Public Comment Draft

Radiation Therapy for Squamous Cell Carcinoma of the Anal Canal: An ASTRO Clinical Practice Guideline

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Preamble

As a leading organization in radiation oncology, the American Society for Radiation Oncology (ASTRO) is dedicated to improving quality of care and patient outcomes. A cornerstone of this goal is the development and dissemination of clinical practice guidelines based on systematic methods to evaluate and classify evidence, combined with a focus on patient-centric care and shared decision making. ASTRO develops and publishes guidelines without commercial support, and members volunteer their time.

Disclosure Policy—ASTRO has detailed policies and procedures related to disclosure and management of industry relationships to avoid actual, potential, or perceived conflicts of interest. All task force members are required to disclose industry relationships and personal interests from 12 months before initiation of the writing effort. Disclosures for the chair and vice chair go through a review process with final approval by ASTRO's Conflict of Interest Review Committee. For the purposes of full transparency, task force members' comprehensive disclosure information is included in this publication. Peer reviewer disclosures are also reviewed and included (Supplementary Materials, Appendix E1). The complete disclosure policy for Formal Papers is online.

Selection of Task Force Members—ASTRO strives to avoid bias and is committed to creating a task force that includes a diverse and inclusive multidisciplinary group of experts considering race, ethnicity, gender, experience, practice setting, and geographic location. Representatives from organizations and professional societies with related interests and expertise are also invited to serve on the task force.

Methodology—ASTRO's task force uses evidence-based methodologies to develop guideline recommendations in accordance with the National Academy of Medicine standards.[1,2] The evidence identified from key questions (KQs) is assessed using the **P**opulation, **I**ntervention, **C**omparator, **O**utcome, **T**iming, **S**etting (PICOTS) framework. A systematic review of the KQs is completed, which includes creation of evidence tables that summarize the evidence base task force members use to formulate recommendations. Table 1 describes ASTRO's recommendation grading system. See Appendix E2 in Supplementary Materials for a list of abbreviations used in the guideline.

Consensus Development—Consensus is evaluated using a modified Delphi approach. Task force members confidentially indicate their level of agreement on each recommendation based on a 5-point Likert scale, from "strongly agree" to "strongly disagree". A prespecified threshold of ≥75% (≥90% for expert opinion recommendations) of raters who select "strongly agree" or "agree" indicates consensus is achieved. Recommendation(s) that do not meet this threshold are removed or revised. Recommendations edited in response to task force or reviewer comments are resurveyed before submission of the document for approval.

Annual Evaluation and Updates—Guidelines are evaluated annually beginning 2 years after publication for new, potentially practice-changing studies that could result in a guideline update. In addition, ASTRO's Guideline Subcommittee will commission a replacement or reaffirmation within 5 years of publication.

Table 1 ASTRO recommendation grading classification system

ASTRO's recommendations are based on evaluation of multiple factors including the QoE and panel consensus, which, among other considerations, inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments.

Strength of Recommendation	Definition	Overall QoE Grade	Recommendation Wording
Strong	• Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. • All or almost all informed people would make the recommended choice.	Any (usually high, moderate, or expert opinion)	"Recommend/ Should"
Conditional	• Benefits are finely balanced with risks and burden, or appreciable uncertainty exists about the magnitude of benefits and risks. • Most informed people would choose the recommended course of action, but a substantial number would not. • A shared decision-making approach regarding patient values and preferences is particularly important.	Any (usually moderate, low, or expert opinion)	"Conditionally Recommend"

Overall QoE Grade	Type/Quality of Study	Evidence Interpretation
High	• 2 or more well-conducted and highly generalizable RCTs or meta-analyses of such trials.	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.
Moderate	• 1 well-conducted and highly generalizable RCT or a meta-analysis of such trials **OR** • 2 or more RCTs with some weaknesses of procedure or generalizability **OR** • 2 or more strong observational studies with consistent findings.	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.
Low	• 1 RCT with some weaknesses of procedure or generalizability **OR** • 1 or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes **OR** • 2 or more observational studies with inconsistent findings, small sample sizes, or other problems that potentially confound interpretation of data.	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.
Expert Opinion*	• Consensus of the panel based on clinical judgment and experience, due to absence of evidence or limitations in evidence.	Strong consensus (≥90%) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect. Further research may better inform the topic.

Abbreviations: ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCTs = randomized controlled trials.

*A lower quality of evidence, including expert opinion, does not imply that the recommendation is conditional. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials, but there still may be consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden.

ASTRO's methodology allows for use of implementation remarks meant to convey clinically practical information that may enhance the interpretation and application of the recommendation. Although each recommendation is graded according to recommendation strength and QoE, these grades should not be assumed to extend to the implementation remarks.

1. Introduction

Although squamous cell carcinoma (SCC) of the anal canal is a rare malignancy, its incidence has steadily increased over the past 2 decades. The highest incidence of anal cancer occurs in black males and white females, who also experience the highest disease-related mortality rates.[3] Similarly, mortality rates from anal cancer have increased, notably in patients age ≥50 years.[3,4] The incidence of anal cancer in younger patients has also increased, including a significant increase in patients presenting with more advanced disease.[3] The development of anal cancer is largely associated with the human papillomavirus (HPV), which has been detected in nearly 90% of all cases.[5] Immunosuppressed patients, including those with human immunodeficiency virus (HIV), have an approximately 19-fold increased risk of developing anal cancer relative to the general population.[6] Additionally, there is a nearly 5-fold higher risk in young black men.[3]

Anal cancer is unique among gastrointestinal cancers given its low propensity for metastatic spread, with most patients presenting with locoregional disease. Although historically treated with radical surgery using abdominoperineal resection with resultant permanent colostomy, the contemporary treatment of anal cancer with combined chemoradiation now serves as a model for organ-preserving therapy, with most patients able to avoid a permanent colostomy. Chemoradiation is now established as the primary treatment strategy for most patients, based on results of multiple randomized controlled trials (RCTs) conducted over the past 3 decades.[7-12] However, chemoradiation is associated with significant acute and chronic toxicity rates and attempts to de-escalate therapy, namely through elimination of concurrent systemic therapies, have resulted in inferior disease-related outcomes.[7-9,13] Similarly, attempts at improving outcomes with therapeutic escalation (ie, neoadjuvant chemotherapy alone before combined chemoradiation, adjuvant chemotherapy after chemoradiation, and radiation therapy [RT] dose escalation) have not yet resulted in improved disease-related outcomes.[10-12,14] Despite this, technical advances in RT delivery have improved toxicity rates.[15] This ASTRO guideline clarifies standard of care therapy and surveillance for patients with locoregional anal cancer.

2. Methods

2.1. Task force composition

The task force consisted of a multidisciplinary team of radiation, medical, and surgical oncologists; a medical physicist; and a patient representative. This guideline was developed in collaboration with the American Society of Clinical Oncology (ASCO) and the Society of Surgical Oncology, who provided representatives and peer reviewers.

2.2. Document review and approval

The guideline was reviewed by XX official peer reviewers (Appendix E1) and revised accordingly. The modified guideline was posted on the ASTRO website for public comment from XX to XX/XXXX. The final guideline was approved by the ASTRO Board of Directors and endorsed by the TBD.

2.3. Evidence review

In May 2022, ASTRO and ASCO jointly developed and submitted a proposal for the Agency for Healthcare Research and Quality (AHRQ) to develop a comparative effectiveness evidence review for adults with stages I-III squamous cell anal cancer (including the anal canal and anal margin [perianal skin]), which was accepted and funded by the Patient-Centered Outcomes Research Institute (PCORI).[16] This independent literature review and analysis prepared by the University of Minnesota Evidence-Based Practice Center aimed to support 2 complementary guidelines from ASTRO and ASCO. AHRQ performed a systematic search of the databases Ovid MEDLINE, Embase, Cochrane Register of Controlled Trials, and ClinicalTrials.gov. The inclusion criteria incorporated RCTs, nonrandomized study of interventions, observational cohorts with concurrent comparator, interrupted time-series, and other experimental designs using appropriate analytic techniques published between January 2000 to May 2023 and updated on March 4, 2024. Supplemental bibliographic database searches with citation searching of relevant systematic reviews and original research were also performed, from which all eligible studies regardless of publication date were included resulting in 3 additional studies. In total, 32 studies were included for data abstraction. For details on the AHRQ methodology and systematic review explanation, including the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing the number of articles screened, excluded, and included in the evidence review, see the AHRQ systematic review report.[16]

AHRQ's methodology required specific criteria to include studies and perform a comparative effectiveness evidence review. Even practice-defining studies including secondary analyses of RCTS were excluded due to the perceived risk of bias. As a result, the AHRQ methodology generated statements sometimes deemed to be incongruent with clinical practice and was not fully able to provide guidance on treatment planning to maximize treatment efficacy and minimize toxicity. Therefore, in the generation of this guideline, the task force evaluated outcomes (eg, quality of life) of studies that were part of the systematic review but were excluded by AHRQ's methodology during abstract screening. This resulted in the inclusion of 41 additional studies for review. These studies include prospective studies and retrospective studies with ≥50 patients.

The additional data used by the task force to formulate recommendations are summarized in evidence tables available in Supplementary Materials, Appendix E4. References selected and published in this document are representative and not all-inclusive. Additional ancillary articles not in the evidence tables are included in the text; these were not used to support the evidence-based recommendations but may have informed expert opinion.

2.4. Scope of the guideline

The scope of this guideline is focused on adult patients with stages I-III squamous cell anal cancer (including the anal canal and anal margin, defined as cancers arising in the perianal skin within a 5 cm radius of the anal verge). This guideline addresses the indications for RT, systemic therapy, and surgery and provides recommendations for RT treatment planning. Furthermore, it summarizes recommendations for response assessment and follow up. ASCO has developed a complementary guideline (with ASTRO participation) based on the AHRQ systematic review which focuses on systemic therapy; thus, this topic is only covered briefly in the current guideline. See the ASCO anal cancer guideline for details on these subjects.(pending publication-ref)

The key outcomes of interest are oncologic results including overall survival, disease-free survival (DFS), local control, colostomy-free survival, acute and late toxicity, and quality of life. The topics covered in this guideline are specified in the KQs (Table 2). Outside the scope of this guideline are many other important questions that may be the subjects of other guidelines, including indications, dose and technique for adjuvant therapy, RT in the setting of oligometastatic disease, reirradiation for locally recurrent disease or other prior pelvic malignancy, palliative RT, contact RT, intraoperative RT, and detailed discussions of surgical approaches and chemotherapy regimens. Disparities were evaluated as an outcome, but data were limited.

Table 2 KQs in PICO format

KQ	Population	Intervention	Comparator	Outcomes
1	**For adult patients with localized anal cancer, what are the appropriate indications for RT, systemic therapy, or surgery?**			
	Adults with stages I-III squamous cell anal cancer (anal margin and anal canal)	• Surgery • RT, or • Chemotherapy Alone or in combination as neoadjuvant/induction, definitive or adjuvant/maintenance	Same as intervention	• Overall survival • Disease-specific survival • Disease-free survival • Colostomy-free survival • Local control • Complete clinical response • Sphincter preservation • Health-related quality of life • Treatment breaks (frequency or duration), treatment discontinuation, interruptions, or median treatment days

				• Functional outcomes (eg, fecal or urinary incontinence, erectile or sexual dysfunction) • Treatment harms (acute and late toxicity)
2	**For adult patients with localized anal cancer, what are the appropriate RT treatment techniques?**			
	Same as KQ1	RT treatment (eg, IMRT, proton therapy, brachytherapy)	Comparators for different RT modalities (eg, 3-D CRT, photon or electron RT, EBRT)	Same as KQ1
3	**For adult patients with localized anal cancer, what are the appropriate RT dose-fractionation regimens, target volumes, and dose constraints?**			
	Same as KQ1	• Doses • Target (primary and nodal) volumes • Fractionation regimen	Same as intervention	Same as KQ1
4	**For adult patients with localized anal cancer, what are the appropriate surveillance strategies after definitive chemoradiation?**			
	Same as KQ1	Posttreatment surveillance: • Frequency • Modalities (eg, MRI, PET, DRE, anoscopy, flexible sigmoidoscopy, biopsy)	Same as intervention	Same as KQ1

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; DRE = digital rectal examination; EBRT = external beam radiation therapy; IMRT = intensity modulated radiation therapy; KQs = key questions; MRI = magnetic resonance imaging; PET/CT = positron emission tomography/computed tomography; PICO = Population, Intervention, Comparator, Outcome; RT = radiation therapy.

3. Key Questions and Recommendations

3.1. KQ1: Indications for RT, systemic therapy, or surgery (Table 3)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ1.

For adult patients with localized anal cancer, what are the appropriate indications for RT, systemic therapy, or surgery?

Table 3 Indications for RT, systemic therapy, or surgery

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with newly diagnosed anal cancer, definitive treatment with chemoradiation using combined 5-FU plus MMC is recommended. Implementation remark: Consider diversion surgery before definitive treatment for patients with significant symptoms.	Strong	High 7-11,13,14

2. For patients with anal cancer, 5-FU plus cisplatin with RT is conditionally recommended as an alternative to 5-FU plus MMC with RT.	Conditional	Moderate [11,17]
3. For patients with anal cancer undergoing definitive chemoradiation, capecitabine is recommended as an alternative to 5-FU.	Strong	Low [18-20]
4. For select patients with T1N0 anal canal and T1-2N0 anal margin cancer, local excision is conditionally recommended if surgical margins and functional status are not compromised. Implementation remark: Consider for tumors without high-risk histologic features which can be excised with adequate margins without compromise of anal sphincter function.	Conditional	Low [21-24]

Abbreviations: 5-FU = 5-Fluorouracil; KQ = key question; MMC = mitomycin; RT = radiation therapy.

Historically, patients with localized anal cancer were treated with abdominoperineal resection with a high locoregional failure rate and high morbidity associated with permanent colostomy.[25] In 1974, preoperative RT with 5-Fluorouracil (5-FU) and mitomycin (MMC) was shown to have significant response rates and provided a rationale to investigate this approach as an effective alternative to surgery.[26]

Several studies have indicated that chemoradiation, compared with RT alone, improves DFS, locoregional failure rate, and colostomy-free survival with no significant difference in overall survival.[7,8,13] In the European Organisation for Research and Treatment of Cancer (EORTC) trial comparing 5-FU and MMC chemoradiation to RT alone, patients in the chemoradiation arm had an 18% higher rate of locoregional control at 5 years and a 32% higher rate of achieving colostomy-free status.[8] The ACT I (United Kingdom Co-ordinating Committee on Cancer Research Anal Cancer Trial) confirmed that the 5-FU and MMC chemoradiation arm was more effective for locoregional disease control versus RT alone.[7] Although neither study showed an overall survival benefit, a 13-year follow-up to ACT I indicated that for every 100 patients treated with chemoradiation, there are an expected 25.3 fewer patients with locoregional relapse and 12.5 fewer anal cancer deaths compared with RT alone.[13] Further, the addition of MMC to 5-FU improved DFS, colostomy-free survival, and locoregional failure rate. The Radiation Therapy Oncology Group (RTOG) 8704 trial (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) revealed that patients receiving 5-FU and MMC compared with 5-FU alone with RT had a higher 4-year DFS (73% versus 51%) and lower colostomy rate (9% versus 22%), with no differences in overall survival.[9] Based on this high-quality data, chemoradiation using combined 5-FU and MMC as the definitive treatment for localized anal cancer is recommended.

Surgical diversion may be considered before definitive treatment for patients with significant symptoms (eg, fistula or incontinence that may compromise completion of definitive treatment). There currently is no role for routine induction or maintenance chemotherapy.[10-12,14] Further, the increased treatment duration with induction therapy may be associated with a higher risk of locoregional failure.[27] For special populations including elderly patients[28] and patients with HIV, there is insufficient evidence for de-escalating chemoradiation.

Using cisplatin instead of MMC likely results in no difference in outcomes. One RCT found no significant difference in overall survival, DFS, distant metastasis rate, and complete response rate with cisplatin instead of MMC, although the study was not powered to test noninferiority of cisplatin versus MMC.[11] Although RTOG 9811 (Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal)[14] found a higher 5-year cumulative rate of colostomy for the cisplatin arm (10% versus 19%), ACT II (A randomised trial of chemoradiation using combination 5FU/mitomycin or 5FU/cisplatin, with or without maintenance cisplatin/5FU in squamous cell carcinoma of the anus) did not.[17] The long-term update of RTOG 9811 did show improved 5-year DFS and overall survival in the MMC arm.[10] However, it is important to note that the cisplatin arm on RTOG 9811 also included induction chemotherapy, which may have impacted these results. Both RTOG 9811 and ACT II found more acute hematologic toxicity with MMC, but no significant differences in overall rates of acute and late toxicities.[11,14] Finally, large retrospective series show favorable outcomes using cisplatin instead of MMC.[29] Based on this moderate-quality evidence, cisplatin is conditionally recommended as an alternative to MMC.[11,17]

Capecitabine is a safe and efficacious substitute for 5-FU for rectal cancer.[30] In anal cancer, data are limited to 3 retrospective studies which found no significant differences in overall survival, DFS, colostomy-free survival, local failure, distant metastasis, or complete response rates between capecitabine and 5-FU.[18-20] Additionally, 1 of these studies found lower grade 3-4 hematologic toxicities with capecitabine.[19] Capecitabine may be more practical in terms of ease of administration by avoiding the use of long-term indwelling catheters and infusion pumps and requires fewer clinic visits. Thus, capecitabine is recommended as an alternative to 5-FU.[18-20]

There has been a significant increase in use of local excision for T1N0 anal canal cancer over time.[21] Local excision may be an alternative definitive treatment approach to chemoradiation, with potentially less treatment morbidity, for select patients. However, the evidence is insufficient to determine comparative toxicities and effectiveness in relation to survival and colostomy-free outcomes between local excision and chemoradiation. Three database studies retrospectively compared local excision with chemoradiation for stage I anal cancer.[21-23] Although these studies found no differences in overall and cause-specific survival between local excision and chemoradiation, they all had serious or critical deficiencies in quality. For example, in 1 study, patients with more favorable prognostic characteristics (eg, smaller and well-differentiated tumors)

were more likely to undergo local excision.[22] Another study compared local excision alone versus local excision followed by RT or chemoradiation in patients with T1-2N0 anal margin and anal canal cancers and found that locoregional control and survival were significantly better among patients receiving adjuvant therapy.[24] Although this study has similar limitations inherent to its retrospective nature, it does raise concern whether local excision may be inadequate treatment for some early-stage disease.

Local excision for select patients with early T-stage anal margin (T1-2N0) and anal canal (T1N0) cancer without high-risk features (eg, poor differentiation, lymphovascular invasion, or perineural invasion) is conditionally recommended if acceptable margins (≥2 mm for anal canal cancer and ≥1 cm for anal margin cancer) and functional status are achieved.[21-24] Superficially invasive SCC is defined as anal cancer <7 mm that has been completely excised, with <3 mm basement membrane invasion, and its incidence is rising incidence given increased screening.[31,32] Patients with early-stage anal cancer who do not meet these criteria for superficially invasive disease or have high-risk histological features may be considered for chemoradiation. Further, patients with biopsy-proven anal cancer should have staging with physical exam and cross-sectional imaging before considering local excision as definitive treatment. A shared decision-making approach, considering patient preferences, treatment goals, and potential benefits and risks of local excision versus chemoradiation, and careful surveillance are necessary.

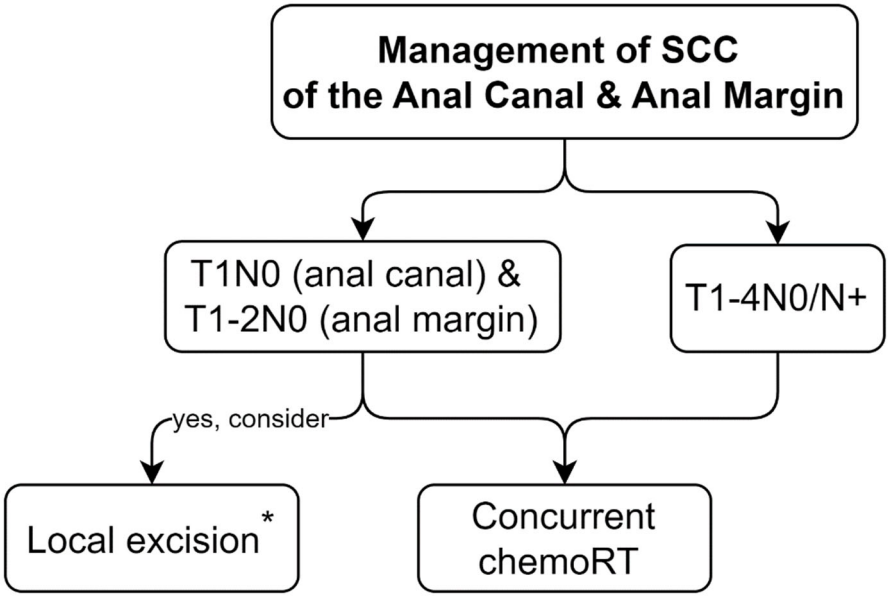

Figure 1 Management of SCC of the Anal Canal and Anal Margin

Abbreviations: chemoRT = chemoradiation; SCC = squamous cell carcinoma

*Local excision is appropriate if no higher risk histologic features are present (ie, poorly differentiated, lymphovascular or perineural invasion) and tumor can be excised with adequate margins (≥2mm for anal canal cancer and ≥1 cm for anal margin cancer) without compromise of the adjacent sphincter muscles.

3.2. KQ2: Appropriate RT treatment techniques (Table 4)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ2.

For adult patients with localized anal cancer, what are the appropriate RT treatment techniques?

Table 4 Appropriate RT treatment techniques

KQ2 Recommendation	Strength of Recommendation	Quality of Evidence (Ref)
1. For patients with anal cancer receiving EBRT, IMRT is recommended.	Strong	Moderate [15]

Abbreviations: KQ = key question; RT = radiation therapy; EBRT = external beam radiation therapy; IMRT = intensity modulated radiation therapy.

Conventional external beam radiation therapy (EBRT) techniques typically use 2 or 4 static photon fields with or without electron fields to treat the anal canal and at-risk lymph nodes. Planning is based on bony anatomy (2-dimensional [2-D] RT) or volumetric computed tomography (CT) imaging (3-D CRT). Combined modality therapy using conventional EBRT approaches is associated with significant acute and late morbidity.[11,14] Intensity modulated radiation therapy (IMRT) is a modern photon therapy technique that uses multiple (typically ≥5) modulated beams or volumetric modulated arc therapy (VMAT). Compared with conventional EBRT, IMRT delivers a more conformal dose distribution resulting in improved sparing of adjacent organs, potentially reducing the risk of acute and late morbidity.[15]

There are no RCTs comparing IMRT to conventional RT for definitive treatment of anal canal SCC. A multicenter phase 2 prospective trial (NRG/RTOG 0529) evaluated the use of IMRT (5040-5400 cGy in 28-30 fractions) with 5-FU and MMC in 52 patients with anal canal SCC.[15,33] Outcomes were compared with patients treated with conventional RT on a prior trial.[14] Grade 3 or higher acute dermatologic and gastrointestinal adverse events were modestly lower with IMRT compared with conventional RT. Survival and disease control outcomes at 5 years were similar with IMRT versus conventional RT.[15] Several retrospective comparative studies using single institutional datasets[34-38] or registry data[39-42] support potential benefit of IMRT versus conventional RT, although these studies are limited by heterogeneity in staging studies (use of PET-CT) and chemotherapy regimens. Potential benefits of IMRT include improved chemotherapy compliance,[41] reduced treatment breaks,[40-42] reduced hospitalization rates,[39,41] improved bowel and sexual function,[37] reduced local recurrence,[35] improved colostomy-free survival,[40] and improved survival.[38,39,42] When IMRT is used, daily image guidance is encouraged to verify target localization as standard practice.

Brachytherapy involves placing radioactive sources in or adjacent to an anal canal tumor, creating steep dose gradients that can deliver high doses to targets while minimizing dose to normal tissues. For definitive treatment of anal cancer, brachytherapy has primarily been used as a boost modality in conjunction

with standard EBRT. Brachytherapy has not been prospectively compared with EBRT for anal cancer and published retrospective series have not demonstrated a clear benefit of brachytherapy compared with EBRT.[36,40,43-47] For example, a pooled analysis did not demonstrate a statistically significant improvement in clinical outcomes with the use of brachytherapy.[45] Accordingly, there is insufficient evidence to support a recommendation for or against the use of brachytherapy for anal cancer.

Proton beams deposit their energy at defined depths and enable a low radiation entry dose and no exit dose, producing a favorable dose distribution when compared with IMRT, which might reduce treatment-related morbidity. In a multicenter, retrospective comparison of patients treated with photon IMRT and intensity modulated proton therapy, there was no significant difference between treatment groups in grade 3 or greater acute toxicity (IMRT, 68%; intensity modulated proton therapy, 67%) or 2-year overall grade 3 or greater late toxicity (IMRT, 3.5%; intensity modulated proton therapy, 1.8%).[48] Moreover, there was no significant difference in 2-year progression-free survival. Notably, RT techniques and chemotherapy protocols varied in this retrospective data set. A prospective multi-institutional single-arm pilot study (*NCT01858025*) evaluated definitive concurrent chemoradiation using pencil beam scanning proton beam in 25 patients with clinically staged T1-4, N0-3 anal canal cancers.[49] The reported rates of grade 2+ acute toxicities were similar to those reported with photon IMRT on RTOG 0529.[33] Available data do not support a recommendation for or against the use of proton therapy for anal cancer, although there may be a role for reirradiation, or when organs at risk dose constraints cannot be met with photon IMRT.

3.3. KQ3: Appropriate RT dose-fractionation regimens, target volumes, and dose constraints (Table 5)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ3.

For adult patients with localized anal cancer, what are the appropriate RT dose-fractionation regimens, target volumes, and dose constraints?

Table 5 Appropriate RT dose-fractionation regimens, target volumes, and dose constraints

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
Primary Tumor		
1. For patients with T1-T2 anal cancer, a dose of 4500-5040 cGy in 25-28 fractions to the primary tumor is recommended. Implementation remark: In patients with tumors ≥4 cm or lymph node-positive disease, a higher dose to the primary tumor may be considered.	Strong	High 12,14,15,50
2. For patients with T3-4 anal cancer, a dose of 5320-5940 cGy in 28-33 fractions to the primary tumor is recommended.	Strong	High 11,14,15,34,50

Lymph Nodes		
3. For patients with anal cancer, inclusion of the primary tumor with margin, the anal canal, rectum, mesorectal nodes, presacral nodes, external/internal iliac nodes, obturator nodes, and inguinal nodes in the CTV is recommended.	Strong	High [7-9,11,13-15,19,47,51]
4. For patients with node-negative anal cancer receiving a sequential RT boost, 3600 cGy in 180 cGy per fraction to entire elective (uninvolved) nodal volume, with or without an additional 900 cGy boost in 180 cGy per fraction to a smaller elective nodal volume that encompasses the true pelvis, is recommended.	Strong	High [7-9,11,13-15,19]
5. For patients with node-positive anal cancer receiving a sequential RT boost, the following is recommended: • 3600 cGy in 180 cGy per fraction to entire elective (uninvolved) nodal volume, AND • 4500 cGy in 180 cGy per fraction to a smaller elective nodal volume that encompasses the true pelvis and positive lymph node regions, AND • 5040-5400 cGy in 180 cGy per fraction to positive lymph nodes.	Strong	High [7-9,11,13-15,19]
6. For patients with anal cancer receiving an integrated RT boost, the following is recommended: • 4000-4200 cGy in 28 fractions or 4500 cGy in 30 fractions to elective (uninvolved) nodal volume, AND • 5040-5400 cGy in 28-30 fractions to clinically positive lymph nodes.	Strong	Moderate [15,50]
Timing		
7. For patients with anal cancer, avoiding extension of overall treatment time for chemoradiation by more than 4 days is conditionally recommended to improve progression-free survival.	Conditional	Moderate [52]

Abbreviations: CTV = clinical target volume; KQ = key question; RT = radiation therapy.

A range of doses to treat the primary tumor have been used in clinical trials. Patients with early-stage anal cancer have been included with those with advanced-stage disease in RCTs, and the most commonly prescribed dose is 4500 to 5040 cGy in 25 to 28 fractions.[9-11,14,33] RTOG 8704[9] and RTOG 9811[14] both specified 4500 cGy be delivered for T1-2 or T2 tumors, respectively, and an additional RT boost was reserved for those with residual tumors at the end of treatment. On RTOG 8704, 70% of patients did not receive a boost and 4-year colostomy failure for patients with stage T1-2 anal cancer receiving chemoradiation with MMC was excellent at 8%.[9] On RTOG 9811,[14] approximately 40% of patients with T2 anal cancer did not receive a boost and 5-year locoregional failure was 10% for T2N0 cases randomized to the MMC arm.[10] Other studies also demonstrate excellent results for patients with early-stage anal cancer receiving 5040 cGy including ACT II[11]

(which enrolled stage T1-2) and RTOG 0529[33] (which enrolled stage T2) with 3-year progression-free survival of 81% and locoregional failure of 5%, respectively. There is currently not sufficient data to guide selection of dose based on T1 versus T2 stage.

T2 tumors >4 cm may be at higher risk of locoregional failure, which is why these were excluded from the current de-escalation trials including ACT 4 (ISRCTN88455282) and DECREASE (Lower-dose chemoradiation in treating patients with early-stage anal cancer [*NCT04166318*]) based on the association between tumor size and colostomy failure in a Danish multicenter cohort study.[53] In this study, tumors ≥6 cm were associated with a 4-fold higher risk of colostomy compared with tumors <4 cm. In addition, tumors 4 to 6 cm had a 2-fold higher rate of colostomy failure compared with tumors <4 cm. In this study 70% of patients received RT without concurrent chemotherapy.[53] It is unknown whether patients with T2 tumors >4 cm would benefit from RT doses higher than 4500 to 5040 cGy in the setting of concurrent chemotherapy (summary in Table 6).

For patients with T3-4 primary tumors, the most commonly prescribed dose is 5320 to 5940 cGy in 28 to 33 fractions. RTOG 0529 delivered 5400 cGy delivered to the primary gross tumor.[33] Meanwhile, RTOG 9811 allowed a range of 5500 to 5900 cGy to be prescribed for patients with T3-4 primary tumors.[14] Some studies have used a lower dose (ie, 5040 cGy),[11] but current practice is ≥5320 cGy.[50] Early randomized studies delivered 6000 cGy to the primary tumor, but this approach is now considered suboptimal given the boost was delivered 6 weeks after the initial phase of radiation to the whole pelvis.[8,13] However, there is no evidence to support dose escalation beyond 6000 cGy. For example, the ACCORD-03 (Induction chemotherapy and dose intensification of the radiation boost in locally advanced anal canal carcinoma) trial evaluated 6000 cGy versus 6500 to 7000 to 7500 cGy and did not show any difference in 5-year colostomy-free survival (74% versus 78%).[12] The chemoradiation regimen used in this study was suboptimal in that some patients also received induction chemotherapy and all patients underwent a scheduled treatment break. We await results of the ACT 5 trial [*ISRCTN88455282*] which randomized patients with advanced anal cancer to 5320 cGy, the current standard dose in the UK,[50] versus 5880 to 6160 cGy in 28 fractions to the primary tumor without a planned treatment break. Given these data, a dose of 5320 to 5940 cGy is recommended for patients with T3-4 tumors with higher doses typically reserved for larger tumors.[12,14,15,34,50]

There are limited data comparing sequential boost with SIB technique, so recommendations for one technique over the other were not made.[54-57] Overall, studies conclude that SIB allows shorter overall treatment duration. Additionally, toxicity appears similar or improved with SIB. From a treatment planning perspective, there are studies for other treatment sites (eg, gynecological and head and neck cancers), that show improved conformality and lower organs at risk doses with an SIB approach compared with sequential boost approach.[58-61]

Modern, prospective clinical trials in anal cancer, including a phase II study[15] and 3 phase III studies[9,11,14] all target the anal canal, rectum, mesorectal nodes, presacral nodes, external/internal iliac nodes,

obturator nodes, and inguinal nodes in the elective clinical target volume (CTV). Among these studies, RTOG 8704 and ACT II included patients with T1-T2 tumors as well as T3-T4 cancers.[9,17] Some early phase III clinical trials[8,13] only irradiated the inguinal region if there were positive inguinal nodes. However, it is now generally accepted to include the inguinal region for all patients given the target volumes in more modern studies.[9,11,14,15,17] Two retrospective studies have directly addressed this question and found there is a risk of inguinal recurrence without elective RT.[47,51] These studies, one including patients with T2N0[47] and the other including patients with T1-4N0-1 anal cancer,[51] both demonstrated higher rates of inguinal recurrence among patients who do not (10%-16%) versus do (≤2%) undergo elective inguinal irradiation. These results are similar to the prospective Trans-Tasman Radiation Oncology Group (TROG) 99.02 trial, which reported an inguinal failure rate of 23% among 40 patients with T1-2N0 anal cancer who did not undergo inguinal irradiation.[62]

The optimal superior extent of the elective nodal CTV has not been directly studied. Reasonable options for the superior border of the RT field include 2 cm above the sacroiliac joint following the approach used in ACT II or the junction of L5-S1 following RTOG 9811.[10,11,14] It is also reasonable to include the superior aspects of the internal/external iliac or common iliac nodal regions in the elective CTV for cases with advanced nodal stage (ie, multiple nodes or external iliac nodal involvement), but specific studies and recommendations addressing this question are beyond the scope of this guideline.[63,64]

The 2 largest RCTs in anal cancer include ACT II and RTOG 9811, which resulted in excellent locoregional disease control and form the basis of modern RT recommendations for anal cancer.[11,14] These studies used a RT sequential boost technique with a shrinking-field approach. However, the studies were conducted in the era of 2-D or 3-D RT with dose prescribed to a point and large boost fields, so the actual doses received by the elective nodal volume is difficult to determine. Therefore, it is necessary to estimate what doses might have been received by the elective nodal volumes in these historical studies. In the ACT II study, all elective nodal regions were prescribed 3060 cGy in 17 fractions using anterior-posterior/posterior-anterior fields with dose prescribed to midplane. A reduced CTV + planning target volume (PTV) margin of 3 cm around the primary tumor and involved lymph nodes was used and both were boosted to a total of 5040 cGy in 28 fractions.[11] An RT dose analysis of 33 patients treated according to ACT II revealed that the mean dose to the inguinal and internal/external iliac nodal volumes was 3650 and 3420 cGy, respectively, when including both the initial and boost phases of treatment.[65] In RTOG 8704 and RTOG 9811, the elective nodal region between L5 to the bottom of the sacroiliac joint was prescribed 3060 cGy in 17 fractions, the inguinal nodal region was prescribed 3600 cGy in 20 fractions, and the true pelvis below the sacroiliac joint was prescribed 4500 cGy in 25 fractions, followed by a boost to 5400 cGy to the primary tumor and involved lymph nodes.[9,14]

Overall, given the uncertainty of RT doses delivered in the 2-D era with a sequential boost technique and doses prescribed in ACT II and RTOG studies, it seems most appropriate to cover elective nodal volumes to at least 3600 cGy. It is not known whether it is beneficial to treat a subvolume of the elective nodal region to

4500 cGy, as was performed in RTOG 9811.[14] Inclusion of an elective nodal region in the true pelvis (superior border at the bottom of the sacroiliac joint) receiving 4500 cGy for patients with clinically involved nodes given that large boost fields to treat primary tumors and positive nodes that were used in these studies is recommended.[7-9,11,13-15,19]

Clinically involved lymph nodes based on imaging or clinical exam were treated with higher doses of RT: 5040 cGy in 28 fractions in ACT II and ≥5400 cGy in RTOG 9811.[14,17] Of note, the optimal imaging features to define positive lymph nodes is yet to be determined and is outside the scope of this guideline.

RTOG 0529 reported excellent locoregional disease control with IMRT using a simultaneous integrated boost (SIB) technique.[33] For patients with T1-2 N0 cancers, the primary tumor received 5040 cGy and elective nodal volume 4200 cGy, all in 28 fractions. Meanwhile, for patients with T3-4 or N1 cancers, the primary tumor received 5400 cGy, clinically involved lymph nodes received 5040 or 5400 cGy (for nodes <3 cm versus ≥3 cm, respectively), while the elective nodal volume received 4500 cGy, all in 30 fractions.[33]

A retrospective study reviewed 385 patients treated in the United Kingdom (UK) with a standardized approach for IMRT with SIB and reported excellent locoregional disease control.[50] In this study, elective nodal regions received 4000 cGy, while involved lymph nodes <3 cm received 5040 cGy, and involved lymph nodes ≥3 cm received 5320 cGy, all in 28 fractions. This is a promising approach to use a slightly lower RT dose to the elective nodal region but has yet to be confirmed in prospective studies such as the PLATO (Personalising anal cancer radiotherapy dose; *ISRCTN88455282*) trials (Table 6).

Table 6 RT dose and fractionation by T & N stage and approach

Stage	Dose and Fractionation	Approach
Primary Tumor		
T1*	4500-5040 cGy in 25-28 fx	Sequential and integrated boost
T2*	4500-5040 cGy in 25-30 fx	Sequential and integrated boost
T3-4	5320-5940 cGy in 28-33 fx	Sequential and integrated boost
Lymph Nodes		
N0	• 3600 cGy in 20 fx to elective nodal volume • 4500 cGy in 25 fx to true pelvis	Sequential boost
	• 4000-4200 cGy in 28 fx OR 4500 cGy in 30 fx to elective nodal volume	Simultaneous boost
N+	• 3600 cGy in 20 fx to elective nodal volume • 4500 cGy in 25 fx to true pelvis/involved node(s) • 5040-5400 cGy in 28-30 fx to involved node(s)	Sequential boost
	• 4000-4200 cGy in 28 fx OR 4500 cGy in 30 fx to elective nodal volume • 5040 cGy in 28-30 fx to positive node(s) <3 cm • 5320-5400 cGy in 28-30 fx to positive node(s) ≥3 cm	Simultaneous boost

Abbreviations: fx = fractions; RT = radiation therapy.

*In patients with tumors ≥4 cm or lymph node-positive disease, a higher dose (eg, 5400 cGy) to the primary tumor may be considered.

The best data to characterize the association of chemoradiation treatment interruptions on outcomes is ACT II given this trial did not use induction chemotherapy, nor was there a planned break in treatment.[17] A post-hoc analysis of these data demonstrates that extension of overall treatment time >42 days for a planned 28 fraction course of chemoradiation over 38 days was associated with worse progression-free survival and overall survival.[52] Another study using the National Cancer Database demonstrated a cutoff of <4.72 fractions per week (2 missed fractions over 30 treatments) was independently associated with reduced overall survival.[66] Other analyses including pooled data[27] from RTOG 87-04 and 9811 and a population based cohort study[67] were not able to directly demonstrate a decrement in patient outcomes resulting from treatment breaks. However, prolonged total treatment duration (eg, RT with induction chemotherapy) was associated with higher risk of locoregional failure and patients who did not complete RT or chemoradiation had worse outcomes (higher cancer specific death and overall death rates; higher risk of salvage abdominoperineal resection, colostomy). Notably, these studies incorporated planned breaks in between the initial and boost courses of RT or used induction chemotherapy, which extends overall treatment times, so the impact of additional treatment interruptions is difficult to discern.[27]

For patients who have unavoidable treatment interruptions, delivery of 6 fractions per week can be used to avoid >4-day extension in overall treatment time. Delivery of 6 fractions per week, with the 6th fraction given on the weekend or as an extra fraction on a weekday ≥6 hours after the day's first fraction, have been incorporated into many trials for head and neck cancer, another squamous cell cancer where extension of overall treatment time can negatively impact tumor control. This accelerated fractionation regimen has been shown to be well tolerated and may improve tumor control for chemoradiation in head and neck cancer,[68,69] but has not been studied in anal cancer. While no recommendations can be made for planning 6 fractions of RT each week for the entire course of chemoradiation for anal cancer, it is reasonable to use it selectively to avoid significant extensions in overall treatment time, such as is being done in the ongoing DECREASE trial (*NCT04166318*).

The optimal normal tissue radiation dose goals for treatment of anal cancer are an important topic because there is significant risk of short and long-term toxicities resulting from chemoradiation. Published studies on this topic are small, so the quality of evidence is low. The guidance for normal tissue dose goals (Table 7) is based on expert opinion and the available literature.[70-80] For predictors of gastrointestinal toxicity, the volume of small bowel loops receiving 3000 to 4500 cGy has been the metric most predictive of acute grade 2+ diarrhea,[74-76] while multiple studies demonstrate that the volume of total bowel loops (small and large bowel but excluding the rectum) receiving high doses of RT is the most predictive of chronic grade 2 to 3+ GI toxicity.[74-77] Given these data, contouring both large and small bowel loops and minimizing the volume receiving high doses of RT is preferred.

If doses higher than 5400 cGy are to be prescribed for anal cancer, it may be helpful to use bowel dosimetric constraints used for bladder cancer, where there are more data to predict late GI toxicities resulting from higher prescribed doses of chemoradiation (6400 cGy). Studies in bladder cancer demonstrate that the V5500 cGy to all bowel loops is most associated with grade 3+ late GI toxicity, with optimal cutoffs of 90 cc to 115 cc to minimize risk.[81-83]

For genitalia and gluteal cleft acute skin toxicity, 1 study revealed that lower volume of anterior or posterior skin receiving 2000 to 3500 cGy was associated with reduced acute grade 2+ dermatitis.[76] For patients with anal cancer with significant perianal skin involvement, it may be necessary to subtract the PTV from the genitalia or gluteal cleft avoidance structure to create a feasible planning objective.

There are high rates of acute grade 3-4 hematologic toxicity during chemoradiation for anal cancer. Numerous dosimetric studies suggest that the volume of total pelvic bone marrow receiving 1000 to 3000 cGy is most associated with hematologic toxicity.[70-73] Since there does not seem to be a specific threshold, the goal should be to keep the volume receiving these doses as low as reasonably achievable. Although some studies suggest that there may be an anatomic subsite of the pelvic bone marrow with more active marrow such as the lumbosacral spine[71] or which could be defined by PET/CT scans,[84] data are conflicting,[70,73] so there is currently not sufficient evidence to support using dosimetric constraints to subsites of the pelvic bone marrow.

Table 7 Guidance on Normal Tissue Dose Goals

OAR* (Refs)	Contour Definition	Dose Limit Range†	Clinical Endpoint
Bone marrow[70-73]	Entire sacrum, iliac crests, acetabula, and proximal femurs (caudal-most extent should be at the level of the ischial tuberosities).	Mean <2000-3000 cGy V1000 cGy <70-90%	Acute ≥ grade 3 hematologic toxicities
Bowel loops[74-78]	Outermost extent of the individual bowel loops. Superior extent of contours should extend 1 cm beyond superior extent of PTV and continue to the most inferior extend in the pelvis. Small and large bowel should be included, though not the rectum.	V5500 cGy < 0.5-6 cc D0.03 cc <5200-5900 cGy	Late ≥ grade 2-3 GI toxicities
Small bowel loops[74-78]	The contour will include the outer edge of individual small bowel loops.	V3500 cGy <40-150 cc V4500 cGy <20-60 cc D0.03 cc <5000-5600 cGy	Acute and late ≥ grade 2-3 GI toxicities
Bladder[33,77]	Outer bladder wall, treating bladder as a solid organ	D50% <3500-4500 cGy D5% <5000-5600 cGy	Acute cystitis
Genitalia[76]	Male genitalia include the penis and scrotum. Female genitalia include the vulva (superiorly to the level of the pubic symphysis)	D50% <2000-3500 cGy	Acute ≥ grade 2 skin toxicity
Gluteal Cleft[76]	5 mm rind of skin within the cleft and extending laterally 1 cm on either side	D50% <2000-3500 cGy	Acute ≥ grade 2 skin toxicity
Femoral head[79]	Contour femurs down to inferior extent of ischial tuberosities	D50% <3000-4500 cGy D5% <4400-5500 cGy	Late femoral head fracture
Vaginal Wall-PTV‡[33,80]	5 mm rind around a vaginal dilator, not including regions that overlap with PTV	D50% <3000-4000 cGy	Late vaginal stenosis

Abbreviations: GI = gastrointestinal; OAR = organ(s) at risk; PTV = planning target volume; RTOG = Radiation Therapy Oncology Group; cGy = centigray

*Dose ranges are provided to reflect typical achievable doses given variation in tumor extent, and to encourage limiting dose to OARs while preserving adequate target coverage. This table is a combination of evidence-based constraints and expert opinion; assuming 25 to 33 once daily fractions given with or without systemic therapy.

†Typically, early-stage anal cancer cases can meet the lower end of the bowel dose constraint, while advanced-stage cases will meet the higher end of the range.

‡Does not apply in cases with vaginal wall invasion or patients without a dilator.

Women undergoing pelvic RT for anal cancer should be counseled about effects on sexual function. Vaginal stenosis can be a long-term complication among women receiving pelvic RT. In small, retrospective studies, vaginal stenosis occurred in 80% of women after pelvic RT for anal cancer and has been shown to be dose related.[80,85] Physical changes have been well described, including adhesions of the vaginal walls, vaginal narrowing and shortening, pelvic floor dysfunction, and loss of elasticity.[86] A concomitant decrease in vaginal mucosal secretions can cause dyspareunia leading to impaired sexual function, ultimately impacting long-term cancer survivorship and quality of life.[87,88] Most data on sexual function after RT is based on patients receiving treatment for gynecologic malignancies and there is a dearth of prospective data to guide long-term oncology cancer care for women receiving pelvic RT for anal cancer. The use of vaginal dilators has been associated with reduced risk of vaginal stenosis, but compliance can be poor.[89] International guidelines support the routine use of vaginal dilators, but recommendations for timing and duration vary.[90,91] A European panel advised starting dilation approximately 4 weeks posttreatment and to use vaginal dilators 2 to 3 times per week for 1 to 3 minutes for 9 to 12 months.[90] In the United States, radiation oncologists surveyed were most likely to

recommend initiating vaginal dilator use within 6 weeks posttreatment 3 times per week for 5 to 10 minutes for >12 months after RT completion.[92]

There are limited data on sexual toxicity related to treatment for anal cancer in men. While there are data demonstrating the impact of prostate irradiation on erectile function, the dose to the neurovascular bundles and penile bulb are much higher for prostate cancer than anal cancer, so the effect cannot be extrapolated. A few recent retrospective studies of patient reported outcomes in anal cancer survivors included a small number of men and demonstrated that scores for sexual function were within 1 standard deviation of the average for cancer survivors, and 1 study showed a nonsignificant reduction in erectile function as well as decreased ejaculation.[93,94] In a prospective quality of life study of 19 men who have sex with men treated for anal cancer, sexual activity scores were worst right after treatment and at 3 months' follow-up, but improved at 6 and 12 months of follow-up.[95]

3.4. KQ4: Appropriate surveillance strategies following definitive chemoradiation (Table 8)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ4.

For adult patients with localized anal cancer, what are the appropriate surveillance strategies following definitive chemoradiation?

Table 8 Appropriate surveillance strategies following definitive chemoradiation

KQ4 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with anal cancer treated with definitive chemoradiation who have resolving tumors, close monitoring with physical exam including clinical inguinal lymph node exam and DRE with or without anoscopy is recommended for 6 months after chemoradiation, before biopsy or initiation of salvage therapy.	Strong	Moderate [96]
2. For patients with anal cancer treated with definitive chemoradiation, cross-sectional imaging is conditionally recommended as an adjunct to physical exam to assess for a cCR. Implementation remark: Consider chest, abdomen, and pelvis CT and/or pelvic MRI and/or FDG-PET/CT.	Conditional	Low [35,97-100]
3. For patients with anal cancer who achieve a cCR after definitive chemoradiation, surveillance with clinical inguinal lymph node exam and DRE with or without anoscopy is recommended: • every 3 months for years 0-2; • then every 6-12 months for years 2-3; and • optional annual follow-up for years 4-5. Implementation remark: Endoscopy is an alternative option to anoscopy.	Strong	Low [17,101]

4. For patients with anal cancer who achieve a cCR after definitive chemoradiation, surveillance with cross-sectional imaging is recommended a minimum of annually until year 2. Implementation remarks: • Typically, chest, abdomen, and pelvis CT is used. • Consider pelvic MRI and/or FDG-PET/CT for equivocal findings on CT.	Strong	Low [15,96]

Abbreviations: cCR = clinical complete response; CT = computed tomography; DRE = digital rectal examination; FDG-PET/CT = 18 F-fluorodeoxyglucose positron emission tomography/computed tomography; KQ = key question; MRI = magnetic resonance imaging; RT = radiation therapy.

Assessing the response to treatment is critical after chemoradiation for anal cancer. Clinical complete response (cCR) is defined as absence of residual primary and nodal disease.[11] Initial prospective trials included a response assessment 6 weeks after completing chemoradiation, and the presence of residual disease would guide subsequent treatment decision making.[9,13] Depending on the clinical response at these early timepoints, patients would be dispositioned to observation, further RT boost dose, or salvage abdominoperineal resection. Data have shown anal cancer can continue to respond to treatment for up to 6 months post-chemoradiation.[96] The ACT II trial had 3 planned clinical assessments at 11, 18 and 26 weeks after the start of chemoradiation.[96] Although the majority of cCR were documented by week 11, a sizable minority of patients attained cCR at the week 18 or 26 timepoints despite residual disease at week 11. Although only 1 RCT assessed early surveillance to determine cCR, the large size and standardized assessment timepoints led the task force to strongly recommend close monitoring with assessment every 2 to 3 months until approximately 6 months after chemoradiation before biopsy or initiation of salvage therapy.[96] This approach can allow patients to avoid the risks of early biopsy and the morbidities of salvage abdominoperineal resection before the chemoradiation has its full opportunity to induce a cCR. Exceptions to waiting 6 months before initiating salvage therapy can be made in cases of clear clinical progression of the primary tumor or regional lymph nodes.

Once cCR has been established, surveillance visits are recommended approximately every 3 months for the first 2 years, then every 6 to 12 months during years 2 to 3,[101] and optional annual follow-up for years 4 to 5. This recommendation is supported by retrospective data suggesting <1% to 4% of recurrences or late grade 3+ toxicities occur beyond 2 to 3 years postchemoradiation.[101] Additional consideration was given to the surveillance protocols used in RCTs (Table 9). The clinical exam, consisting of digital rectal examination (DRE) and inguinal lymph node exam with or without endoscopic examination is the best strategy to surveil for potential recurrence.[96] Endoscopic examination can increase clinical confidence, but some cooperative group trials do not require endoscopic evaluation and the optimal cadence for this test has differed slightly on trials (*NCT03233711*, *NCT04166318*).[15] The optimal frequency for endoscopy is unknown, but studies have suggested performing every 6 to 12 months until year 2.[17,101] Endoscopic examination may be useful when DRE reveals firm scar tissue, fibrotic ridges, or mucosal depression. The presence of mature scar tissue and the

absence of ulceration or other malignant features can prevent unnecessary biopsies during the surveillance period. In 1 retrospective study evaluating patients after treatment of invasive disease, high-resolution anoscopy was used as surveillance, and high-grade squamous intraepithelial lesions were detected in 13% of patients after chemoradiation and 74% of patients after local excision alone.[102] Endoscopic ultrasound has not demonstrated improved detection of local recurrence compared with DRE and therefore is not generally indicated.[103]

Ongoing clinical trials for patients with anal cancer use varying modalities and frequency of cross-sectional imaging for response assessment and/or during surveillance (*NCT03233711*, *NCT04166318*).[15] Cross-sectional imaging with CT, FDG-PET/CT or pelvic MRI has been optional on most prospective trials[33] but seems to be most useful to establish cCR in involved regional lymph nodes 6 months after treatment completion and to assess for lymph node or distant recurrence during the surveillance period. Advanced imaging of the pelvis may also give additional diagnostic information about the primary tumor when clinical exam findings are equivocal. While most small tumors within the anal canal cannot be reliably evaluated with CT alone, FDG-PET/CT and MRI may provide more information. A retrospective study evaluated the use of 3 and 6 month post-chemoradiation pelvic MRI.[104] A 6-month MRI tumor regression grade of 1 to 2 had a 100% negative predictive value and MRI tumor regression grade of 4 to 5 had a 100% positive predictive value for local progression.[104]

Table 9 Surveillance protocols used in contemporary cooperative group trials

Trial (ref)	Clinical exam (DRE and inguinal nodes)	Endoscopic exam (optional)	CT chest, abdomen, pelvis	Other imaging (MRI or FDG-PET/CT)
RTOG 0529[33]	• Every 3 mo post-chemoRT for year 1 • Every 6 mo post-chemoRT for years 2-3 • Annually for years 4-5	At 1st surveillance visit to establish cCR and then at the discretion of the treating team	At 1st surveillance visit and then annually for 2 y. (After 2 y only if guided by clinical suspicion at the discretion of the treating team)	• Option to use FDG-PET/CT instead of CT at 1st surveillance visit and annually • Option to use pelvic MRI at 1st surveillance visit
ECOG-ACRIN EA2165 (*NCT03233711*)	• Every 3 mo post-chemoRT for years 1-2 • Every 6 mo for years 3-5	Every 6 mo for 2y post-chemoRT	• Every 6 mo for years 1-2 and annually for year 3 • Additional imaging as clinically indicated	FDG-PET/CT is optional and does not replace CT scans
ECOG-ACRIN EA2182 (*NCT04166318*)	• Every 3 mo post-chemoRT for years 0-2 • Every 6 mo for year 3 • Annually for years 4-5	At 6, 12, 24, and 36 mo post-chemoRT	Annually for years 1-3 post-chemoRT	• MRI pelvis or FDG-PET/CT optional at 3 and 6 mo post-chemoRT • MRI can replace CT for annual imaging of the abdomen and pelvis

Abbreviations: CAP = chest, abdomen, pelvis; chemoRT = chemoradiation; cCR = clinical complete response; CT = computed tomography; DRE = digital rectal examination; ECOG-ACRIN = Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network; FDG-PET = fluorodeoxyglucose positron emission tomography; MRI = magnetic resonance imaging; RTOG = Radiation Therapy Oncology Group.

4. Conclusions and Future Directions

Anal cancer is highly curable, but treatment is multidisciplinary and highly individualized based on tumor stage. Thus, it is critical to understand detailed best practices and their supporting evidence to avoid both under-treating resulting in suboptimal cancer-related outcomes, and over-treating which can unnecessarily increase toxicity. This guideline includes recommendations based on level I evidence when available, but given the rarity and heterogeneity of this disease, this task force evaluated and distilled additional data as well, in a pragmatic effort to provide clear guidance for radiation oncologists who must make treatment decisions for their patients.

Current general investigational strategies for patients with locoregional disease being tested in cooperative groups include treatment de-escalation in early-stage patients (*NCT04166318*) and treatment escalation with in Nivolumab advanced patients (*NCT03233711*). The DECREASE trial (*NCT04166318*) also aims to validate imaging features of lymph nodes at low risk for cancer involvement by size, morphologic and metabolic criteria.

With the goal of decreasing toxicity for all patients, adaptive RT is a potential treatment strategy leveraging MRI or CT-based platforms that involves adjusting the daily RT plan based on patient-specific anatomic changes. As the tumor shrinks, the clinical and planning target volumes or organs at risk can be adjusted, potentially allowing for reduced margins and decreased toxicities compared with conventionally planned photon IMRT. An ongoing 20-patient pilot study is examining the feasibility of daily CT-based dose-adapted RT for the treatment of locally advanced anal cancer (*NCT05838391*).

There is still much work to be done to better optimize tumor and functional outcomes for all patients, including those with advanced age or HIV. Furthermore, optimizing rehabilitation for anal and vaginal function will be critical areas of emphasis in the coming years, with the goal of improving both quantity and quality of life for these patients.

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References

1. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. In: Graham R, Mancher, M, Miller Wolman, D, et al. *Clinical Practice Guidelines We Can Trust.* Washington (DC): National Academies Press (US); 2011.
2. Institute of Medicine (US) Committee on Standards for Systematic Reviews of Comparative Effectiveness Research; Eden J LL, Berg A, et al. *Finding What Works in Health Care: Standards for Systematic Reviews.* Washington (DC): National Academies Press (US); 2011.
3. Deshmukh AA, Suk R, Shiels MS, et al. Recent Trends in Squamous Cell Carcinoma of the Anus Incidence and Mortality in the United States, 2001-2015. *J Natl Cancer Inst.* 2020;112(8):829-838.
4. Cancer Stat Facts: Anal Cancer. National Cancer Institute. https://seer.cancer.gov/statfacts/html/anus.html. Published 2023. Accessed 2024.
5. Grulich AE, Poynten IM, Machalek DA, Jin F, Templeton DJ, Hillman RJ. The epidemiology of anal cancer. *Sex Health.* 2012;9(6):504-508.
6. Colon-Lopez V, Shiels MS, Machin M, et al. Anal Cancer Risk Among People With HIV Infection in the United States. *J Clin Oncol.* 2018;36(1):68-75.
7. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research. *Lancet.* 1996;348(9034):1049-1054.
8. 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(5):2040-2049.

9. 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(9):2527-2539.
10. 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(35):4344-4351.
11. 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. *The Lancet Oncology.* 2013;14(6):516-524.
12. Peiffert D, Tournier-Rangeard L, Gerard J-P, 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(1):1941-1948.
13. 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(7):1123-1128.
14. 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(1):1914-1921.
15. Kachnic LA, Winter KA, Myerson RJ, et al. Long-Term Outcomes of NRG Oncology/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 Anal Canal Cancer. *Int J Radiat Oncol Biol Phys.* 2022;112(1):146-157.
16. Troester A, Parikh R, Southwell B, et al. Treatment of Stages I-III Squamous Cell Anal Cancer: A Comparative Effectiveness Systematic Review. *JNCI: Journal of the National Cancer Institute.* 2024.
17. Glynne-Jones R, Kadalayil L, Meadows HM, et al. Tumour- and treatment-related colostomy rates following mitomycin C or cisplatin chemoradiation with or without maintenance chemotherapy in squamous cell carcinoma of the anus in the ACT II trial. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.* 2014;25(8):1616-1622.
18. 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(5):1202-1211.
19. 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(5):1087-1095.
20. Peixoto RDA, Wan DD, Schellenberg D, Lim HJ. A comparison between 5-fluorouracil/mitomycin and capecitabine/mitomycin in combination with radiation for anal cancer. *J Gastrointest Oncol.* 2016;7(4):665-672.
21. Chai CY, Tran Cao HS, Awad S, Massarweh NN. Management of Stage I Squamous Cell Carcinoma of the Anal Canal. *JAMA surgery.* 2018;153(3):209-215.
22. Gao X, Goffredo P, Kahl AR, Charlton ME, Weigel RJ, Hassan I. Chemoradiation versus local excision in treatment of stage I anal squamous cell carcinoma: A population-based analysis. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology.* 2020;46(9):1663-1667.
23. Deshmukh AA, Zhao H, Das P, et al. Clinical and Economic Evaluation of Treatment Strategies for T1N0 Anal Canal Cancer. *American Journal of Clinical Oncology: Cancer Clinical Trials.* 2018;41(7):626-631.
24. Leon O, Hagberg O, Johnsson A. Primary surgery with or without postoperative radiotherapy in early stage squamous cell carcinoma in the anal canal and anal margin. *Acta Oncol.* 2018;57(9):1209-1215.
25. Ryan DP, Compton CC, Mayer RJ. Carcinoma of the anal canal. *New England Journal of Medicine.* 2000;342(1):792-800.
26. Nigro ND, Vaitkevicius VK, Considine B, Jr. Combined therapy for cancer of the anal canal: a preliminary report. *Dis Colon Rectum.* 1974;17(3):354-356.
27. 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(3):5061-5066.

28. Martinez-Cannon BA, Perez ACT, Hincapie-Echeverri J, et al. Anal cancer in older adults: A Young International Society of Geriatric Oncology review paper. *J Geriatr Oncol.* 2022;13(7):914-923.
29. Holliday EB, Morris VK, Johnson B, et al. Definitive Intensity-Modulated Chemoradiation for Anal Squamous Cell Carcinoma: Outcomes and Toxicity of 428 Patients Treated at a Single Institution. *The oncologist.* 2022;27(1):40-47.
30. Hofheinz RD, Wenz F, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. *Lancet Oncol.* 2012;13(6):579-588.
31. Darragh TM, Colgan TJ, Cox JT, et al. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Arch Pathol Lab Med.* 2012;136(1):1266-1297.
32. Arana R, Flejou J-F, Si-Mohamed A, Bauer P, Etienney I. Clinicopathological and virological characteristics of superficially invasive squamous-cell carcinoma of the anus. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland.* 2015;17(1):965-972.
33. 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(1):27-33.
34. Dasgupta T, Rothenstein D, Chou JF, et al. Intensity-modulated radiotherapy vs. conventional radiotherapy in the treatment of anal squamous cell carcinoma: a propensity score analysis. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2013;107(2):189-194.
35. Cardenas ML, Spencer CR, Markovina S, et al. Quantitative FDG-PET/CT predicts local recurrence and survival for squamous cell carcinoma of the anus. *Adv Radiat Oncol.* 2017;2(3):281-287.
36. Lohynska R, Mazana E, Novakova-Jiresova A, et al. Improved survival in patients with fdg-pet/ct-based radiotherapy treatment planning for squamous cell anal cancer. *Neoplasma.* 2020;67(5):1157-1163.
37. Sauter C, Peeken JC, Borm K, et al. Quality of life in patients treated with radiochemotherapy for primary diagnosis of anal cancer. *Sci Rep.* 2022;12(1):4416.
38. Untiedt S, Rolf D, Scobioala S, et al. Impact of dose escalation on colostomy-free survival and treatment outcome in squamous cell anal carcinoma. *Strahlenther Onkol.* 2023;199(8):749-760.
39. 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(1):177-185.
40. Vendrely V, Lemanski C, Pommier P, et al. Treatment, outcome, and prognostic factors in non-metastatic anal cancer: The French nationwide cohort study FFCD-ANABASE. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2023;183:109542.
41. Bryant AK, Huynh-Le M-P, Simpson DR, Mell LK, Gupta S, Murphy JD. Intensity Modulated Radiation Therapy Versus Conventional Radiation for Anal Cancer in the Veterans Affairs System. *Int J Radiat Oncol Biol Phys.* 2018;102(1):109-115.
42. 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(2):4383-4392.
43. Arcelli A, Buwenge M, Macchia G, et al. Long-term results of chemoradiation plus pulsed-dose-rate brachytherapy boost in anal canal carcinoma: A mono-institutional retrospective analysis. *Journal of Contemporary Brachytherapy.* 2019;11(1):21-27.
44. Gryc T, Ott O, Putz F, et al. Interstitial brachytherapy as a boost to patients with anal carcinoma and poor response to chemoradiation: Single-institution long-term results. *Brachytherapy.* 2016;15(6):865-872.
45. Faivre J-C, 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). *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2018;129(3):463-470.
46. Bacci M, Quero L, Barbier E, et al. What is the optimal treatment for T1N0 anal squamous cell carcinoma? Analysis of current practices in the prospective French FFCD ANABASE cohort. *Dig Dis.* 2021;53(6):776-784.
47. 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(1):60-66.
48. Mohiuddin JJ, Jethwa KR, Grandhi N, et al. Multi-institutional Comparison of Intensity Modulated Photon Versus Proton Radiation Therapy in the Management of Squamous Cell Carcinoma of the Anus. *Adv Radiat Oncol.* 2021;6(5):100744.

49. Wo JY, Plastaras JP, Metz JM, et al. Pencil Beam Scanning Proton Beam Chemoradiation Therapy With 5-Fluorouracil and Mitomycin-C for Definitive Treatment of Carcinoma of the Anal Canal: A Multi-institutional Pilot Feasibility Study. *Int J Radiat Oncol Biol Phys.* 2019;105(1):90-95.
50. Shakir R, Adams R, Cooper R, et al. Patterns and Predictors of Relapse Following Radical Chemoradiation Therapy Delivered Using Intensity Modulated Radiation Therapy With a Simultaneous Integrated Boost in Anal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys.* 2020;106(2):329-339.
51. Ortholan C, Resbeut M, Hannoun-Levi J-M, 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(5):1988-1995.
52. Glynne-Jones R, Meadows HM, Lopes A, Muirhead R, Sebag-Montefiore D, Adams R. Impact of compliance to chemoradiation on long-term outcomes in squamous cell carcinoma of the anus: results of a post hoc analysis from the randomised phase III ACT II trial. *Annals of oncology : official journal of the European Society for Medical Oncology.* 2020;31(1):1376-1385.
53. Sunesen KG, Norgaard M, Lundby L, et al. Cause-specific colostomy rates after radiotherapy for anal cancer: A danish multicentre cohort study. *J Clin Oncol.* 2011;29(2):3535-3540.
54. Khosla D, Kapoor R, Dey T, et al. Simultaneous Integrated Boost (SIB) Versus Sequential Boost in Anal Cancer Patients: A Single-Center Experience. *J Gastrointest Cancer.* 2024;55(2):759-767.
55. Rotondi M, Facondo G, Mossa S, et al. Comparative analysis of toxicity in patients with anal cancer undergoing definitive simultaneous integrated boost (SIB) or sequential integrated boost (SeqB) radiotherapy. *Int J Colorectal Dis.* 2023;38(1):125.
56. 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(1):172.
57. Tomasoa NB, Meulendijks D, Nijkamp J, Cats A, Dewit L. Clinical outcome in patients treated with simultaneous integrated boost - intensity modulated radiation therapy (SIB-IMRT) with and without concurrent chemotherapy for squamous cell carcinoma of the anal canal. *Acta Oncol.* 2016;55(6):760-766.
58. Feng CH, Hasan Y, Kopec M, Al-Hallaq HA. Simultaneously integrated boost (SIB) spares OAR and reduces treatment time in locally advanced cervical cancer. *J Appl Clin Med Phys.* 2016;17(5):76-89.
59. Farzin M, Molls M, Astner S, Rondak IC, Oechsner M. Simultaneous integrated vs. sequential boost in VMAT radiotherapy of high-grade gliomas. *Strahlenther Onkol.* 2015;191(12):945-952.
60. Stromberger C, Ghadjar P, Marnitz S, et al. Comparative treatment planning study on sequential vs. simultaneous integrated boost in head and neck cancer patients: Differences in dose distributions and potential implications for clinical practice. *Strahlenther Onkol.* 2016;192(1):17-24.
61. Sukhikh ES, Sukhikh LG, Lushnikova PA, Tatarchenko MA, Abdelrahman AR. Dosimetric and radiobiological comparison of simultaneous integrated boost and sequential boost of locally advanced cervical cancer. *Phys Med.* 2020;73:83-88.
62. Matthews JHL, Burmeister BH, Borg M, et al. T1-2 anal carcinoma requires elective inguinal radiation treatment--the results of Trans Tasman Radiation Oncology Group study TROG 99.02. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2011;98(1):93-98.
63. Nilsson MP, Nilsson ED, Johnsson A, Leon O, Gunnlaugsson A, Scherman J. Patterns of recurrence in anal cancer: A detailed analysis. *Radiation Oncology.* 2020;15(1):125.
64. Das P, Crane CH, Ajani JA. Current treatment for localized anal carcinoma. *Curr Opin Oncol.* 2007;19(4):396-400.
65. Aggarwal A, Gayadeen S, Robinson D, et al. Clinical target volumes in anal cancer: calculating what dose was likely to have been delivered in the UK ACT II trial protocol. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2012;103(3):341-346.
66. Mehta S, Ramey SJ, Kwon D, et al. Impact of radiotherapy duration on overall survival in squamous cell carcinoma of the anus. *J Gastrointest Oncol.* 2020;11(2):277-290.
67. Raphael MJ, Ko G, Booth CM, et al. Factors Associated with Chemoradiation Therapy Interruption and Noncompletion among Patients with Squamous Cell Anal Carcinoma. *JAMA Oncology.* 2020;6(6):881-887.
68. Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. *Lancet (London, England).* 2003;362(9388):933-940.
69. Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet.* 2019;393(10166):40-50.
70. Julie DAR, Oh JH, Apte AP, et al. Predictors of acute toxicities during definitive chemoradiation using intensity-modulated radiotherapy for anal squamous cell carcinoma. *Acta Oncol.* 2016;55(2):208-216.

71. Lee AY, Golden DW, Bazan JG, et al. Hematologic Nadirs During Chemoradiation for Anal Cancer: Temporal Characterization and Dosimetric Predictors. *Int J Radiat Oncol Biol Phys.* 2017;97(2):306-312.
72. Bazan JG, Luxton G, Mok EC, Koong AC, Chang DT. Normal tissue complication probability modeling of acute hematologic toxicity in patients treated with intensity-modulated radiation therapy for squamous cell carcinoma of the anal canal. *Int J Radiat Oncol Biol Phys.* 2012;84(3):700-706.
73. Rose B, Mitra D, Hong TS, et al. Irradiation of anatomically defined pelvic subsites and acute hematologic toxicity in anal cancer patients undergoing chemoradiation. *Pract Radiat Oncol.* 2017;7(5):e291-e297.
74. 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(2):400-408.
75. Nilsson MP, Gunnlaugsson A, Johnsson A, Scherman J. Dosimetric and Clinical Predictors for Acute and Late Gastrointestinal Toxicity Following Chemoradiotherapy of Locally Advanced Anal Cancer. *Clinical oncology (Royal College of Radiologists (Great Britain)).* 2022;34(1):e35-e44.
76. Lukovic J, Hosni A, Liu A, et al. Evaluation of dosimetric predictors of toxicity after IMRT with concurrent chemotherapy for anal cancer. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2023;178:109429.
77. De B, Corrigan KL, Rooney MK, et al. Patient-Reported Bowel and Urinary Function in Long-Term Survivors of Squamous Cell Carcinoma of the Anus Treated With Definitive Intensity Modulated Radiation Therapy And Concurrent Chemotherapy. *Int J Radiat Oncol Biol Phys.* 2022;114(1):78-88.
78. Muirhead R, Drinkwater K, O'Cathail SM, et al. Initial Results from the Royal College of Radiologists' UK National Audit of Anal Cancer Radiotherapy 2015. *Clin Oncol.* 2017;29(3):188-197.
79. Baxter NN, Habermann EB, Tepper JE, Durham SB, Virnig BA. Risk of pelvic fractures in older women following pelvic irradiation. *JAMA.* 2005;294(2):2587-2593.
80. Son CH, Law E, Oh JH, et al. Dosimetric Predictors of Radiation-Induced Vaginal Stenosis After Pelvic Radiation Therapy for Rectal and Anal Cancer. *Int J Radiat Oncol Biol Phys.* 2015;92(3):548-554.
81. Huddart RA, Hall E, Hussain SA, et al. Randomized noninferiority trial of reduced high-dose volume versus standard volume radiation therapy for muscle-invasive bladder cancer: results of the BC2001 trial (CRUK/01/004). *Int J Radiat Oncol Biol Phys.* 2013;87(2):261-269.
82. McDonald F, Waters R, Gulliford S, Hall E, James N, Huddart RA. Defining bowel dose volume constraints for bladder radiotherapy treatment planning. *Clin Oncol (R Coll Radiol).* 2015;27(1):22-29.
83. Hafeez S, Webster A, Hansen VN, et al. Protocol for tumour-focused dose-escalated adaptive radiotherapy for the radical treatment of bladder cancer in a multicentre phase II randomised controlled trial (RAIDER): radiotherapy planning and delivery guidance. *BMJ Open.* 2020;10(12):e041005.
84. Rose BS, Jee K-W, Niemierko A, et al. Irradiation of FDG-PET-Defined Active Bone Marrow Subregions and Acute Hematologic Toxicity in Anal Cancer Patients Undergoing Chemoradiation. *Int J Radiat Oncol Biol Phys.* 2016;94(4):747-754.
85. Mirabeau-Beale K, Hong TS, Niemierko A, et al. Clinical and treatment factors associated with vaginal stenosis after definitive chemoradiation for anal canal cancer. *Pract Radiat Oncol.* 2015;5(3):e113-e118.
86. Damast S, Jeffery DD, Son CH, et al. Literature Review of Vaginal Stenosis and Dilator Use in Radiation Oncology. *Pract Radiat Oncol.* 2019;9(6):479-491.
87. Grigsby PW, Russell A, Bruner D, et al. Late injury of cancer therapy on the female reproductive tract. *Int J Radiat Oncol Biol Phys.* 1995;31(5):1281-1299.
88. Mirabeau-Beale KL, Viswanathan AN. Quality of life (QOL) in women treated for gynecologic malignancies with radiation therapy: a literature review of patient-reported outcomes. *Gynecol Oncol.* 2014;134(2):403-409.
89. Law E, Kelvin JF, Thom B, et al. Prospective study of vaginal dilator use adherence and efficacy following radiotherapy. *Radiother Oncol.* 2015;116(1):149-155.
90. Bakker RM, ter Kuile MM, Vermeer WM, et al. Sexual rehabilitation after pelvic radiotherapy and vaginal dilator use: consensus using the Delphi method. *Int J Gynecol Cancer.* 2014;24(8):1499-1506.
91. Miles T, Bergmark K, Bruner DW, et al. International Guidelines on Vaginal Dilation After Pelvic Radiotherapy. *Owen Mumford Ltd.* 2012.
92. Kachnic LA, Bruner DW, Qureshi MM, Russo GA. Perceptions and practices regarding women's vaginal health following radiation therapy: A survey of radiation oncologists practicing in the United States. *Pract Radiat Oncol.* 2017;7(5):356-363.
93. Taylor JP, Wei IH, Smith JJ, et al. Assessment of Patient-Reported Outcomes in Patients With Anal Squamous-Cell Cancer Undergoing Combined Modality Therapy. *Dis Colon Rectum.* 2022;65(1):1448-1455.

94. Corrigan KL, Rooney MK, De B, et al. Patient-Reported Sexual Function in Long-Term Survivors of Anal Cancer Treated With Definitive Intensity Modulated Radiation Therapy and Concurrent Chemotherapy. *Pract Radiat Oncol.* 2022;12(5):e397-e405.
95. Mauro GP, da Conceicao Vasconcelos KGM, Carvalho HDA. Quality of Life and Sexual Function of Men Who Have Sex With Men Treated for Anal Cancer: A Prospective Trial of a Neglected Population. *J Sex Med.* 2021;18(8):1461-1466.
96. 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. *The Lancet Oncology.* 2017;18(3):347-356.
97. Duimering A, Riauka T, Nijjar Y, et al. Prognostic utility of pre- and post-treatment FDG-PET parameters in anal squamous cell carcinoma. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2019;136:21-28.
98. Susko MS, Lazar AA, Jackie Wang C-C, et al. Use of advanced PET-volume metrics predicts risk of local recurrence and overall survival in anal cancer. *PLoS One.* 2021;16(2):e0246535.
99. 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(5):e149-e154.
100. Adusumilli P, Elsayed N, Theophanous S, et al. Combined PET-CT and MRI for response evaluation in patients with squamous cell anal carcinoma treated with curative-intent chemoradiotherapy. *Eur Radiol.* 2022;32(8):5086-5096.
101. Frazer ML, Yang G, Felder S, et al. Determining Optimal Follow-up for Patients with Anal Cancer following Chemoradiation. *American Journal of Clinical Oncology: Cancer Clinical Trials.* 2020;43(5):319-324.
102. Cappello C, Cuming T, Bowring J, Rosenthal AN, Chindawi N, Nathan M. High-Resolution Anoscopy Surveillance After Anal Squamous Cell Carcinoma: High-Grade Squamous Intraepithelial Lesion Detection and Treatment May Influence Local Recurrence. *Dis Colon Rectum.* 2020;63(1):1363-1371.
103. Peterson CY, Weiser MR, Paty PB, et al. Does endoscopic ultrasound improve detection of locally recurrent anal squamous-cell cancer? *Dis Colon Rectum.* 2015;58(2):193-198.
104. Kochhar R, Renehan AG, Mullan D, Chakrabarty B, Saunders MP, Carrington BM. The assessment of local response using magnetic resonance imaging at 3- and 6-month post chemoradiotherapy in patients with anal cancer. *Eur Radiol.* 2017;27(2):607-617.

Appendix E1 Peer Reviewers and Disclosures (Comprehensive)

- Table is added prior to publication

Appendix E2 Abbreviations

2-D = 2-dimensional
3-D = 3-dimensional
3-D CRT = 3-dimensional conformal radiation therapy
5-FU = 5-Fluorouracil
AHRQ = Agency for Healthcare Research and Quality
ASCO = American Society of Clinical Oncology
ASTRO = American Society for Radiation Oncology
cCR = clinical complete response
cGy = centigray
CT = computed tomography
CTV = clinical target volume
DFS = disease-free survival
DRE = digital rectal examination

EBRT = external beam radiation therapy
EORTC = European Organisation for Research and Treatment of Cancer
FDG = 18 F-fluorodeoxyglucose
GI = gastrointestinal
HIV = human immunodeficiency virus
IMRT = Intensity modulated radiation therapy
KQ = key question
MMC = mitomycin C
MRI = magnetic resonance imaging PET/CT = positron emission tomography/computed tomography
PCORI = Patient-Centered Outcomes Research Institute
PICOTS = Population, Intervention, Comparator, Outcome, Timing, Setting framework
PTV = planning target volume
RCTs = randomized controlled trials
RT = radiation therapy
RTOG = Radiation Therapy Oncology Group
SCC = squamous cell carcinoma(s)
SIB = simultaneous integrated boost
TROG = Trans-Tasman Radiation Oncology Group
VMAT = volumetric modulated arc therapy