ARS Appropriate Use Criteria

ANAL CANCER

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CONFLICT OF INTEREST DISCLOSURE STATEMENT

All panelists were required to declare all conflicts of interest for the previous 36 months prior to initiating work on this document. These complete disclosure forms are retained by the American Radium Society in perpetuity.

The ARS Appropriate Use Criteria Steering Committee reviewed these disclosures with the chair of this document and approved participation of the panelists prior to starting development of this work.

Disclosures potentially relevant to the content of this guideline are provided.

Dr. Das receives consulting fees/honorarium for the Data Safety Monitoring Board of Eisai Medical Research.
Dr. Goodman serves on the Advisory Board for RenovoRx.
Dr. Lee receives consulting fees/honorarium from AstraZeneca, Varian, and ViewRay. He receives a research grant from AstraZeneca.
Dr. Sharma receives consulting fees/honorarium from Sirtex Medical.
Dr. Small receives consulting fees/honorarium from Varian and Carl Zeiss.
Dr. Jabbour receives research grants from Merck and Nestle. She receives personal fees from Elekta.

ACKNOWLEDGEMENTS: The ARS AUC 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; Jennifer Zook, MD.

SUMMARY OF LITERATURE REVIEW

INTRODUCTION

Although anal cancer is relatively rare, it has seen a dramatic increase in incidence over the past several decades. Compared to an estimated 5,260 cases diagnosed in 2010 in the United States, the number has ballooned to an expected 8,580 cases in 2018 representing 17% of lower GI malignancies.[1] Adenocarcinoma rates have been stable, and so the rise in incidence has been isolated to squamous cell carcinoma (SCC) of which approximately 90% 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, and although coverage is improving still only 43.4% of teenagers were up to date with this vaccinations as of 2016.[6]

Beginning in the early 1980s, the traditional management of abdominoperineal resection (APR) for tumors of the anal region was progressively replaced by radiotherapy (RT) alone and eventually by chemoradiation (CRT). The emergence of a successful nonsurgical treatment for anal cancer was a paradigm shift.[7] Although there are no randomized trials comparing APR with RT or CRT, CRT has supplanted other forms of therapy primarily because of its superior local control (LC) and colostomy-free survival (CFS) rates for most patients with anal cancer. APR results in a permanent colostomy with its associated functional, anatomic, and psychological complications. The treatment of anal cancer with CRT has served as a prototype for organ-preserving treatment attempts of esophageal[8] and other cancers.[9-12]

Histology

Tumors of the anal region are most frequently keratinizing or nonkeratinizing SCC. Basaloid cancers arise from the functional zone just above the dentate line and are considered by most investigators to be types of SCC. These and other subtypes are treated like SCC, as there is no prognostic significance. Primary adenocarcinoma of the anus is rare, and the role of routine CRT for adenocarcinoma is not firmly demonstrated in the literature. A systematic review noted that prognosis is poor with a high rate of distant metastases, and concluded that a combined modality plan involving chemoradiation and surgery offers the best chance at survival.[13] However, one of the 16 series included in this review involved a Rare Cancer Network (RCN) retrospective multicenter study[14] reporting on a group of 82 patients. Outcomes following definitive CRT did not greatly differ from those receiving planned APR and they were similar to results reported for SCC of the anus.[15] The authors suggested reserving APR for salvage. This organ-sparing approach has a growing body of literature to support it for anorectal adenocarcinoma and prospective investigations are ongoing.[16,17] Small-cell carcinoma of the anal region is even more rare, and experience in treating it is limited. Other rare histologies include melanoma, lymphoma (including mucosa-associated lymphoid tissue lymphomas), and sarcoma.

Because SCC histology is by far the most common, it should be noted that the evidence cited in this review is primarily applicable to SCC of the anal canal; treatments of other histologies are not as well defined in the literature.

Prognostic Factors

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[18] and such tumors contribute to inferior disease-free (DFS) and overall survival (OS) rates. Results from RTOG 9811 demonstrated that male sex and positive lymph nodes were independent prognostic factors for DFS in patients with anal cancer treated with CRT, and male sex, positive lymph nodes and tumor size greater than 5 cm were independent prognostic factors for OS. Compared with N0 and ≤5 cm patients in the best prognostic group, those who were N+ and >5 cm has worse OS (48% vs. 81%, respectively) and DFS (30% vs. 74%, respectively). Notably, the location or number of involved lymph nodes was not prognostic.[19] Improved local control (LC) and OS have been correlated with HPV and p16 positivity.[20-22]

Distant Metastases

Systemic spread of anal SCC occurs in under 10% of cases[23], with the liver and lungs as the most common sites of distant spread. Treatment of such metastases in patients is varied. The risk for distant metastases in adenocarcinoma of the anus is 28% higher.[24]

Prevention

Anal cancer is preceded by high-grade anal intraepithelial neoplasia (AIN). AIN can be caused by infection with human papillomavirus (HPV), primarily types 16 and 18. The quadrivalent HPV vaccine, when given prior to HPV

exposure, has been shown to reduce the rates of AIN and should be considered in populations at high risk for anal cancer, which includes men who have sex with men, women with cervical or vulvar cancer, or individuals who are immunosuppressed.[25] A 9-valent vaccine is also available, protecting against HPV 6, 11, 18, 31, 33, 45, 52, and 58, which is predicted to prevent an additional 464 cases of anal cancer annually compared to the quadrivalent vaccine.[26] The Advisory Committee on Immunization Practices, The American Academy of Pediatrics, and American Society or Clinical Oncology have all released statements recommending the use of either the quadrivalent or 9-valent vaccine in boys and girls age 11 to 12 years, in females age 13 to 26 years, males age 13 to 21 years, and men who have sex with men up to age 26 who have not been previously vaccinated.[27,28]

TOPIC 1.
CLINICAL CONDITION: 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 compromising a 5 cm radius from the squamous mucocutaneous junction. The staging follows that of anal cancer. Due to tumor location and consequent proclivity for early diagnosis, patients with these tumors tend to have a better prognosis.

Subtopic 1.
Treatment of Early Stage Epidermoid Tumors of the Anal Margin

Patients with very early stage (T1N0M0) anal margin cancer are very well managed by local wide excision[29], similar to treatment for a skin cancer. For T1N0 well differentiated cancers of the anal margin undergoing local excision, adequate margin has been defined as >1 cm.[30-32] (See Variant 1.)

Definitive local radiation without chemotherapy can provide excellent local control (86% to 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.[33,34]

Subtopic 2.
Early Stage Epidermoid Tumors of the Anal Margin Treated with Surgical Excision with Inadequate Margins

For inadequate margins, re-excision is the preferred treatment if believed a margin negative resection is possible. Local RT may be delivered with or without with 5-fluorouracil (5-FU) or Capecitabine +/- mitomycin (MMC) when surgical margins are inadequate.[35] The recommended RT dose without chemotherapy in these cases is between 50 and 54 Gy over 5 to 6 weeks.

Subtopic 3.
Treatment of Locally Advanced Epidermoid Tumors of the Anal Margin

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 due to an increased risk of nodal failure.[36]

TOPIC 2.
CLINICAL CONDITION: SQUAMOUS CELL CARCINOMA OF THE ANAL CANAL

Subtopic 1.
Work-up & Staging

Several clinical staging systems have been proposed and used in the past, including classifications from the Mayo Clinic, Roswell Park, and the Centre Léon Bérard. The TNM classification system has been used in the treatment guidelines because it is suitable for a disease treated primarily with nonsurgical means and is clinically staged. It is important to note that there are changes to the new 2016 edition of the AJCC staging system.[37] The major change in this Eighth Edition is a revision of the nodal staging reflecting the results from RTOG 9811 that there were no notable outcome differences beyond nodal positivity. Specifically, the location and number of involved lymph nodes were not prognostic.[19] Thus, patients should now be staged as N0 or N1, and the N1 category is further subdivided by the nodal regions involved.

Because anal cancer is now 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, while both should be evaluated other

potential sexually transmitted diseases including human immunodeficiency virus (HIV) prior to initiation of RT. In addition, women of child bearing age should be referred for fertility preservation consultation prior to treatment. Positron emission tomography (PET) in addition to diagnostic computed tomography (CT) for identifying the primary tumor and involved nodes should be used.[38] A meta-analysis of PET in anal cancer revealed the pooled sensitivity and specificity of nodal detection to be 94% and 76%, respectively, and the RT plan was modified in 12-59% of patients. Another meta-analysis demonstrated that when PET/CT was used in initial staging, the rate of nodal upstaging was 21 % (95 % CI 13-30) and the TNM stage was altered in 41% of patients.[39] Whenever possible, it is preferable to perform the PET/CT in the 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[40], and pathologic staging with a sentinel lymph node biopsy may be considered.[41,42] Magnetic resonance imaging can also be helpful in delineating the volume and extent of primary and nodal tumor involvement and diffusion-weighted (DWI) MRI technique appears to provide additional information compared to T_2-weighted (T_2-w) images.[43]

Subtopic 2.
Surgical Management

Radical surgery in the form of APRs that resulted in permanent colostomies was the standard treatment of choice for anal cancers until the 1970s, but many patients could not have complete resections and results were suboptimal with APR yielding 5-year OS and LC of only approximately 50% and 30%, respectively.[44,45] 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 of16 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 following 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%.[45] Reciprocal findings for radiotherapy alone note a 5-year OS of 90%–100% and a local failure rate of 10%–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 and/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 following incidental R0/1 tumor resection were matched to 20 comparable patient who were treated with standard CRT without surgery. Patients treated postoperatively received significantly lower RT doses (median 54.0 Gy vs. 59.7 Gy) and less frequently concomitant chemotherapy than those treated definitely. The 5-year LC and 5-year OS rates were 97.5% and 90.0%, with similar toxicity and 95% 5-year colostomy-free survival in both groups,[46] but these results are limited since these were early stage tumors.

Biopsies for initial diagnosis and for establishing local residual or recurrent disease should also be done with caution in the interest of sphincter function.

Subtopic 3.
RT Alone- External Beam

The efficacy of RT alone in patients with anal cancer has been well studied. Touboul et al. reported on 270 patients with T1-T4 carcinoma of the anal canal treated with RT alone up to 65 Gy with a 4-6 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.[47] 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.[48] 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 who have stage I anal cancer. [49]

Subtopic 4.
RT Alone - Interstitial Brachytherapy
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. Local control 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.[50] No direct comparison of brachytherapy to CRT has been made; however, these results appear inferior to those of combined-modality treatment.

Subtopic 5.
RT Alone Versus CRT
Concurrent chemotherapy and radiation yield results superior to those of radiation alone or radical surgical resection.[51-53] Consequently, chemoradiation is now the standard of care. Two major randomized studies have compared the use of RT alone to combined CRT. Bartelink et al. reported the results of a study by the European Organization for Research and Treatment of Cancer (EORTC) that compared RT alone to RT plus concurrent chemotherapy for patients with T3-T4, any N, tumors and patients with T1-T2 with 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.[54] The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) 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.[55] (See Variant 2 ,Variant 3, and Variant 4.) There was no significant benefit to induction chemotherapy prior to concurrent CRT.[56,57]

Subtopic 6.
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%). The DFS rate increased from 51% with 5-FU and RT compared to 73% with RT combined with 5-FU and MMC.[10] The addition of MMC also improved CFS rate from 9% to 22% without a significant difference in OS.

Subtopic 7.
Use of Cisplatin
Due to the toxicity associated with MMC, investigators assessed the efficacy of replacing MMC with cisplatin when delivered concurrently with RT and 5-FU.[58-60] The phase III ACT II 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 study included 940 patients (46% T3-T4 primaries; 32% with involved nodes randomized to either RT with 5-FU (1000 mg/m2/day CI days 1-4 and 29-32) and MMC (12 mg/m2 bolus on day 1), or RT with 5-FU and cisplatin (60 mg/m2 bolus on days 1 and 29). In a 2 x 2 factorial design, a second randomization evaluated the benefit of adjuvant 5-FU/cisplatin chemotherapy (an additional two cycles of 5-FU days 71-74 and 92-95 and cisplatin days 71 and 92). RT was prescribed to 50.4 Gy (anterior & posterior RT fields), with a field reduction at 30.6 Gy, and treatment was delivered without a planned break. At a median follow up of 5.1 years both cisplatin and MMC arms demonstrated similar rates of clinical complete response (89.6% vs. 90.5%), and there was no difference in PFS with maintenance chemotherapy. In addition, the rates of any grade 3 or 4 toxicities were similar in both arms (72 vs 73%), with the MMC arm demonstrating higher rates of non-clinically significant grade 3 or 4 hematologic toxicity (26% vs. 16%).[61]

The Radiation Therapy Oncology Group (RTOG) 9811 randomized 649 patients to upfront 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[62], the use of MMC was associated with better DFS (67.8% versus 57.8% at 5 years, P=.006) and OS (78.3% versus 70.7% at 5

years, P=.026) when compared to the CDDP arm. There was a trend toward statistical significance in terms of locoregional relapse and CFS favoring the MMC arm. It was reported that MMC was associated with greater grade 3-4 acute hematologic toxicity than CDDP (late toxicity was the same). RTOG 9811 confirmed that induction chemotherapy with CDDP and concurrent CRT was inferior to upfront concurrent CRT with MMC. The use of induction in the CDDP arm, however, is a potential confounder.

In contrast to RTOG 9811, the UK ACT II trial did not include induction chemotherapy in the cisplatin arm. 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 double the risk of local failure compared to patients with treatment times ≤ 53 days (HR=1.86, 95% CI 1.31-2.64, P = 0.0006).[63] Further, a longer duration of RT given concurrently with two-drug chemotherapy was found to be detrimental based on the EORTC pooled analysis of RT oncology trials in anal cancer (PARADAC).[64] It has been hypothesized that worse outcomes in the cisplatin arm of RTOG 9811 may be attributed to the fact that overall treatment time was extended in this arm, potentially leading to inferior outcomes. Since these studies were published, techniques to reduce treatment breaks and overall treatment time using intensity-modulated RT therapy (IMRT) with or without simultaneous integrated boost (SIB) have been established (**see Subtopic 11**).

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.

Subtopic 8.
Use of Capecitabine
Standard treatment for anal cancer is CRT with MMC with infusional 5-FU, which requires central venous catheter placement associated with risks of infection and thrombosis. Capecitabine, an oral tumor activated fluoropyrimidine carbamate, 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 radiotherapy, Monday through Friday.[65] Retrospective studies as well as Phase I and II studies have evaluated the role of capecitabine in the multimodality treatment of anal cancer.[66] A meta-analysis compared capecitabine and 5-FU and concluded that capecitabine is an acceptable and more convenient alternative to infusional 5-FU.[67] The rate of complete response and locoregional control using capecitabine ranged from 77% to 89.1% and 79% to 94% respectively, comparable with prior studies utilizing infusional 5-FU. In a retrospective study from the United Kingdom comparing patients treated with IMRT and single dose MMC (12 mg/m2) with either capecitabine (n=52) or 5-FU (n=147), overall grade ≥3 toxicities were similar, with the only significant difference involving less capecitabine/MMC patients experiencing grade 3 hematologic toxicity (4% vs. 27%). A numerically but non-significantly lower chemotherapy completion rate attributed mainly to toxicity was seen for the capecitabine group at 81% vs. 90%, but 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/MMC regimen.[68-73]

Subtopic 9.
Use of Epidermal Growth Factor Receptor (EGFR) Inhibition
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.[74,75] EGFR inhibition has been studied as a potential treatment target for this population and has demonstrated low rates of response[76] and unacceptable toxicity.[77] A phase II study incorporating the addition of cetuximab to concurrent cisplatin, 5-FU, and RT (45 to 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.[78] 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.[79] Thererfore, cetuximab is not recommended in this setting.

Subtopic 10.
Radiation Techniques & 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 to 3D-CRT techniques.[80-82] The multi-institutional RTOG 0529 phase II study examined the ability of IMRT to reduce acute

morbidity in anal cancer. As compared to RTOG 9811 that utilized 3D CRT, reducing acute toxicity resulted in fewer patients needing a treatment break (49% vs. 62%) and the typical break was significantly shorter.[83] Dosimetrically IMRT can reduce doses to normal structures (e.g gastrointestinal, genitourinary, and bone/bone marrow) and clinically is associated with decreased acute toxicity compared to historic outcomes, with less patients experiencing grade 3+ gastrointestinal, hematologic and dermatologic toxicity.[84-87] A retrospective review by Bazan et al. compared treatment of anal cancer with IMRT with conventional RT and demonstrated that conventional RT required more treatment breaks and longer treatment duration. They reported better OS at 3 years, locoregional control, and PFS with IMRT compared to conventional RT (88%, 92%, and 84%, respectively for IMRT versus 52%, 57%, and 57%, respectively for conventional RT).[88]

For RTOG 0529, long-term results presented at ASTRO 2017 are encouraging with cancer control outcomes appearing similar to RTOG 9811, with 8-yr OS, DFS, and CFS of 68% vs. 69%, 62% vs. 57%, and 66% vs. 63%, respectively**.** Further, there was a low rate of late toxicities. Of note, 5 of the 6 colostomies in RTOG 0529 were performed for loco-regional failures, whereas in 98-11 about 1/3 of the 38 colostomies were related to treatment complications.[85,89] The expert panel now prefers the use of IMRT over 3D-CRT, and defines it as "usually appropriate" including when performed outside of a protocol setting. 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, there were 3 who 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,[85] many years that have since passed with access to high quality contouring atlases and PET/CT and MRI integration into planning should make concerns with IMRT less of an issue.[90,91] Various contouring atlases now exist to provide guidance for anorectal volume delineation.[92-94]

Simulation should be done with a full bladder when possible for bowel sparing. For consistency, give the patient clear instructions (e.g. first empty bladder and then drink 16 oz of water 1 hour before simulation and each subsequent treatment). Consider CT-based image guidance before RT to decrease PTV margins (e.g. 5 mm) and to provide patient feedback regarding consistency of bladder filling. To minimize bowel dose for larger patients, consider simulating prone on a belly board,[95] as this appears well tolerated with respect to dermatitis due to IMRT decreasing skin dose and toxicity as compared to 3D conformal RT. To minimize skin toxicity in the groin, especially for smaller patients consider simulating supine in the frog leg position as this is a more comfortable position than prone, and slimmer patients do not benefit as much in terms of bowel sparing from being prone. IMRT, VMAT or helical tomotherapy was associated with a significantly lower risk of acute grade ≥3 toxicity compared to a fixed-gantry technique.[96] To ensure adequate dosing to involved skin, consider using radiation dosimeters/measuring devices to help ensure delivery of the intended dose and assess the need for bolus. Attentive management of symptoms will help avoid and minimize treatment breaks, but they should be employed if necessary such as for ANC<500/mm3, platelets<50,000, grade ≥3 diarrhea and/or vomiting, and grade 4 dermatitis.

Subtopic 11.
Use of Simultaneous Integrated Boost IMRT Technique

One method of shortening treatment time and potentially improving outcomes is to utilize an IMRT technique with SIB. This 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. RTOG 0529 did not involve any isolated nodal failures in microscopic disease coverage. 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, T2-4N0-3M0 anal cancer patients received 5-FU and MMC on days 1 and 29 of dose-painted IMRT. RT dose was dependent on stage: T2N0: 42 Gy elective nodal and 50.4 Gy anal tumor planning target volumes (PTVs) in 28 fractions; T3-4N0-3: 45 Gy elective nodal, 50.4 Gy ≤3 cm or 54 Gy >3 cm regional nodal and 54 Gy anal tumor PTVs in 30 fractions. Fifty-two evaluable patients with Stage II (54%), IIIA (25%), and 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.[85] IMRT allows greater avoidance than 3D planning, and a secondary analysis of RTOG 0529 showed that GI toxicity correlated both with volume of both tightly contoured small bowel and loosely contoured anterior pelvic contents.[95] A retrospective comparison of IMRT SIB with doses per RTOG 0529 versus 3D-CRT sequential boost technique with 36 Gy to elective nodes resulted in similar clinical

outcomes.[97] Additional single institution studies confirm the findings of reduced toxicity with favorable oncologic outcomes, and support the use of SIB-IMRT in the combined modality treatment of anal cancer patients.[98-102]

Subtopic 12.
Dose to Primary & 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.[103,104] However no randomized controlled trials have been performed to analyze the efficacy of brachytherapy in this setting and a recent systemic review using PRISMA methodology 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 evidences from studies on brachytherapy boost for anal cancer are lacking currently and warrants further investigation.[105]

Table 1 indicates the biological effective dose for various treatment regimens that may be used via either a SIB or sequential boost technique. A minimum dose of at least 45 Gy using a 3D-CRT technique was used in RTOG 9811 and has been established for even the earliest stage of anal cancer, T1N0.[11] 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/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.[106] Several older studies suggest that doses in excess of 55.8 Gy result in improved LC versus lower doses.[107]

Furthermore, the ACCORD 03 phase III trial from France randomized patients with tumors ≥4 cm and/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 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). There was no difference in the primary endpoint of 5-year CFS thus showing no benefit to dose escalation or induction chemotherapy.[56] In a pooled analysis of the prospective KANAL 2 and ACCORD 03 trials both involving patients with a primary ≥4cm or pelvic node involvement, it was found that patients receiving a dose >60 Gy had improved CFS.[108] As 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 safely explore dose escalation in future trials (See PLATO trial in Future Directions).

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 surgical series.[109] Consequently, all 4 groups of lymph nodes are typically included in radiotherapy fields described in CRT series (See Variant 5.) It may be reasonable to consider withholding groin RT for patients with tumors <4 cm in size.[110] In series of 119 patients who didn't 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 = 0.034). The 5-year inguinal recurrence rate was 21% for tumors ≥4 cm vs. 2% for tumors <4 cm in size (p = 0.003) in a similar study.[36] In another smaller retrospective series of 29 patients, regional failure was similar when patients had either elective treatment up to L5/S1 border versus only the bottom of the SI joint. For groin negative patients, inguinal failure was 23% in the inguinal observation group vs. 0% if prophylactic RT was delivered. Although the size of the primary for those with and without failures were not described, the authors recommended prophylactic inguinal RT for all patients.[111] Others have reported groin failures at 12% and 30% for T1-T2 and T3-T4 respectively in patients with untreated inguinal nodes.[112] In RTOG 9811, the elective dose to the groin was 30.6 - 36 Gy (via a photon or en face electron technique). A dose of 36 Gy to elective nodal areas has been shown to result in no failures in retrospective series[96,113,114] and as noted previously there have been no elective nodal failures in RTOG 0529 involving 42 Gy/28 fractions or 45 Gy/25 fractions. Although para-aortic (PA) lymph node involvement is defined as metastatic disease, extended radiation fields to cover gross disease may be an option. In a series of 30 patients with PA nodes at initial diagnosis, 17 were alive without evidence of disease following CRT after a median follow-up time of 3.1 years.[115]

Subtopic 13.
Suitability for Definitive Treatment

Most patients with anal cancer, even locally advanced disease, have good or acceptable general performance status Karnofsky performance score (KPS) ≥ 60). Poor performance status may preclude adherence to a standard course of

CRT. Known human immunodeficiency virus (HIV) infection is not necessarily a contraindication to standard recommended treatments, and these patients should continue on antiretroviral therapy throughout CRT. However, patients with cytopenias or with frank manifestations of acquired immunodeficiency syndrome may have a decreased ability to tolerate treatment. A patient's overall performance status, complete blood count, and T cell counts (CD3/CD4 status)[116] should be considered in selecting therapy. Ideally, the viral load should be below 10,000, and the CD4 count should be above 200.[117] Modern HIV therapies have made the treatment of anal cancer with standard CRT much more feasible, although cases should be individualized pending large randomized trials results.

Other relative reasons that might preclude definitive treatment include previous pelvic RT or surgery and underlying medical, psychiatric, and/or social reasons.

Subtopic 14.
Salvage Treatment

The mean time to a complete response after CRT is about 1 month[118] and it can occur even beyond 8 months[51]. The locoregional recurrence rate after chemoradiation ranges from 10% to 30%.[119,120] Patients who are suspected to have recurrent or persistent disease following CRT based on clinical exam should undergo restaging and biopsy, keeping in mind that persistent disease following CRT should only be biopsied after a prolonged period of several months (ie. > 26wks) to warrant salvage surgery unless obvious clinical or radiographic progression. Imaging techniques may assist with assessing extent of locoregional recurrence and distant disease. A negative post-treatment PET-CT in patients with anal cancer treated with CRT demonstrated a 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.[121] In addition, MRI using phased-array coils and volumetric multidetector CT provides detailed visualization and delineation of local anatomy and extent of recurrence, which should be carefully considered when considering salvage surgery with the aim of achieving and RO resection.[43] MRI has been recommended by the European Society for Medical Oncology (ESMO) as the preferred modality of choice to stage anal cancer, taking into account the maximum tumor diameter, invasion of adjacent structures and regional lymph node involvement. In the setting of suspected recurrence radiologists must recognize post therapy appearances, and when to suspect residual or recurrent disease to guide clinicians and achieve optimal patient outcome.

Progressive or recurrent disease after CRT is best treated with APR for salvage. Patients with recurrent anal cancer following 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.[122] Negative prognostic factors for survival are increased tumor size, lymph node involvement, radical resection, and recurrence after salvage APR.[123] Mullens et al. reported a 5-year survival rate of 64% in a cohort of 31 patients with a median follow-up of 29 months.[119] 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 (33 months for negative margin versus 14.2 months for positive margin).[124] A recent study demonstrated that secondary recurrence is significantly associated more frequently with a R1 resection and pN $\geq$ 1 and a significantly higher risk of death following surgery.[125]A salvage APR involves wide margins and in the case of larger recurrences that are close to the vagina or bladder an en-bloc resection is required because of the risk of fistulae associated with prior RT. In addition, healing may be compromised in a previously irradiated area requiring reconstructive tissue flap approaches for perineal closure.[126,127]

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.[11] In this study of 25 patients with persistent disease, 22 underwent biopsies following 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 MD Anderson 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 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).[128] 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 chemoradiation. 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.[129-131] In a recent multicenter, single-arm, phase 2 study in 69 patients with metastatic or unresectable locally recurrent anal squamous cell carcinoma with good performance status 8 cycles of modified DCF (40 mg/m^2 docetaxel and 40 mg/m^2 cisplatin on day 1 and 1200 mg/m^2 per day of fluorouracil for 2 days, every 2 weeks) were delivered as first line therapy demonstrating provided long-lasting response with good tolerability.[132] Further investigations are ongoing. In an immunotherapy study including 24 patients with PD-L1 positive advanced squamous cell carcinomas of the anal canal receiving pembrolizumab 10 mg/kg once every 2 weeks for up to 2 years or until confirmed progression or unacceptable toxicity, 4 patients had confirmed partial response, for an overall response rate of 17%, 10 (42%) had confirmed stable disease, resulting in a disease control rate of 58%. One additional patient with non-squamous histology had confirmed stable disease. The treatment was tolerable and there were no treatment-related deaths or discontinuations reported.[133](See Variant 6 and Variant 7.)

Subtopic 15.
Timing of Assessment of Treatment Response Before Salvage Treatment
Guidelines for the management of anal cancer have historically recommended assessment of response at 6–12 weeks after starting treatment, although contemporary recommendations suggest starting 8-12 weeks following completion of CRT.[134,135] The UK Anal Cancer Trial (ACT I) 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 boost did not significantly impact LC rates.[136] Data from the ACT II trial was retrospectively analyzed with attempt to further characterize the time course of clinical tumor responses after CRT**.** Complete clinical response (cCR) defined as the absence of 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 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 three assessments.[118] 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.[137,138]

TOPIC 3.
FUTURE DIRECTIONS

Subtopic 1.
Role of Immunotherapy
HPV causes a local immunosuppressive microenvironment, and inflammatory cytokines are inhibited by viral proteins which mitigates both innate and adaptive immune responses. The prevalence of tumor PD-L1 expression in patients with SCC of the anus has been described in the range of 46-56%, and has been associated with significantly worse PFS with trends toward worse OS.[139,140] Given the prevalence of PD-L1 expression in this population, it is reasonable to consider the use of immune checkpoint inhibitors in the treatment of this disease. Early Phase IB and II trial data with unknown PD-L1 receptor status show that stable disease is common with occasional complete responses, with progression at latest follow-up noted in just 22-33%. 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).[141] Eligible patients must be T3-4, any N or N+. The preferred RT technique on trial is IMRT with SIB dosing/volumes as per the 30-fraction regimen for RTOG 0529, but 3D conformal RT is allowed.

Subtopic 2.
Personalization of Radiation Dose

The question of optimal RT dosing is an area of active investigation. Results from the initial work from Nigro et al. initial work suggest that lower doses of RT may be sufficient for earlier stage patient patients. Although doses beyond 54 Gy have not been proven more effective, dose escalation has traditionally involved 3D conformal RT with planned and/or unexpected treatment breaks which could limit treatment efficacy. With the reduced toxicity of IMRT improved outcomes might be possible with higher doses. In the UK, 3 separate trials (ACT3, ACT4, and ACT5) are part of a larger integrated protocol entitled: PersonaLising Anal cancer radioTherapy dOse (PLATO) which aims to optimize radiotherapy dose (in combination with chemotherapy) for low, intermediate, and high-risk anal cancer.[142] The primary outcome in all studies is locoregional failure rate.

For patients with earlier stage tumors, dose-deescalation studies are being considered. The upcoming EA2132 De-Intensified ChemoRadiation for Early-Stage Anal SqCell Cancer (DECREASE trial) is a randomized Phase II trial for early stage anal cancer aimed to determine if de-intensified CRT will achieve 2-year disease control ≥ 85%. Patients enrolled in this study will be stratified for T stage (T1 versus T2) and HIV status and will be randomized to standard dose chemoradiation (50.4Gy/28 fractions to the primary tumor and 42Gy/28 fractions to elective pelvic and inguinal nodes) or a deintensified regimen (for T1 tumors: 36 Gy/20 fractions to the primary tumor and 32Gy/20 fractions to elective pelvic and inguinal nodes; for T2 tumors: 41.4 Gy/23 fractions to the primary tumor and 34.5Gy/23 fractions to elective pelvic and inguinal nodes). 5-FU (1000mg/m^2/d days 1-4) or Capecitabine (825 mg/m^2 BID M-F on days of RT) with Mitomycin C (10 mg/m^2 on day 1) will be used for both arms in this study. In addition, ACT3 is a non-randomized phase II 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 >1mm as suggested by Arana et al.[30], and with CRT (MMC & Capecitabine concurrent with RT to the anal area alone to 41.4 Gy in 23 fractions) for those with margins ≤1mm. For those with intermediate-risk anal margin/canal carcinoma (T2 ≤4 cm and N0), ACT4 is a randomized phase II trial for comparing PTV Anal (PTVA)/PTV Elective Nodal (PTVE) doses of 50.4/40.0 Gy in 28 fractions to 41.4/34.5 Gy in 23 fractions for the standard and the 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/ T4 and/or N+), ACT5 is a randomized phase II/III trial comparing a more standard-dose of CRT (53.2 Gy in 28 fractions) to two escalated doses of CRT (58.8Gy and 61.6 Gy, also in 28 fractions). Chemotherapy may involve MMC and either Capecitabine or 5-FU. The hope with this study is improved disease control while maintaining acceptable toxicity profiles.

Despite a relatively good prognosis for many patients, it is important to recognize that CRT for anal SCC has the potential to cause significant acute and long-term morbidity.[143,144] Severe long term toxicity affecting quality of life due to incontinence, diarrhea, ulceration, and buttock pain was seen in up to one third of patients in a systematic review by Pan YB et al.[145] This underscores the need for active investigation to de-escalate therapy when possible and take a pro-active role in avoiding and managing side effects. Of note, a retrospective study recently noted discrepancies in patient and clinical symptom scoring, identifying the potential for patient-reported outcomes as useful tools for anal cancer clinical toxicity assessments.[146] Glynne-Jones R et al. performed an analysis of published randomized clinical trials and noted that there was great heterogeneity in the assessed primary and secondary endpoints, as well as their definitions.[147] The authors concluded that a core set of oncologic and patient-reported outcome measures, utilizing standardized definitions, is essential to maximize the generalizability of and progress from clinical trials examining RT and systemic treatment in the management of SCC of the anus.

SUMMARY OF RECOMMENDATIONS

- The panel recommends strongly that RT concurrent with 5-FU and MMC is the standard of care for curative-intent treatment of non-metastatic 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 locally advanced anal cancer patients which 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 abdominal-perineal resection (APR) be reserved for salvage and may be appropriate in such cases.

Summary of Evidence

Of the 147 references cited in the ARS Appropriateness Criteria Anal Cancer document, 123 of them are categorized as therapeutic references including 16 well-designed studies, 31 good quality studies, and 76 studies that may have design limitations.

There are 37 references that may not be useful as primary evidence. There are 7 references that are meta-analysis studies.

The 147 references cited in ARS Appropriateness Criteria Anal Cancer document were published from 1965 to 2018.

Although there are references that report on studies with design limitations, 47 well-designed or good quality studies provide good evidence.

Supporting Documents

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

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Table 1: Biologically effective dose (BED) of various anal cancer radiation regimens for acute & late effects

D (total dose)	d (dose/fx)	n (# fx)	Gy_{10} (acute effects)	Gy_3 (late effects)
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

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 /# 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 /# Fx) **Note: if tumor encroachment on anal canal then consider elective nodal radiation**				
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	↑

KEY: RT = Radiation Therapy; SIB = IMRT Simultaneous integrated boost; SEQ = Sequential boost; fx = fractions; APR = abdominoperineal resection; PTVP = PTV Anal Primary Tumor; PTVE = PTV Elective Nodes; * = presacral, external iliac, internal iliac, mesorectal nodes; 3D conformal RT = Three-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy
Rating: **A**-Usually appropriate; **M**-May be appropriate; **U**-Usually not appropriate
Strength of Evidence: S-Strong; **M**-Moderate; **L**-Limited; **EC**-Expert consensus; **EO**-Expert opinion
Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel's recommendation

Clinical Condition: **Carcinoma of the Anal Canal**
Variant 2: **T3N0M0 with a 6 cm primary.**

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	↑
External beam alone	U	1	S	↑
APR	U	2	S	↑
If RT +/- Chemotherapy: RT Dose				
PTVP (Gy /# 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 /# 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	↑

*** Ongoing ACT4 clinical trial to evaluate efficacy of lower doses in intermediate risk (T2 ≤ 4cm, N0) tumors**

KEY: RT = Radiation Therapy; SIB = IMRT Simultaneous integrated boost; SEQ = Sequential boost; fx = fractions; APR = abdominoperineal resection; PTVP = PTV Anal Primary Tumor; PTVE = PTV Elective Nodes; * = presacral, external iliac, internal iliac, mesorectal nodes; 3D conformal RT = Three-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy
Rating: **A**-Usually appropriate; **M**-May be appropriate; **U**-Usually not appropriate
Strength of Evidence: S-Strong; **M**-Moderate; **L**-Limited; **EC**-Expert consensus; **EO**-Expert opinion
Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel's recommendation

Clinical Condition: **Carcinoma of the Anal Canal**
Variant 3: **T1N1aM0, nonexcised single right inguinal 2-cm node + M0.**

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	↑
If RT +/- Chemotherapy: RT Dose				
PTVP (Gy /# 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 /# Fx)				
45 / 25	M	4	M	↑
50 - 50.4 / 25 - 28	A	7	M	↑
54.0 / 30	M	5	M	↑
PTVE (Gy /# 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	↑

***Ongoing EA2132 DECREASE clinical trial to evaluate efficacy of lower doses in earlier stage (T1/T2) tumors**

KEY: RT = Radiation Therapy; SIB = IMRT Simultaneous integrated boost; SEQ = Sequential boost; fx = fractions; APR = abdominoperineal resection; PTVP = PTV Anal Primary Tumor; PTVN = PTV Nodes; PTVE = PTV Elective Nodes; * = presacral, external iliac, internal iliac, mesorectal nodes; 3D conformal RT = Three-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; CRT = chemoradiation
Rating: **A**-Usually appropriate; **M**-May be appropriate; **U**-Usually not appropriate
Strength of Evidence: S-Strong; **M**-Moderate; **L**-Limited; **EC**-Expert consensus; **EO**-Expert opinion
Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel's recommendation

Clinical Condition: **Carcinoma of the Anal Canal**
Variant 4: **T2N0M0 3.0 cm tumor.***

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	↑
External beam alone	U	1	S	↑
APR	U	1.5	S	↑
If RT +/- Chemotherapy: RT Dose				
PTVP (Gy /# 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 /# 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	↑

***Note - For small anal canal tumors presenting after local excision (positive or negative margins) definitive CRT recommendations are the same as for nonexcised primary tumors**

KEY: RT = Radiation Therapy; SIB = IMRT Simultaneous integrated boost; SEQ = Sequential boost; fx = fractions; APR = abdominoperineal resection; PTVP = PTV Anal Primary Tumor; PTVE = PTV Elective Nodes; * = presacral, external iliac, internal iliac, mesorectal nodes; 3D conformal RT = Three-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; CRT = chemoradiation
Rating: **A**-Usually appropriate; **M**-May be appropriate; **U**-Usually not appropriate
Strength of Evidence: S-Strong; **M**-Moderate; **L**-Limited; **EC**-Expert consensus; **EO**-Expert opinion
Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel's recommendation

Clinical Condition: **Carcinoma of the Anal Canal**
Variant 5: **T4N1cM0 (6 cm tumor invading vagina with fistula; 4 cm internal iliac & bilateral inguinal nodes ≤ 2 cm.)**

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 /# 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 ≤3cm (Gy /# Fx)				
45 / 25	U	3	M	↓
50 - 50.4 / 25 - 28	A	7	M	↑
54.0 / 30	A	7	M	↑
PTVN >3cm (Gy /# 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 /# 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	↑

***Note - Patients with small, asymptomatic fistulas may not require diverting colostomy prior to CRT**

KEY: RT = Radiation Therapy; SIB = IMRT Simultaneous integrated boost; SEQ = Sequential boost; fx = fractions; APR = abdominoperineal resection; PTVP = PTV Anal Primary Tumor; PTVN≤3cm = PTV Nodes ≤ 3 cm; PTVN>3cm = PTV Nodes > 3 cm; PTVE = PTV Elective Nodes; * = presacral, external iliac, internal iliac, mesorectal nodes; 3D conformal RT = Three-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; CRT = chemoradiation
Rating: **A**-Usually appropriate; **M**-May be appropriate; **U**-Usually not appropriate
Strength of Evidence: S-Strong; **M**-Moderate; **L**-Limited; **EC**-Expert consensus; **EO**-Expert opinion
Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel's recommendation

Clinical Condition: **Carcinoma of the Anal Canal**
Variant 6: **T3N0M0, 50.4 Gy dose with 5-FU + MMC with initial complete response, now with positive biopsy of 1cm suspicious area at primary at 7 months, with no clinically suspicious lymph nodes, amenable to surgery in a good performance status patient.**

TREATMENT	Rating Category	Group Median Rating	SOE	SOR
Additional Staging Imaging*				
MRI pelvis or; Contrasted CT Chest Abdomen Pelvis or; PET CT	A	8	M S 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	↑

***Note - Selection of imaging based on clinical scenario and ACR radiology recommendations**
****Note - Consider postoperative RT for close margins or after local excision**

KEY: RT = Radiation Therapy; MRI = magnetic resonance imaging; CT = computed tomography; PET CT = positron emission tomography computed tomography
Rating: **A**-Usually appropriate; **M**-May be appropriate; **U**-Usually not appropriate
Strength of Evidence: S-Strong; **M**-Moderate; **L**-Limited; **EC**-Expert consensus; **EO**-Expert opinion
Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel's recommendation

Clinical Condition: **Anal Cancer**
Variant 7: **T3N1cM0, 50.4 Gy dose with 5-FU + MMC with initial complete response, now with primary tumor controlled and positive biopsy of palpable inguinal node at 3 years, amenable to surgery in a good performance status patient.**

TREATMENT	Rating Category	Group Median Rating	SOE	SOR
Additional Staging Imaging*				
MRI pelvis or; Contrasted CT Chest Abdomen Pelvis or; PET CT	A	8	M S 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	↑

***Note - Selection of imaging based on clinical scenario and ACR radiology recommendations**
****Note - Consider postoperative RT for close margins or after local excision**

KEY: RT = Radiation Therapy; MRI = magnetic resonance imaging; CT = computed tomography; PET CT = positron emission tomography computed tomography
Rating: **A**-Usually appropriate; **M**-May be appropriate; **U**-Usually not appropriate
Strength of Evidence: S-Strong; **M**-Moderate; **L**-Limited; **EC**-Expert consensus; **EO**-Expert opinion
Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel's recommendation