years, $P = .026$) compared with the CDDP arm. There was a trend toward statistical significance in terms of locoregional relapse and CFS favoring the MMC arm. MMC was associated with greater grade 3 to 4 acute hematologic toxicity, although late toxicity was similar in both arms. Based on the current evidence, concurrent CRT with 5-FU and MMC remains the standard of care; however, cisplatin-based chemotherapy may be considered as an alternative regimen in patients who are not expected to tolerate the hematologic toxicity associated with MMC.

Use of capecitabine—Capecitabine has been widely used in other gastrointestinal cancers with proven efficacy and safety and is considered a reasonable treatment alternative to 5-FU in locally advanced anal cancer. Unlike intravenous 5-FU delivered during weeks 1 and 5 of CRT, capecitabine is given orally twice daily at 825 mg/m^2 during the entirety of radiation therapy, Monday through Friday.[50] A meta-analysis comparing capecitabine and 5-FU showed that complete response and locoregional control rates using capecitabine ranged from 77% to 89.1% and 79% to 94%, respectively, comparable with prior studies using infusional 5-FU.[51] In a retrospective study from the United Kingdom comparing patients treated with intensity modulated RT (IMRT) and single-dose MMC with either capecitabine (n = 52) or 5-FU (n = 147), overall grade ≥3 toxicities were similar, with the only significant difference involving patients who received less capecitabine and MMC experiencing grade 3 hematologic toxicity (4% vs 27%). Treatment duration and 1-year oncologic outcomes were the same. Future prospective studies with longer follow-up will help further understanding of outcomes with the capecitabine and MMC regimen.[52-57]

Use of epidermal growth factor receptor inhibition—Epidermal growth factor receptor (EGFR) is highly overexpressed in SCC of the anal canal, and it has been shown that patients with EGFR expression have significantly shorter PFS and OS compared with patients without EGFR expression.[58,59] EGFR inhibition has been studied as a potential treatment target for this population and has demonstrated low rates of response[60] and unacceptable toxicity.[61] A phase 2 study incorporating the addition of cetuximab to concurrent cisplatin, 5-FU, and RT (45-54 Gy) in patients with stage I to III SCC of the anal canal demonstrated a 68% 3-year PFS and 83% 3-year OS; however, grade 4 toxicity occurred in 32%, with 5% treatment-related deaths.[62] A similar study was conducted in patients with stage I to III HIV-associated anal SCC. In this study, 3-year PFS was 73% and 3-year OS was 79%, with grade 4 toxicity occurring in 24% and 4% treatment related deaths.[63] Therefore, cetuximab is not recommended in this setting.

Radiation techniques and dose—With the advent of IMRT, inverse planning and delivery of external beam RT has increased the therapeutic ratio, which has been associated with reduction in elapsed days of treatment and improved survival compared with 3-dimensional (3D) CRT techniques.[64-66] The RTOG 0529 phase 2 study examined the ability of IMRT to reduce acute morbidity in anal cancer. Compared with RTOG 9811 that used 3D CRT, reducing acute toxicity resulted in fewer patients needing a treatment break (49% vs 62%), and the typical break was significantly shorter.[67] Dosimetrically, IMRT can reduce doses to normal structures and is clinically associated with decreased acute toxicity compared with historic outcomes, with fewer patients experiencing grade 3+ gastrointestinal, hematologic, or dermatologic toxicity.[68-71] IMRT is also associated with better OS at 3 years, locoregional control, and PFS with IMRT compared with conventional RT (88%, 92%, and 84%, respectively, for IMRT vs 52%, 57%, and 57%, respectively, for conventional RT).[72]

For RTOG 0529, long-term results are encouraging with cancer control outcomes appearing similar to RTOG 9811, with 8-year OS, DFS, and CFS of 68% versus 69%, 62% versus 57%, and 66% versus 63%, respectively. Further, there was a low rate of late toxicities. Of note, 5 of the 6 colostomies in RTOG 0529 were performed for locoregional failures, whereas in 9811 about one-third of the 38 colostomies were related to treatment complications.[69,73] However, it is important to note that even for patients enrolled in RTOG 0529, technical issues with IMRT were thought to be challenging, in particular with regard to target volume contouring. Of the 52 evaluable patients, 3 experienced a marginal miss, including within a perirectal node, in the vagina for a tumor with deep anterior extension and within extensively involved skin that did not receive bolus. While important to note that quality control was an issue with 81% of study plans needing revision after central review,[69] many years that have since passed with access to high quality contouring atlases to provide guidance for anorectal volume, in addition to PET/CT and MRI integration into planning, concerns with IMRT has become less of an issue.[74-78]

Use of simultaneous integrated boost IMRT technique—In a pooled analysis from RTOG 8704 and RTOG 9811, the overall treatment time had a detrimental effect on LC and CFS, with overall treatment times >53 days having nearly a doubled risk of local failure

compared with patients with treatment times ≤53 days (hazard ratio = 1.86; 95% confidence interval, 1.31-2.64; $P = .0006$).[79] Further, a longer duration of RT given concurrently with 2-drug chemotherapy was found detrimental to outcome based on the European Organization for Research and Treatment of Cancer pooled analysis of RT oncology trials in anal cancer.[80] It has been hypothesized that worse outcomes in the cisplatin arm of RTOG 9811 may be attributed to extended overall treatment time, potentially leading to inferior outcomes. Since these studies were published, techniques to reduce treatment breaks and overall treatment time using IMRT with or without a simultaneous integrated boost (SIB) have been established. IMRT with an SIB allows for greater efficiency in the RT planning process than sequential boosts. RTOG 0529 and multiple single-institution trials have evaluated the SIB technique with no detriment in oncologic outcomes despite typically employing a lower dose per fraction for lower-risk areas. For its primary aim, RTOG 0529 investigated whether dose-painted IMRT with 5-FU and MMC could reduce grade 2+ combined acute gastrointestinal and genitourinary toxicity by at least 15% compared with the conventional radiation arm from RTOG 9811 (concurrent 5-FU and MMC). In this study, patients with T2-4N0-3M0 anal cancer received 5-FU and MMC on days 1 and 29 of dose-painted IMRT. RT dose was dependent on stage: T2N0 received 42-Gy elective nodal and 50.4-Gy anal tumor planning target volumes (PTVs) in 28 fractions; T3-4N0-3 received 45-Gy elective nodal, 50.4 Gy for ≤3 cm or 54 Gy for >3 cm regional nodal, and 54-Gy anal tumor PTVs in 30 fractions. Fifty-two evaluable patients with stage II (54%), IIIA (25%), or IIIB (21%) were included in the analysis. Although the primary endpoint was not met, this approach was associated with significant sparing of acute grade 2+ hematologic and grade 3+ dermatologic and gastrointestinal toxicity.[69] IMRT allows greater avoidance than 3D planning, and a secondary analysis of RTOG 0529 showed that gastrointestinal toxicity correlated both with volume of both tightly contoured small bowel and loosely contoured anterior pelvic contents.[81] A retrospective comparison of IMRT and an SIB with doses per RTOG 0529 versus 3D CRT sequential boost technique with 36 Gy to elective nodes resulted in similar clinical outcomes.[82]

Dose to primary and lymph nodes—The appropriate RT dose for anal cancer has not been fully elucidated. Typically the radiation boost is delivered with external beam radiation; however, brachytherapy boosts have also been used with acceptable toxicity and high local control rates reported.[83,84] No randomized controlled trials have been performed to analyze the efficacy of brachytherapy in this setting, and a recent systemic review identified 10 studies in a database search. After evaluation of LC, OS, DFS, CFS, sphincter function, and toxicities, the conclusion of this review was that high-level evidence from studies on brachytherapy boost for anal cancer is currently lacking and warrants further investigation.[85]

Table 6 indicates the biologically effective dose for various treatment regimens that may be used via either an SIB or the sequential boost technique. A minimum dose of at least 45 Gy administered via 3D CRT was used in RTOG 9811 and has been established as a standard for even the earliest stage of anal cancer, T1N0.[86] If patients had T3-4 (any N) disease or residual disease in T2 tumors after the initial 45 Gy, a further 10 to 14 Gy in 2-Gy fractions was delivered to the primary tumor and involved nodes for a total dose of 55.8 to 59.4 Gy. Huang et al reported improved control with higher doses in a series of 28 patients, all with

tumors >5 cm. If treatment with a dose ≥54 Gy was delivered within 60 days, the crude freedom from local progression was 89% versus 42% for the rest of the group.[87] Several older studies suggest that doses in excess of 55.8 Gy result in improved LC versus lower doses.[88]

Furthermore, the Action to Control Cardiovascular Risk in Diabetes trial 03 phase 3 from France randomized patients with tumors ≥4 cm or node positivity to 1 of 4 treatment arms (2 x 2 factorial design). The first randomization was plus or minus induction chemotherapy (2 cycles of 5-FU and cisplatin). All patients then received 45 Gy with 5-FU and cisplatin. Three weeks after completion of CRT, patients were randomized to 1 of 2 boost doses: the standard boost dose (15 Gy) or the high boost dose (20 Gy for complete responders and 25 Gy for partial responders). No difference in the primary endpoint of 5-year CFS was shown, and thus no benefit to dose escalation or induction chemotherapy.[42] In a pooled analysis of the prospective KANAL 2 and Action to Control Cardiovascular Risk in Diabetes 03 trials, both involving patients with a primary ≥4-cm tumor or pelvic node involvement, it was found that patients receiving a dose >60 Gy had improved CFS.[89] Because the use of IMRT in RTOG 0529 yielded expected tumor control rates while minimizing toxicity and treatment delays that may be associated with outcome, IMRT could provide a way to explore dose escalation safely in future trials.

Anal cancers spread to the perirectal, inguinal, internal, and external iliac groups of lymph nodes. This pattern of lymph node spread occurs in approximately 30% of patients in a surgical series.[90] Consequently, all 4 groups of lymph nodes are typically included in RT fields described in a CRT series (Table 7). It may be reasonable to consider withholding groin RT for patients with tumors <4 cm in size.[91] In a series of 119 patients who did not receive RT to the inguinal nodes, 91% of whom received MMC and 5-FU, at a median follow-up of 65 months, the 5-year inguinal recurrence rate was 0% for T1, 10% for T2, 21% for T3, and 19% for T4 tumors ($P = .034$). The 5-year inguinal recurrence rate was 21% for tumors ≥4 cm versus 2% for tumors <4 cm in size ($P = .003$) in a similar study.[21] Others have reported groin failures at 12% and 30% for T1-T2 and T3-T4, respectively, in patients with untreated inguinal nodes.[92] In RTOG 9811, the elective dose to the groin was 30.6 to 36 Gy, and a dose of 36 Gy to elective nodal areas has been shown to result in no failures in retrospective series.[93-95] There have been no elective nodal failures in RTOG 0529 involving 42 Gy in 28 fractions or 45 Gy in 25 fractions.

Suitability for definitive treatment—A patient's overall performance status, viral load, and T cell counts[96] should be considered in selecting therapy. Ideally, Karnofsky performance score should be ≥60, viral load should be below 10,000, and the CD4 count should be above 200.[97] Modern HIV therapies have made treatment of anal cancer with standard CRT much more feasible.

Salvage treatment—The mean time to a complete response after CRT is about 1 month,[98] though a complete response can occur even beyond 8 months.[37] The locoregional recurrence rate after chemoradiation ranges from 10% to 30%.[99,100] Patients who are suspected to have recurrent or persistent disease after CRT based on clinical examination should undergo restaging and biopsy, keeping in mind that persistent disease after CRT

should only be biopsied after a prolonged period of several months (ie, >26 weeks) to warrant salvage surgery unless obvious clinical or radiographic progression is found. Imaging techniques may assist with assessing the extent of locoregional recurrence and distant disease. A negative post-treatment PET/CT in patients with anal cancer treated with CRT demonstrated sensitivity and specificity of 100% and 74%, respectively, for recurrent or residual disease. In this study, the negative and positive predictive values were 100% and 71%, respectively.[101] In addition, MRI using phased-array coils and volumetric multidetector CT provides detailed visualization and delineation of local anatomy and extent of recurrence.[29]

Progressive or recurrent disease after CRT is best treated with APR for salvage. Patients with recurrent anal cancer after chemoradiation treated with salvage APR surgery demonstrate a 5-year survival rate of 40% to 60% compared with a 3-year OS rate of 5% for patients who are unsuitable for surgery.[102] Negative prognostic factors for survival are increased tumor size, lymph node involvement, radical resection, and recurrence after salvage APR.[103] A negative resection margin at the time of salvage APR has been shown to be an important prognostic factor and is associated with improved DFS and median survival.[104] A recent study demonstrated that secondary recurrence is significantly associated more frequently with an R1 resection and pN ≥ 1 and a significantly higher risk of death after surgery.[105]

For patients who are medically inoperable or those with recurrences that are not surgically resectable, reirradiation with or without chemotherapy can be considered. Flam et al have shown that the use of 9 Gy along with 5-FU and CDDP can result in salvage for patients with biopsy-proven evidence of residual malignancy.[86] In this study of 25 patients with persistent disease, 22 underwent biopsies after salvage CRT, and 12 (55%) had no evidence of residual tumor. Of these 12 patients, 4 remained disease free for 4 years, 4 underwent APR and remained free of disease, and 4 died. In the 10 patients who had residual disease after salvage treatment, 9 underwent APR, 7 died (6 of progressive disease), and 3 remained free of disease. Overall, 50% of salvage patients were alive without disease at 4 years. In addition to reirradiation using external beam therapy for patients with localized recurrent anal cancer who cannot undergo surgery, CT-guided interstitial brachytherapy has been shown to result in durable tumor control and long-term survival with effective palliation. A study from the MD Anderson Cancer Center reported results from 20 patients who had received interstitial brachytherapy for locally recurrent rectal cancer (n = 17) and locally recurrent anal cancer (n = 3) using an implant dose prescribed to 80 Gy at a 1-cm margin or 120 Gy to 100% of the gross tumor volume. The 1-year rates of LC and OS were 80% and 95%, respectively, and 76% reported palliation of symptoms from 1 to 6 months from the time of implant. Palliation was permanent in 54% of patients, and loss or palliation was reported at a median of 8 months (range, 5-17 months).[106] Risks of reirradiation should be considered and include anal ulcers, bleeding, strictures, stenosis, fistulae, and necrosis.

For patients with inguinal recurrence who were not initially treated with groin irradiation, inguinal nodal recurrences may be salvaged with CRT. However, if there is inguinal recurrence after groin radiation, an inguinal lymph node dissection should be performed

if the recurrence is operable and the patient is able to tolerate surgery, and an APR can be avoided if there is no recurrence in the anus.

For those patients with recurrent anal cancer where surgery or reirradiation with or without chemotherapy is not an option, systemic therapy may be considered.[107-110] Pembrolizumab immunotherapy may also be considered for PD-L1-positive tumors based on early studies of immunotherapy in this setting (Tables 8 and 9).[111]

Timing of assessment of treatment response before salvage treatment— Guidelines for the management of anal cancer have historically recommended assessment of response at 6 to 12 weeks after starting treatment, although contemporary recommendations suggest starting 8 to 12 weeks after completion of CRT.[112,113] The UK trial ACT 1 examined the impact of variations in the duration of the treatment gap and overall treatment time and failed to demonstrate that the overall treatment time and gap before a boost did not significantly affect LC rates.[114] Data from ACT 2 was retrospectively analyzed in an attempt to further characterize the time course of clinical tumor responses after CRT. Complete clinical response (cCR), defined as the absence of a primary and nodal tumor by clinical examination, was noted to be 52%, 71%, and 78% at 11, 18, and 26 weeks from the start of CRT, respectively. In addition, 72% of patients who did not achieve a cCR by 11 weeks had no clinical evidence of a tumor at 26 weeks. The 5-year OS in patients who had achieved a cCR at 11, 18, and 26 weeks was 83%, 84%, and 87%, respectively, and was lower for those patients who did not have a cCR at 72%, 59%, and 46% for assessments 1, 2, 3, respectively. Similarly, PFS in both the overall trial population and the subgroup was longer in patients who had a cCR, compared with patients who did not have a cCR, at all 3 assessments.[98] These data suggest that as long as progression is not noted, assessing tumors for a cCR up to at least 26 weeks from initiation of CRT is prudent to avoid unnecessary salvage surgery in patients who are slow to respond. There are current investigations into the relationship between interim PET imaging during CRT for anal canal cancer and clinical outcome to assist with earlier response assessment.[115,116]

Future directions

Role of immunotherapy—The prevalence of tumor PD-L1 expression in patients with SCC of the anus has been described in the range of 46% to 56% and has been associated with significantly worse PFS with trends toward worse OS.[117,118] The role of immunotherapy in the definitive setting is under active investigation in the cooperative group trial EA2165, “Nivolumab after combined modality therapy in treating patients with high-risk stage II-IIIB anal cancer” (NCT03233711).[119]

Personalization of radiation dose—The question of optimal RT dosing is an area of active investigation. In the UK, 3 separate trials (ACT 3, ACT 4, and ACT 5) are part of a larger integrated protocol entitled Personalising Anal Cancer Radiotherapy Dose, which aims to optimize radiation therapy dose for low-, intermediate-, and high-risk anal cancer.[120] The primary outcome in all studies is locoregional failure rate.

For patients with earlier-stage tumors, dose de-escalation studies are being considered. The upcoming EA2132 De-Intensified Chemoradiation for Early-Stage Anal Squamous Cell

Cancer trial is a randomized phase 2 trial for early-stage anal cancer aimed at determining whether deintensified CRT will achieve 2-year disease control of ≥85%. Patients enrolled in this study will be stratified for T stage (T1 vs T2) and HIV status and will be randomized to standard-dose chemoradiation (50.4 Gy in 28 fractions to primary tumor and 42 Gy in 28 fractions to elective nodes) or a deintensified regimen (for T1 tumors: 36 Gy in 20 fractions to primary tumor and 32 Gy in 20 fractions to elective nodes; for T2 tumors: 41.4 Gy in 23 fractions to primary tumor and 34.5 Gy in 23 fractions to elective nodes). 5-FU or capecitabine with MMC will be used for both arms in this study. In addition, ACT 3 is a nonrandomized phase 2 trial for patients with T1N0 anal margin tumors who have undergone local excision. This study aims to investigate whether acceptably low rates of recurrence are seen with surgery alone for margins >1 mm as suggested by Arana et al[15] and with CRT (MMC and capecitabine concurrent with RT to the anal area alone to 41.4 Gy in 23 fractions) for those with margins ≤1 mm. For those with intermediate-risk anal margin or canal carcinoma (T2 ≤4 cm and N0), ACT 4 is a randomized phase 2 trial comparing PTV anal and PTV elective nodal doses of 50.4 and 40.0 Gy in 28 fractions to 41.4 and 34.5 Gy in 23 fractions for the standard and experimental reduced-dose arms, respectively, again with concurrent MMC and capecitabine. The goal for this trial is to decrease toxicity while maintaining disease control rates. For high-risk disease (T3 or T4 or N+), ACT 5 is a randomized phase 2/3 trial comparing a more standard dose of CRT (53.2 Gy in 28 fractions) to 2 escalated doses of CRT (58.8 Gy and 61.6 Gy, also in 28 fractions).

Conclusions

- The panel recommends strongly that RT concurrent with 5-FU and MMC be the standard of care for curative-intent treatment of nonmetastatic anal cancer, with oral capecitabine as an acceptable alternative to 5-FU.
- The panel does not recommend induction chemotherapy, which is usually not appropriate for this situation.
- The panel recommends strongly that doses of RT between 50 and 59.4 Gy to the primary tumor are appropriate for this situation.
- The panel recommends strongly that IMRT is usually appropriate and preferred over 3D conformal RT.
- The panel recommends the use of SIB IMRT in the combined-modality treatment of patients with locally advanced anal cancer as it is usually appropriate for this situation.
- The panel recommends strongly that assessments for treatment response are usually appropriate starting at approximately 8 weeks from completion of therapy. As complete responses are common as late as 26 weeks from initiation of CRT, the panel does not recommend biopsy of stable or regressing disease before this time.
- The panel recommends strongly that APR be reserved for salvage and that it may be appropriate in such cases.

Acknowledgments—

The American Radium Society Appropriate Use Criteria Steering Committee; Sue Yom, MD, PhD; Joseph M. Herman, MD, MSc, MSHCM; Andre Konski, MD; Andrea Taylor; Theodore S. Hong, MD; Jennifer L. Pretz, MD; A. William Blackstock, MD; Albert C. Koong, MD; Miguel Rodriguez-Bigas, MD; Charles R. Thomas Jr, MD; and Jennifer Zook, MD.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30. [PubMed: 29313949]
2. Viens LJ, Henley SJ, Watson M, et al. Human papillomavirus-associated cancers - United States, 2008-2012. MMWR Morb Mortal Wkly Rep 2016;65:661–666. [PubMed: 27387669]
3. Hoots BE, Palefsky JM, Pimenta JM, Smith JS. Human papillomavirus type distribution in anal cancer and anal intraepithelial lesions. Int J Cancer 2009;124:2375–2383. [PubMed: 19189402]
4. 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. [PubMed: 22445259]
5. Lin C, Franceschi S, Clifford GM. Human papillomavirus types from infection to cancer in the anus, according to sex and HIV status: A systematic review and meta-analysis. Lancet Infect Dis 2018;18:198–206. [PubMed: 29158102]
6. Walker TY, Elam-Evans LD, Singleton JA, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 years - United States, 2016. MMWR Morb Mortal Wkly Rep 2017;66:874–882. [PubMed: 28837546]
7. Anwar S, Welbourn H, Hill J, Sebag-Montefiore D. Adenocarcinoma of the anal canal - a systematic review. Colorectal Dis 2013;15:1481–1488. [PubMed: 23809885]
8. Ajani JA, Winter KA, Gunderson LL, et al. US intergroup anal carcinoma trial: Tumor diameter predicts for colostomy. J Clin Oncol 2009;27:1116–1121. [PubMed: 19139424]
9. Rodel F, Wieland U, Fraunholz I, et al. Human papillomavirus DNA load and p16INK4a expression predict for local control in patients with anal squamous cell carcinoma treated with chemoradiotherapy. Int J Cancer 2015;136:278–288. [PubMed: 24839133]
10. Serup-Hansen E, Linnemann D, Skovrider-Ruminski W, Hogdall E, Geertsen PF, Havsteen H. Human papillomavirus genotyping and p16 expression as prognostic factors for patients with American Joint Committee on Cancer stages I to III carcinoma of the anal canal. J Clin Oncol 2014;32:1812–1817. [PubMed: 24821878]
11. Sun G, Dong X, Tang X, Qu H, Zhang H, Zhao E. The prognostic value of HPV combined p16 status in patients with anal squamous cell carcinoma: A meta-analysis. Oncotarget 2018;9:8081–8088. [PubMed: 29487716]
12. Moher D, Liberati A, Tetzlaff J, Altman DG, and PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:e1000097. [PubMed: 19621072]
13. Jones J, Hunter D. Consensus methods for medical and health services research. BMJ 1995;311:376–380. [PubMed: 7640549]
14. Frost DB, Richards PC, Montague ED, Giacco GG, Martin RG. Epidermoid cancer of the anorectum. Cancer 1984;53:1285–1293. [PubMed: 6692319]
15. Arana R, Flejou JF, Si-Mohamed A, Bauer P, Etienney I. Clinicopathological and virological characteristics of superficially invasive squamous-cell carcinoma of the anus. Colorectal Dis 2015;17:965–972. [PubMed: 25784158]
16. Darragh TM, Colgan TJ, Thomas Cox J, et al. The Lower Anogenital Squamous Terminology Standardization project for HPV-associated lesions: Background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Int J Gynecol Pathol 2013;32:76–115. [PubMed: 23202792]

17. Delhorme JB, Antoni D, Mak KS, et al. Treatment that follows guidelines closely dramatically improves overall survival of patients with anal canal and margin cancers. Crit Rev Oncol Hematol 2016; 101:131–138. [PubMed: 26995081]
18. Steele SR, Varma MG, Melton GB, et al. Practice parameters for anal squamous neoplasms. Dis Colon Rectum 2012;55:735–749. [PubMed: 22706125]
19. Touboul E, Schlienger M, Buffat L, et al. Conservative versus nonconservative treatment of epidermoid carcinoma of the anal canal for tumors longer than or equal to 5 centimeters. A retrospective comparison. Cancer 1995;75:786–793. [PubMed: 7828129]
20. Balamucki CJ, Zlotecki RA, Rout WR, et al. Squamous cell carcinoma of the anal margin: The University of Florida experience. Am J Clin Oncol 2011;34:406–410. [PubMed: 20881476]
21. Blinde SE, Schasfoort R, Mens JW, Verhoef C, Olofsen M, Nuyttens JJ. Inguinal lymph node recurrence in the untreated groin of patients with anal carcinoma. Dis Colon Rectum 2014;57: 578–584. [PubMed: 24819097]
22. Amin MB, Edge S, Greene F, et al. AJCC Cancer Staging Manual. 8th ed. Cham, Switzerland: Springer International Publishing; 2017.
23. Gunderson LL, Moughan J, Ajani JA, et al. Anal carcinoma: Impact of TN category of disease on survival, disease relapse, and colostomy failure in US Gastrointestinal Intergroup RTOG 98-11 phase 3 trial. Int J Radiat Oncol Biol Phys 2013;87:638–645. [PubMed: 24035327]
24. Mahmud A, Poon R, Jonker D. PET imaging in anal canal cancer: A systematic review and meta-analysis. Br J Radiol 2017;90:20170370. [PubMed: 28972796]
25. Jones M, Hruby G, Solomon M, Rutherford N, Martin J. The role of FDG-PET in the initial staging and response assessment of anal cancer: A systematic review and meta-analysis. Ann Surg Oncol 2015;22:3574–3581. [PubMed: 25652048]
26. Wade DS, Herrera L, Castillo NB, Petrelli NJ. Metastases to the lymph nodes in epidermoid carcinoma of the anal canal studied by a clearing technique. Surg Gynecol Obstet 1989;169:238–242. [PubMed: 2672386]
27. Engledow AH, Skipworth JR, Blackman G, et al. The role of (1)(8) fluoro-deoxy glucose combined position emission and computed tomography in the clinical management of anal squamous cell carcinoma. Colorectal Dis 2011;13:532–537. [PubMed: 20070338]
28. Mistrangelo M, Pelosi E, Bello M, et al. Role of positron emission tomography-computed tomography in the management of anal can-cer. Int J Radiat Oncol Biol Phys 2012;84:66–72. [PubMed: 22592047]
29. Prezzi D, Mandegaran R, Gourtsoyianni S, et al. The impact of MRI sequence on tumour staging and gross tumour volume delineation in squamous cell carcinoma of the anal canal. Eur Radiol 2018;28:1512–1519. [PubMed: 29134349]
30. Greenall MJ, Quan SH, Urmacher C, DeCosse JJ. Treatment of epidermoid carcinoma of the anal canal. Surg Gynecol Obstet 1985;161:509–517. [PubMed: 3934775]
31. Hardcastle JD, Bussey HJ. Results of surgical treatment of squamous cell carcinoma of the anal canal and anal margin seen at St. Mark's Hospital 1928-66. Proc R Soc Med 1968;61:629–630. [PubMed: 4173822]
32. Berger B, Menzel M, Breucha G, Bamberg M, Weinmann M. Post-operative versus definitive chemoradiation in early-stage anal cancer. Results of a matched-pair analysis. Strahlenther Onkol 2012;188:558–563. [PubMed: 22569957]
33. Touboul E, Schlienger M, Buffat L, et al. Epidermoid carcinoma of the anal canal. Results of curative-intent radiation therapy in a series of 270 patients. Cancer 1994;73:1569–1579. [PubMed: 8156483]
34. Newman G, Calverley DC, Acker BD, Manji M, Hay J, Flores AD. The management of carcinoma of the anal canal by external beam radiotherapy, experience in Vancouver 1971-1988. Radiother Oncol 1992;25:196–202. [PubMed: 1470696]
35. Buckstein M, Arens Y, Wisnivesky J, Gaisa M, Goldstone S, Sigel K. A population-based cohort analysis of chemoradiation versus radiation alone for definitive treatment of stage I anal cancer in older patients. Dis Colon Rectum 2018;61:787–794. [PubMed: 29771796]
36. James RD, Pointon RS, Martin S. Local radiotherapy in the management of squamous carcinoma of the anus. Br J Surg 1985;72:282–285. [PubMed: 3986477]

37. Cummings BJ, Keane TJ, O'Sullivan B, Wong CS, Catton CN. Epidermoid anal cancer: Treatment by radiation alone or by radiation and 5-fluorouracil with and without mitomycin C. Int J Radiat Oncol Biol Phys 1991;21:1115–1125. [PubMed: 1938508]
38. Martenson JA, Lipsitz SR, Lefkopoulou M, et al. Results of combined modality therapy for patients with anal cancer (E7283). An Eastern Cooperative Oncology Group study. Cancer 1995;76:1731–1736. [PubMed: 8625041]
39. Zilli T, Schick U, Ozsahin M, Gervaz P, Roth AD, Allal AS. Node-negative T1-T2 anal cancer: Radiotherapy alone or concomitant chemoradiotherapy? Radiother Oncol 2012;102:62–67. [PubMed: 21993403]
40. 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. [PubMed: 9164216]
41. 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. [PubMed: 20354531]
42. Peiffert D, Tournier-Rangeard L, Gerard JP, et al. Induction chemotherapy and dose intensification of the radiation boost in locally advanced anal canal carcinoma: Final analysis of the randomized UNICANCER ACCORD 03 trial. J Clin Oncol 2012;30:1941–1948. [PubMed: 22529257]
43. Spithoff K, Cummings B, Jonker D, Biagi JJ, and Gastrointestinal Cancer Disease Site Group. Chemoradiotherapy for squamous cell cancer of the anal canal: A systematic review. Clin Oncol (R Coll Radiol) 2014;26:473–487. [PubMed: 24721444]
44. 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. [PubMed: 8823332]
45. 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. [PubMed: 18430910]
46. Sebag-Montefiore D, Meadows HM, Cunningham D, et al. Three cytotoxic drugs combined with pelvic radiation and as maintenance chemotherapy for patients with squamous cell carcinoma of the anus (SCCA): Long-term follow-up of a phase II pilot study using 5-fluorouracil, mitomycin C and cisplatin. Radiother Oncol 2012;104:155–160. [PubMed: 22857859]
47. 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:e607–613. [PubMed: 21514072]
48. James RD, Glynne-Jones R, Meadows HM, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): A randomised, phase 3, open-label, 2 x 2 factorial trial. Lancet Oncol 2013;14:516–524. [PubMed: 23578724]
49. 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. [PubMed: 23150707]
50. Allegra CJ, Yothers G, O'Connell MJ, et al. Neoadjuvant 5-FU or capecitabine plus radiation with or without oxaliplatin in rectal cancer patients: A phase III randomized clinical trial. J Natl Cancer Inst 2015;107.
51. Souza KT, Pereira AA, Araujo RL, Oliveira SC, Hoff PM, Riechelmann RP. Replacing 5-fluorouracil by capecitabine in localised squamous cell carcinoma of the anal canal: Systematic review and meta-analysis. Ecancermedicalscience 2016;10:699. [PubMed: 28105070]
52. Glynne-Jones R, Meadows H, Wan S, et al. EXTRA—a multicenter phase II study of chemoradiation using a 5 day per week oral regimen of capecitabine and intravenous mitomycin C in anal cancer. Int J Radiat Oncol Biol Phys 2008;72:119–126. [PubMed: 18472366]

53. Goodman KA, Julie D, Cercek A, et al. Capecitabine with mitomycin reduces acute hematologic toxicity and treatment delays in patients undergoing definitive chemoradiation using intensity modulated radiation therapy for anal cancer. Int J Radiat Oncol Biol Phys 2017;98:1087–1095. [PubMed: 28721892]

54. Jones CM, Adams R, Downing A, et al. Toxicity, tolerability, and compliance of concurrent capecitabine or 5-fluorouracil in radical management of anal cancer with single-dose mitomycin-c and intensity modulated radiation therapy: Evaluation of a national cohort. Int J Radiat Oncol Biol Phys 2018;101:1202–1211. [PubMed: 29859793]

55. 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. [PubMed: 25167226]

56. Oliveira SC, Moniz CM, Riechelmann R, et al. Phase II study of capecitabine in substitution of 5-FU in the chemoradiotherapy regimen for patients with localized squamous cell carcinoma of the anal canal. J Gastrointest Cancer 2016;47:75–81. [PubMed: 26691173]

57. 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. [PubMed: 24885554]

58. Richter I, Jirasek T, Dvorak J, Cermakova E, Bartos J. The prognostic significance of epidermal growth factor receptor expression in patients with anal carcinoma. Neoplasma 2016;63:435–441. [PubMed: 26925790]

59. Doll CM, Moughan J, Klimowicz A, et al. Significance of co-expression of epidermal growth factor receptor and ki67 on clinical outcome in patients with anal cancer treated with chemoradiotherapy: An analysis of NRG Oncology RTOG 9811. Int J Radiat Oncol Biol Phys 2017;97:554–562. [PubMed: 28126304]

60. Levy A, Azria D, Pignon JP, et al. Low response rate after cetuximab combined with conventional chemoradiotherapy in patients with locally advanced anal cancer: Long-term results of the UNICANCER ACCORD 16 phase II trial. Radiother Oncol 2015;114:415–416. [PubMed: 25769380]

61. 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. [PubMed: 24026540]

62. Garg MK, Zhao F, Sparano JA, et al. Cetuximab plus chemoradiotherapy in immunocompetent patients with anal carcinoma: A phase II Eastern Cooperative Oncology Group-American College of Radiology Imaging Network Cancer Research Group trial (E3205). J Clin Oncol 2017;35:718–726. [PubMed: 28068178]

63. Sparano JA, Lee JY, Palefsky J, et al. Cetuximab plus chemoradiotherapy for HIV-associated anal carcinoma: A phase II AIDS Malignancy Consortium trial. J Clin Oncol 2017;35:727–733. [PubMed: 27937092]

64. Elson JK, Kachnic LA, Kharofa JR. Intensity-modulated radiotherapy improves survival and reduces treatment time in squamous cell carcinoma of the anus: A National Cancer Data Base study. Cancer 2018;124:4383–4392. [PubMed: 30329160]

65. Jhaveri J, Rayfield L, Liu Y, et al. Impact of intensity modulated radiation therapy on survival in anal cancer. J Gastrointest Oncol 2018;9:618–630. [PubMed: 30151258]

66. Pollom EL, Wang G, Harris JP, et al. The impact of intensity modulated radiation therapy on hospitalization outcomes in the SEER-Medicare population with anal squamous cell carcinoma. Int J Radiat Oncol Biol Phys 2017;98:177–185. [PubMed: 28258896]

67. Konski A, Garcia M Jr., John M, et al. Evaluation of planned treatment breaks during radiation therapy for anal cancer: Update of RTOG 92-08. Int J Radiat Oncol Biol Phys 2008;72:114–118. [PubMed: 18472363]

68. Kachnic LA, Tsai HK, Coen JJ, et al. Dose-painted intensity-modulated radiation therapy for anal cancer: A multi-institutional report of acute toxicity and response to therapy. Int J Radiat Oncol Biol Phys 2012;82:153–158. [PubMed: 21095071]

69. Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: A phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for

the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 2013;86:27–33. [PubMed: 23154075]

70. Call JA, Haddock MG, Quevedo JF, Larson DW, Miller RC. Concurrent chemotherapy and intensity modulated radiation therapy in the treatment of anal cancer: A retrospective review from a large academic center. Pract Radiat Oncol 2013;3:26–31. [PubMed: 24674260]
71. Rattan R, Kapoor R, Bahl A, Gupta R, Oinam AS, Kaur S. Comparison of bone marrow sparing intensity modulated radiotherapy (IMRT) and three-dimensional conformal radiotherapy (3DCRT) in carcinoma of anal canal: a prospective study. Ann Transl Med 2016;4:70. [PubMed: 27004217]
72. Bazan JG, Hara W, Hsu A, et al. Intensity-modulated radiation therapy versus conventional radiation therapy for squamous cell carcinoma of the anal canal. Cancer 2011;117:3342–3351. [PubMed: 21287530]
73. Kachnic LA, Winter K, Myerson RJ, et al. Two-year outcomes of RTOG 0529: A phase II evaluation of dose-painted IMRT in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. ASCO Meeting Abstracts 2011;29:368.
74. Albertsson P, Alverbratt C, Liljegren A, et al. Positron emission tomography and computed tomographic (PET/CT) imaging for radiation therapy planning in anal cancer: A systematic review and meta-analysis. Crit Rev Oncol Hematol 2018;126:6–12. [PubMed: 29759568]
75. Rusten E, Rekstad BL, Undseth C, et al. Target volume delineation of anal cancer based on magnetic resonance imaging or positron emission tomography. Radiat Oncol 2017;12:147. [PubMed: 28874205]
76. Myerson RJ, Garofalo MC, El Naqa I, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: A Radiation Therapy Oncology Group consensus panel contouring atlas. Int J Radiat Oncol Biol Phys 2009;74:824–830. [PubMed: 19117696]
77. Ng M, Leong T, Chander S, et al. Australasian Gastrointestinal Trials Group (AGITG) contouring atlas and planning guidelines for intensity-modulated radiotherapy in anal cancer. Int J Radiat Oncol Biol Phys 2012;83:1455–1462. [PubMed: 22401917]
78. Muirhead R, Adams RA, Gilbert DC, et al. Anal cancer: Developing an intensity-modulated radiotherapy solution for ACT2 fractionation. Clin Oncol (R Coll Radiol) 2014;26:720–721. [PubMed: 25183394]
79. Ben-Josef E, Moughan J, Ajani JA, et al. Impact of overall treatment time on survival and local control in patients with anal cancer: A pooled data analysis of Radiation Therapy Oncology Group trials 87-04 and 98-11. J Clin Oncol 2010;28:5061–5066. [PubMed: 20956625]
80. Matzinger O, Roelofsen F, Mineur L, et al. 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. [PubMed: 19643599]
81. Olsen JR, Moughan J, Myerson R, et al. Predictors of radiation therapy-related gastrointestinal toxicity from anal cancer dose-painted intensity modulated radiation therapy: Secondary analysis of NRG Oncology RTOG 0529. Int J Radiat Oncol Biol Phys 2017; 98:400–408. [PubMed: 28463160]
82. Franco P, De Bari B, Arcadipane F, et al. Comparing simultaneous integrated boost vs sequential boost in anal cancer patients: Results of a retrospective observational study. Radiat Oncol 2018;13:172. [PubMed: 30201015]
83. Lestrade L, De Bari B, Pommier P, et al. Role of brachytherapy in the treatment of cancers of the anal canal. Long-term follow-up and multivariate analysis of a large monocentric retrospective series. Strahlenther Onkol 2014;190:546–554. [PubMed: 24615188]
84. Moureau-Zabotto L, Ortholan C, Hannoun-Levi JM, et al. Role of brachytherapy in the boost management of anal carcinoma with node involvement (CORS-03 study). Int J Radiat Oncol Biol Phys 2013;85:e135–142. [PubMed: 23195780]
85. Frakulli R, Buwenge M, Cammelli S, et al. Brachytherapy boost after chemoradiation in anal cancer: A systematic review. J Contemp Brachytherapy 2018;10:246–253. [PubMed: 30038645]
86. Flam MS, John M, Lovalvo LJ, et al. Definitive nonsurgical therapy of epithelial malignancies of the anal canal. A report of 12 cases. Cancer 1983;51:1378–1387. [PubMed: 6402289]

87. Huang K, Haas-Kogan D, Weinberg V, Krieg R. Higher radiation dose with a shorter treatment duration improves outcome for locally advanced carcinoma of anal canal. World J Gastroenterol 2007;13:895–900. [PubMed: 17352019]

88. Rich TA, Ajani JA, Morrison WH, Ota D, Levin B. Chemoradiation therapy for anal cancer: radiation plus continuous infusion of 5-fluorouracil with or without cisplatin. Radiother Oncol 1993;27:209–215. [PubMed: 8210457]

89. Faivre JC, Peiffert D, Vendrely V, et al. Prognostic factors of colostomy free survival in patients presenting with locally advanced anal canal carcinoma: A pooled analysis of two prospective trials (KANAL 2 and ACCORD 03). Radiother Oncol 2018;S0167-8140:33446–33447.

90. Cohen AM, Wong WD. Anal squamous cell cancer nodal metastases: Prognostic significance and therapeutic considerations. Surg Oncol Clin N Am 1996;5:203–210. [PubMed: 8789503]

91. Zilli T, Betz M, Bieri S, et al. Elective inguinal node irradiation in early-stage T2N0 anal cancer: Prognostic impact on locoregional control. Int J Radiat Oncol Biol Phys 2013;87:60–66. [PubMed: 23608237]

92. Ortholan C, Resbeut M, Hannoun-Levi JM, et al. Anal canal cancer: Management of inguinal nodes and benefit of prophylactic inguinal irradiation (CORS-03 Study). Int J Radiat Oncol Biol Phys 2012;82:1988–1995. [PubMed: 21570207]

93. De Bari B, Lestrade L, Franzetti-Pellanda A, et al. Modern intensity-modulated radiotherapy with image guidance allows low toxicity rates and good local control in chemoradiotherapy for anal cancer patients. J Cancer Res Clin Oncol 2018;144:781–789. [PubMed: 29441419]

94. Henkenberens C, Meinecke D, Michael S, Bremer M, Christiansen H. Reduced radiation dose for elective nodal irradiation in node-negative anal cancer: Back to the roots? Strahlenther Onkol 2015;191:845–854. [PubMed: 26307627]

95. Lepinoy A, Lescut N, Puyraveau M, et al. Evaluation of a 36 Gy elective node irradiation dose in anal cancer. Radiother Oncol 2015;116:197–201. [PubMed: 26277433]

96. Bryant AK, Mudgway R, Huynh-Le MP, et al. Effect of CD4 count on treatment toxicity and tumor recurrence in human immunodeficiency virus-positive patients with anal cancer. Int J Radiat Oncol Biol Phys 2018;100:478–485. [PubMed: 29102276]

97. Kauh J, Koshy M, Gunthel C, Joyner MM, Landry J, Thomas CR Jr. Management of anal cancer in the HIV-positive population. Oncology (Williston Park) 2005;19:1634–1640; 1645. [PubMed: 16396154]

98. Glynne-Jones R, Sebag-Montefiore D, Meadows HM, et al. Best time to assess complete clinical response after chemoradiotherapy in squamous cell carcinoma of the anus (ACT II): A post-hoc analysis of randomised controlled phase 3 trial. Lancet Oncol 2017;18:347–356. [PubMed: 28209296]

99. 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. [PubMed: 17103253]

100. 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. [PubMed: 17638059]

101. 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. [PubMed: 27341410]

102. Renehan AG, Saunders MP, Schofield PF, O'Dwyer ST. Patterns of local disease failure and outcome after salvage surgery in patients with anal cancer. Br J Surg 2005;92:605–614. [PubMed: 15739215]

103. Hagemans JAW, Blinde SE, Nuyttens JJ, et al. Salvage abdominoperineal resection for squamous cell anal cancer: A 30-year single-institution experience. Ann Surg Oncol 2018;25:1970–1979. [PubMed: 29691737]

104. Eeson G, Foo M, Harrow S, McGregor G, Hay J. Outcomes of salvage surgery for epidermoid carcinoma of the anus following failed combined modality treatment. Am J Surg 2011;201:628–633. [PubMed: 21545912]

105. Pedersen TB, Gocht-Jensen P, Klein MF. 30-day and long-term outcome following salvage surgery for squamous cell carcinoma of the anus. Eur J Surg Oncol 2018;44:1518–1521. [PubMed: 30251642]
106. Bishop AJ, Gupta S, Cunningham MG, et al. Interstitial brachytherapy for the treatment of locally recurrent anorectal cancer. Ann Surg Oncol 2015;22:S596–602. [PubMed: 25905584]
107. Sclafani F, Rao S. Systemic Therapies for Advanced Squamous Cell Anal Cancer. Curr Oncol Rep 2018;20:53. [PubMed: 29728940]
108. Rogers JE, Eng C. Pharmacotherapy of anal cancer. Drugs 2017;77:1519–1530. [PubMed: 28770514]
109. Sclafani F, Morano F, Cunningham D, et al. Platinum-fluoropyrimidine and paclitaxel-based chemotherapy in the treatment of advanced anal cancer patients. Oncologist 2017;22:402–408. [PubMed: 28209745]
110. Kim S, Francois E, Andre T, et al. Docetaxel, cisplatin, and fluorouracil chemotherapy for metastatic or unresectable locally recurrent anal squamous cell carcinoma (Epitopes-HPV02): A multicentre, single-arm, phase 2 study. Lancet Oncol 2018;19:1094–1106. [PubMed: 30042063]
111. Ott PA, Piha-Paul SA, Munster P, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal. Ann Oncol 2017;28:1036–1041. [PubMed: 28453692]
112. Sajid MS, Farag S, Leung P, Sains P, Miles WF, Baig MK. Systematic review and meta-analysis of published trials comparing the effectiveness of transanal endoscopic microsurgery and radical resection in the management of early rectal cancer. Colorectal Dis 2014;16:2–14. [PubMed: 24330432]
113. Stewart DB, Gaertner WB, Glasgow SC, et al. The AmericanSociety of Colon and Rectal Surgeons clinical practice guidelines for anal squamous cell cancers (revised 2018). Dis Colon Rectum 2018;61:755–774. [PubMed: 29878949]
114. Glynne-Jones R, Sebag-Montefiore D, Adams R, et al. “Mind the gap”—the impact of variations in the duration of the treatment gap and overall treatment time in the first UK Anal Cancer Trial (ACT I). Int J Radiat Oncol Biol Phys 2011;81:1488–1494. [PubMed: 20934265]
115. Hong JC, Cui Y, Patel BN, et al. Association of interim FDG-PET imaging during chemoradiation for squamous anal canal carcinoma with recurrence. Int J Radiat Oncol Biol Phys 2018;102:1046–1051. [PubMed: 29891206]
116. Goldman KE, White EC, Rao AR, Kaptein JS, Lien WW. Posttreatment FDG-PET-CT response is predictive of tumor progression and survival in anal carcinoma. Pract Radiat Oncol 2016;6:e149–e154. [PubMed: 26948134]
117. Govindarajan R, Gujja S, Siegel ER, et al. Programmed cell death-ligand 1 (PD-L1) expression in anal cancer. Am J Clin Oncol 2018;41:638–642. [PubMed: 27849650]
118. Zhao YJ, Sun WP, Peng JH, et al. Programmed death-ligand 1 expression correlates with diminished CD8+ T cell infiltration and predicts poor prognosis in anal squamous cell carcinoma patients. Cancer Manag Res 2018;10:1–11. [PubMed: 29296096]
119. Appelt AL, Ploen J, Harling H, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: A prospective observational study. Lancet Oncol 2015;16:919–927. [PubMed: 26156652]
120. Habr-Gama A, Sao Juliao GP, Vailati BB, et al. Organ preservation in cT2N0 rectal cancer after neoadjuvant chemoradiation therapy: The impact of radiation therapy dose-escalation and consolidation chemotherapy. Ann Surg 2019;269:102–107. [PubMed: 28742703]

The American Radium Society Appropriate Use Criteria and its expert panels have developed criteria for determining appropriate radiologic procedures for diagnosis and treatment of specified medical condition(s). Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the US Food and Drug Administration have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and treating radiation oncologist in light of all the circumstances presented in an individual examination.

Table 1

Literature search strategy for 2018 American Radium Society Appropriate Use Criteria for anal cancer*

1	exp Antineoplastic Protocols/ or exp Antineoplastic Agents/ or exp combined modality therapy/ or drug therapy/ or dt.fs. or th.fs. or chemo$.tw. or immunotherap$.tw.	(4999053)
2	exp radiotherapy/ or rt.fs. or radiot$.tw. or radiat$.tw. or radiochemo$.tw.	(578404)
3	1 or 2	(5369790)
4	(cancer$ or carcinoma$ or neoplas$ or squamous$ or adenocarcinoma$ or malignanc$ or tumor$ or tumour$). Tw	(2886386)
5	exp Anal Canal/	(17184)
6	4 and 5	(3013)
7	((cancer$ or carcinoma$ or neoplas$ or squamous$ or adenocarcinoma$ or malignanc$ or tumor$ or tumour$) adj3 (anus or anal or anorect$ or an-rect$)).tw.	(5595)
8	exp Anus Neoplasms/	(5904)
9	exp Anal Gland Neoplasms/	(206)
10	or/6-9	(10155)
11	3 and 10	(4086)
12	limit 11 to yr = “2008-Current”	(2042)
13	limit 12 to English language	(1808)

Literature search summary

Of the 56 citations in the original bibliography, 33 citations were retained in the final document. Articles were removed from the original bibliography if they were more than 10 years old and did not contribute to the evidence or they were no longer cited in the revised narrative text.

A new literature search was conducted in October 2018 to identify additional evidence published since the “American Radium Society Appropriateness Criteria Anal Cancer” topic was finalized. Using the search strategy described, 1808 articles were found. The literature was reviewed for quality of study design, cohort size, selection bias, variability of evaluation of participants regarding time from exposure, and methods of assessments. No articles were added to the bibliography, either because the articles were already cited in the original bibliography or owing to poor study design demonstrated in the articles, irrelevance to the topic, or unclear, misinterpreted, or biased results. The authors added 3 citations from bibliographies, websites, or books not found in the new literature search.

* Literature search performed on: October 15, 2018. The beginning date was January 1, 2008, and the end date was October 15, 2018. Database: Ovid MEDLINE without Revisions <1996 to October Week 2 2018>

Table 2

Clinical condition: epidermoid tumor of the anal margin (variant 1: T1N0M0 of anal margin initially treated with local excision)

Treatment	Rating category*	Group median rating	SOE	SOR†
Local excision, negative margins				
Observation	A	8	S	↑
External beam alone	U	3	M	↑
RT + 5-FU + MMC	U	2	M	↑
RT + capecitabine + MMC	U	2	M	↑
RT + 5-FU + CDDP	U	2	M	↑
Local excision, positive margins				
Re-excision	A	8	S	↑
External beam alone if re-excision not feasible	A	8	S	↑
RT + 5-FU + MMC if re-excision not feasible	M	5	M	↑
RT + capecitabine + MMC if re-excision not feasible	M	5	M	↑
RT + 5-FU + CDDP if re-excision not feasible	M	5	M	↑
APR if re-excision not feasible	U	1	M	↑
For positive margins where re-excision not feasible: RT dose				
PTVP, Gy/no. fx				
41.4/23	U	1	M	↑
45.0/25	U	2	M	↑
50-50.4/25-28	M	6	M	↑
54.0/30	A	8	S	↑
PTVE, Gy/no. fx‡				
0 (no encroachment on anal canal)	A	8	S	↑
30.6-45/17-30 (encroachment on anal canal)	M	5	M	-
Radiation Technique				
If tumor bed only; 3D conformal RT (consider electrons)	A	8	S	↑
If treating tumor bed and lymph nodes; IMRT	A	8	S	↑

Abbreviations: ↑ = strong recommendation; ↓ = weak recommendation; 3D = 3-dimensional; 5-FU = 5-fluorouracil; A = usually appropriate; APR = abdominoperineal resection; CDDP = cisplatin; fx = fractions; IMRT = intensity modulated radiation therapy; L = limited; M = may be appropriate (rating category); M = moderate (SOE); MMC = mitomycin C; PTVE = PTV elective nodes; PTVP = PTV anal primary tumor; RT = radiation therapy; S = strong; SOE = strength of evidence; SOR = strength of recommendation; U = usually not appropriate.

[*] The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

[†] Additional considerations do not strengthen or weaken the panel's recommendation.

[‡] If tumor encroachment is present on the anal canal, then consider elective nodal radiation.

Table 3

Clinical condition: carcinoma of the anal canal (variant 2: T3N0M0 with a 6-cm primary)

	Rating Category*	Group median rating	SOE	SOR†
RT + 5-FU + MMC	A	9	S	↑
RT + capecitabine + MMC	M	6	S	↑
RT + 5-FU + CDDP	A	7.5	S	↑
RT + 5-FU	U	2.5	S	↑
RT + capecitabine	U	3	EO	↑
External beam alone	U	1	S	↑
APR	U	2	S	↑
If RT ± chemotherapy: RT dose				
PTVP (Gy/no. fx)				
45/25	U	3	M	↓
50-50.4/25-28	M	5	M	↑
54.0/30	A	8	M	↑
59.4/33	A	8	M	↑
PTVE (Gy/no. fx)				
30.6/17	U	3	M	↓
36.0/20	M	4	M	-
40-42/25-28‡	M	6	M	↑
45.0/25-30	A	8	M	↑
Dose-level technique				
SEQ	A	8	M	↑
SIB	A	8	M	↑
SEQ boost RT technique (if used)				
IMRT	A	9	S	↑
3D conformal RT	M	4	S	-
PTVE nodal treatment volume				
None	U	1	L	↑
Inguinal alone	U	1	M	↑
Pelvic§ alone	U	1	M	↑
Pelvic§ + inguinal	A	9	S	↑

Abbreviations: ↑ = strong recommendation; ↓ = weak recommendation; 3D = 3-dimensional; 5-FU = 5-fluorouracil; A = usually appropriate; APR = abdominoperineal resection; CDDP = cisplatin; EO = expert opinion; fx = fractions; IMRT = intensity modulated radiation therapy; L = limited; M = may be appropriate (rating category); M = moderate (SOE); MMC = mitomycin C; PTVE = PTV elective nodes; PTVP = PTV anal primary tumor; RT = radiation therapy; S = strong; SEQ = sequential boost; SIB = simultaneous integrated boost; SOE = strength of evidence; SOR = strength of recommendation; U = usually not appropriate.

*The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

†Additional considerations do not strengthen or weaken the panel's recommendation.

‡Ongoing Anal Cancer Trial 4 clinical trial to evaluate efficacy of lower doses in intermediate-risk (T2, ≤4 cm, N0) tumors.

§Presacral, external iliac, internal iliac, and mesorectal nodes.

Table 4

Clinical condition: carcinoma of the anal canal (variant 3: T1N1aM0, nonexcised single right inguinal 2-cm node + M0)

	Rating Category*	Group median rating	SOE	SOR†
RT + 5-FU + MMC	A	9	S	↑
RT + capecitabine + MMC	M	6	S	↑
RT + 5-FU + CDDP	A	7.5	S	↑
RT + 5-FU	U	2.5	S	↑
RT + capecitabine	U	3	EO	↑
RT alone	U	1	S	↑
APR + node dissection + CRT				
If RT ± chemotherapy: RT dose				
PTVP (Gy/no. fx)				
45/25	M	4	M	-
50-50.4/25-28	A	7	M	↑
54.0/30	A	8	M	↑
59.4/33	U	3	M	↑
PTVN (Gy/no. fx)				
45/25‡	M	4	M	↑
50-50.4/25-28	A	7	M	↑
54.0/30	M	5	M	↑
PTVE (Gy/no. fx)				
30.6/17	U	1	M	↓
36.0/20	U	3	M	-
40-42/25-28	M	6	M	↑
45.0/25-30	A	8	M	↑
Dose-level technique				
SEQ	A	8	M	↑
SIB	A	8	M	↑
SEQ boost RT technique (if used)				
IMRT	A	9	S	↑
3D conformal RT	M	4	S	-
PTVE nodal treatment volume				
Pelvic§ alone	U	2.5	L	↑
Pelvic§ + inguinal	A	8	M	↑

Abbreviations: ↑ = strong recommendation; ↓ = weak recommendation; 3D = 3-dimensional; 5-FU = 5-fluorouracil; A = usually appropriate; APR = abdominoperineal resection; CDDP = cisplatin; EO = expert opinion; fx = fractions; IMRT = intensity modulated radiation therapy; L = limited; M = may be appropriate (rating category); M = moderate (SOE); MMC = mitomycin C; PTVE = PTV elective nodes; PTVP = PTV anal primary tumor; RT = radiation therapy; S = strong; SEQ = sequential boost; SIB = simultaneous integrated boost; SOE = strength of evidence; SOR = strength of recommendation; U = usually not appropriate.

* The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

[†]Additional considerations do not strengthen or weaken the panel's recommendation.

[‡]Ongoing EA2132 De-Intensified Chemoradiation for Early-Stage Anal Squamous Cell Cancer clinical trial to evaluate efficacy of lower doses in earlier-stage (T1/T2) tumors.

[§]Presacral, external iliac, internal iliac, and mesorectal nodes.

Table 5

Clinical condition: carcinoma of the anal canal (variant 4: T2N0M0 3-cm tumor*)

	Rating category†	Group median rating	SOE	SOR‡
RT + 5-FU + MMC	A	9	S	↑
RT + capecitabine + MMC	M	6	S	↑
RT + 5-FU + CDDP	A	7.5	S	↑
RT + 5-FU	U	2.5	S	↑
RT + capecitabine	U	3	EO	↑
External beam alone	U	1	S	↑
APR				
If RT ± chemotherapy:RT dose				
PTVP (Gy/no. fx)				
45.0/25	U	2	M	↓
50-50.4/25-28	A	8	M	↑
54.0/30	A	7.5	M	↑
59.4/33	M	5	M	↑
PTVE (Gy/no. fx)				
30.6/17	U	3	M	↓
36.0/20	M	4	M	-
40-42/25-28	A	7	M	↑
45.0/25-30	A	8	M	↑
Dose-level technique				
SEQ	A	8	M	↑
SIB	A	8	M	↑
SEQ boost RT technique (if used)				
IMRT	A	9	S	↑
3D conformal RT	M	4	S	-
PTVE nodal treatment volume				
None	U	1	L	↑
Inguinal alone	U	1	M	↑
Pelvic§ alone	U	1	M	↑
Pelvic§ + inguinal	A	9	S	↑

Abbreviations: ↑ = strong recommendation; ↓ = weak recommendation; 3D = 3-dimensional; 5-FU = 5-fluorouracil; A = usually appropriate; APR = abdominoperineal resection; CDDP = cisplatin; EO = expert opinion; fx = fractions; IMRT = intensity modulated radiation therapy; L = limited; M = may be appropriate (rating category); M = moderate (SOE); MMC = mitomycin C; PTVE = PTV elective nodes; PTVP = PTV anal primary tumor; RT = radiation therapy; S = strong; SEQ = sequential boost; SIB = simultaneous integrated boost; SOE = strength of evidence; SOR = strength of recommendation; U = usually not appropriate.

*For small anal canal tumors presenting after local excision (positive or negative margins), definitive chemoradiation therapy recommendations are the same as for nonexcised primary tumors.

†The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

[‡] Additional considerations do not strengthen or weaken the panel's recommendation.

[§] Presacral, external iliac, internal iliac, and mesorectal nodes.

Table 6

Biologically effective dose of various anal cancer radiation regimens for acute and late effects

Total dose	Dose/fx	No. fx	Acute effects, Gy_{10}	Late effects, Gy_3
30.6	1.80	17	36.1	49.0
34.5	1.50	23	39.7	51.8
36.0	1.80	20	42.5	57.6
40.0	1.43	28	45.7	59.0
40.0	1.60	25	46.4	61.3
42.0	1.50	28	48.3	63.0
41.4	1.80	23	48.9	66.2
42.0	1.68	25	49.1	65.5
45.0	1.50	30	51.8	67.5
45.0	1.80	25	53.1	72.0
50.4	1.68	30	58.9	78.6
50.4	1.80	28	59.5	80.6
50.0	2.00	25	60.0	83.3
53.2	1.90	28	63.3	86.9
54.0	1.80	30	63.7	86.4
59.4	1.80	33	70.1	95.0
58.8	2.10	28	71.1	100.0
61.6	2.20	28	75.2	106.8

Abbreviation: fx = fractions.

Table 7

Clinical condition: carcinoma of the anal canal (variant 5: T4N1cM0 [*])

Treatment	Rating category [†]	Group median rating	SOE	SOR [‡]
RT + 5-FU + MMC	A	9	S	↑
RT + capecitabine + MMC	M	6	S	↑
RT + 5-FU + CDDP	A	7.5	S	↑
RT + 5-FU	U	2.5	S	↑
RT + capecitabine	U	3	EO	↑
RT alone	U	1	S	↑
APR + node dissection + CRT	U	2	S	↑
Diverting colostomy + CRT [§]	A	8	EO	↑
If RT ± chemotherapy: RT dose				
PTVP (Gy/no. fx)				
45/25	U	2	M	↓
50-50.4/25-28	M	4	M	↑
54.0/30	A	7	M	↑
56.0-59.4/28-33	A	9	M	↑
PTVN ≤3 cm (Gy/no. fx)				
45/25	U	3	M	↓
50-50.4/25-28	A	7	M	↑
54.0/30	A	7	M	↑
PTVN >3 cm (Gy/no. fx)				
45/25	U	2	M	↓
50-50.4/25-28	M	4	M	↑
54.0/30	A	8	M	↑
56.0-59.4/28-33	A	7	M	↑
PTVE (Gy/no. fx)				
30.6/17	U	3	M	↓
36.0/20	M	4	M	-
40-42/25-28	M	5	M	↑
45.0/25-30	A	8	M	↑
Dose level technique				
SEQ	A	8	M	↑
SIB	A	8	M	↑
SEQ boost RT technique (if used)				
IMRT	A	9	S	↑
3D conformal RT M	4	S	-	
PTVE RT nodal treatment volume				
Pelvic [//] alone	U	2.5	L	↑
Pelvic [//] + inguinal	A	8	M	↑

Abbreviations: ↑ = strong recommendation; ↓ = weak recommendation; 3D = 3-dimensional; 5-FU = 5-fluorouracil; A = usually appropriate; APR = abdominoperineal resection; CDDP = cisplatin; CRT = chemoradiation therapy; EO = expert opinion; fx = fractions; IMRT = intensity modulated radiation therapy; L = limited; M = may be appropriate (rating category); M = moderate (SOE); MMC = mitomycin C; PTVE = PTV elective nodes; PTVP = PTV anal primary tumor; RT = radiation therapy; S = strong; SEQ = sequential boost; SIB = simultaneous integrated boost; SOE = strength of evidence; SOR = strength of recommendation; U = usually not appropriate.

[*] Six-centimeter tumor invading vagina with fistula; 4-cm internal iliac and bilateral inguinal nodes ≤2 cm.

[†] The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

[‡] Additional considerations do not strengthen or weaken the panel's recommendation

[§] Patients with small, asymptomatic fistulas may not require diverting colostomy before CRT.

[‖] Presacral, external iliac, internal iliac, and mesorectal nodes.

Table 8

Clinical condition: carcinoma of the anal canal (variant 6: T3N0M0, 50.4 Gy dose with 5-FU + MMC*)

Treatment	Rating category†	Group median rating	SOE	SOR‡
Additional staging imaging§				
MRI of the pelvis;	A	8	M	↑
Contrasted CT of chest, abdomen, and pelvis;			S	↑
Or PET/CT			M	-
Imaging shows no other suspicious areas				
Brachytherapy alone	M	4	L	↑
Reirradiation ± chemotherapy	U	2	L	↑
Local excision of primary recurrence	U	3	EO	↑
APR	A	9	M	↑
Surgery and postoperative RT ± chemotherapy‖	U	3	EO	↑
Preoperative RT ± chemotherapy followed by surgery	U	3	EO	↑
Chemotherapy	U	2	M	↑
Immunotherapy	U	2.5	L	↑

Abbreviations: ↑ = strong recommendation; A = usually appropriate; APR = abdominoperineal resection; CT = computed tomography; EO = expert opinion; L = limited; M = may be appropriate (rating category); M = moderate (SOE); MMC = mitomycin C; MRI = magnetic resonance imaging; PET = positron emission tomography; RT = radiation therapy; S = strong; SOE = strength of evidence; SOR = strength of recommendation; U = usually not appropriate.

*With initial complete response; now with positive biopsy of 1-cm suspicious area at primary at 7 months with no clinically suspicious lymph nodes and amenable to surgery in a patient with good performance status.

†The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

‡Additional considerations do not strengthen or weaken the panel's recommendation.

§Selection of imaging based on clinical scenario and ACR radiology recommendations.

‖Consider postoperative RT for close margins or after local excision.

Table 9

Clinical condition: anal cancer (variant 7: T3N1cM0, 50.4 Gy dose with 5-FU + MMC[*])

	Rating category[†]	Group median rating	SOE	SOR[‡]
Additional staging imaging[§]				
MRI of the pelvis;	A	8	M	↑
Contrasted CT of the chest, abdomen, and pelvis;			S	↑
Or PET/CT			M	-
Imaging shows no other suspicious areas				
Local excision of nodal recurrence	A	7	EO	↑
Inguinal node dissection	A	7	EO	↑
APR and node dissection	U	1	M	↑
Surgery and postoperative RT ± chemotherapy[‖]	A	8	EO	↑
Reirradiation of the nodal bed ± chemotherapy	M	5	L	↑
Immunotherapy	U	2	M	↑

Abbreviations: ↑ = strong recommendation; A = usually appropriate; APR = abdominoperineal resection; CT = computed tomography; EO = expert opinion; L = limited; M = may be appropriate (rating category); M = moderate (SOE); MMC = mitomycin C; MRI = magnetic resonance imaging; PET = positron emission tomography; RT = radiation therapy; S = strong; SOE = strength of evidence; SOR = strength of recommendation; U = usually not appropriate.

[*]With initial complete response; now with primary tumor controlled and positive biopsy of palpable inguinal node at 3 years and amenable to surgery in a patient with good performance status.

[†]The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

[‡]Additional considerations do not strengthen or weaken the panel's recommendation.

[§]Selection of imaging based on clinical scenario and ACR radiology recommendations.

[‖]Consider postoperative RT for close margins or after local excision.