Systemic Therapy for Stage I-III Anal Squamous Cell Carcinoma: ASCO Guideline

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ABSTRACT

ASCO Guidelines provide recommendations with comprehensive review and analyses of the relevant literature for each recommendation, following the guideline development process as outlined in the ASCO Guidelines Methodology Manual. ASCO Guidelines follow the ASCO Conflict of Interest Policy for Clinical Practice Guidelines.

Clinical Practice Guidelines and other guidance ("Guidance") provided by ASCO is not a comprehensive or definitive guide to treatment options. It is intended for voluntary use by clinicians and should be used in conjunction with independent professional judgement. Guidance may not be applicable to all patients, interventions, diseases or stages of diseases. Guidance is based on review and analysis of relevant literature and is not intended as a statement of the standard-of-care. ASCO does not endorse third-party drugs, devices, services, or therapies and assumes no responsibility for any harm arising from or related to the use of this information. See complete disclaimer in Appendix 1 and 2 (online only).

PURPOSE To provide evidence-based guidance for clinicians who treat patients with stage I-III anal cancer.

METHODS A systematic review of the literature conducted by the Minnesota Evidence-based Practice Center provided the evidence base for this guideline. An ASCO Expert Panel reviewed this evidence and came to consensus on a set of evidence-based recommendations.

RESULTS The systematic review contained three randomized controlled trials and three nonrandomized studies of interventions that were relevant to the guideline topic and informed the recommendations.

RECOMMENDATIONS Mitomycin-C (MMC) with a fluoropyrimidine (fluorouracil [FU] or capecitabine) is recommended as the radiosensitizing component of chemoradiation (CRT) for anal cancer; the Expert Panel recognizes that capecitabine is often used as an orally administered alternative to FU and is currently being used in ongoing clinical trials. Cisplatin with FU is an additional chemotherapy combination that may be recommended as radiosensitizing chemotherapy. Because of the myelosuppression associated with MMC, the preferable regimen for patients with immunosuppression is cisplatin and FU. Cisplatin is not recommended for patients with renal dysfunction, significant neuropathy, or hearing loss, and there is no evidence to recommend substituting carboplatin for cisplatin. Dose and schedule options for recommended chemotherapy agents are included within the full text of the guideline. Routine induction chemotherapy before CRT and additional chemotherapy after CRT are not recommended for patients with localized anal cancer.

Additional information is available at www.asco.org/gastrointestinal-cancer-guidelines.

ACCOMPANYING CONTENT

Appendix

Data Supplement

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TARGET POPULATION AND AUDIENCE

Target Population

The target population for this guideline is patients with stages I-III anal cancer.

Target Audience

The target audience includes medical oncologists, radiation oncologists, surgical oncologists, and other clinicians who treat patients with anal cancer.

INTRODUCTION

In 2024, there were estimated 10,540 new cases and 2,190 deaths due to anal and anorectal cancers.[1] This type of cancer is relatively rare, yet age-adjusted death rates rose an average 5.1% each year from 2013 to 2022.[2] The most common type of anal cancer is squamous cell carcinoma (SCC),[3] and most cases are linked to human papillomavirus (HPV) infection. Common risk factors include HIV infection and smoking.[4] In addition, rates are higher among Black men and White women.[5] With the increased incidence of anal cancer, there is an increasing need for more advanced and effective treatment options. In addition to survival outcomes, complete response is an important outcome of interest as complete responders to definitive chemoradiation (CRT) may be able to avoid abdominoperineal resection, which involves loss of the anal sphincter and a permanent colostomy.

For many decades, definitive CRT has been the standard of care in anal cancer, originally established in a 1974 study by Nigro et al[6] that demonstrated that CRT offered similar cure rates as surgery. Further support for fluorouracil (FU) + mitomycin-C (MMC) radiosensitizing chemotherapy was provided by the United Kingdom Co-ordinating Committee on Cancer Research (UKCCCR) Anal Cancer Trial I phase III randomized clinical trial (RCT), which included 577 patients from centers predominantly located in the United Kingdom.[7] Patients were accrued between December 1987 and March 1994, and randomly assigned to radiotherapy (45 Gy in 20 or 25 fractions over 4 or 5 weeks using external-beam irradiation) or CRT, with the CRT group receiving the same radiotherapy and FU (1,000 mg/m^2 once a day for 4 days or 750 mg/m^2 once a day for 5 days) by intravenous (IV) infusion during the first and last weeks of radiation therapy (RT), combined with MMC (12 mg/m^2). After 12 years, the survival rate was 5.6% higher, locoregional recurrence was 25.3% lower, and there were 12.5% fewer deaths from anal cancer in the CRT group. Twelve-year overall survival (OS) was not significantly different across groups, but the study authors attribute this to an excess of early deaths in the CRT group, which included deaths unrelated to anal cancer. CRT increased acute harms, but there was no difference in late harms. Another key RCT, Radiation Therapy Oncology Group (RTOG)/Eastern Cooperative Oncology Group 87-04, was published in 1996; this 310-person study compared CRT with FU to CRT with FU and MMC,[8] and was conducted in response to interest in alternatives to this combination, which had not being assessed in an RCT. Among 291 assessable patients, although toxicity was higher in the MMC group, the rate of positive post-treatment biopsies was lower in the MMC group versus FU alone (7.7% *v* 15%, respectively; $P = .135$), thus supporting continued use of FU and MMC as the standard of care. More recently, a small evidence base of studies assessing combination chemotherapy options for radiosensitization has been published. This newer evidence is reviewed for this guideline and recommendations are provided for systemic therapy for stage I to stage III anal cancer, including type of radiosensitizing chemotherapy, dose and schedule of administration, as well as alternative strategies for patients with immunosuppression.

GUIDELINE QUESTIONS

This clinical practice guideline addresses four clinical questions:

1. What are the recommended radiosensitizing doublet or single chemotherapy agents for patients with stage I-III anal cancer?
2. What are the recommended dose and schedule for the chemotherapy options included in Recommendations 1.1 and 1.2?
3. Is induction chemotherapy recommended for patients with stage I-III anal cancer?
4. Is ongoing adjuvant chemotherapy recommended for patients with stage I-III anal cancer?

METHODS

Systematic Review Development Process

In response to a call for proposals, ASCO submitted questions for a systematic evidence review on this topic to the Patient-Centred Outcomes Research Institute (PCORI) and the Agency for Healthcare Research and Quality (AHRQ) in May 2022. The submission was made jointly with the American Society for Radiation Oncology (ASTRO), with the intent that both societies would ultimately use the systematic review as the evidence base for complementary guidelines that included recommendations specific to their own target audiences. The proposal was accepted and approved for funding by PCORI in October 2022, and AHRQ contracted with the Minnesota Evidence-based Practice Center (EPC) at the University of Minnesota in Minneapolis, Minnesota to undertake the review. Although PCORI provided funding for the evidence review that is the basis of this guideline, the organization does not participate in the writing of guidelines or specifically fund guideline development. All funding for the development of the guideline was provided by ASCO.

The systematic review development process was consistent with AHRQ systematic review development methodology (https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview). The search of MEDLINE, Embase, Cochrane Register of Controlled Trials, and ClinicalTrials.gov was initially conducted from January 2000 through May 2023, and updated to March 4, 2024, before publication. The review also included scanning of reference lists of systematic reviews and included studies for earlier articles regardless of publication dates that were intended to inform a guideline that was to be developed by ASTRO. For the ASCO guideline development process, articles published between 2000 and 2024 were considered eligible for the evidence base. For articles that were relevant to ASCO's clinical questions, study design was limited to RCTs or comparative observational studies. The EPC systematic review was registered in the PROSPERO database of systematic reviews (registration No.: CRD42023456886).

Guideline Development Process

This guideline was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (see Appendix Table A1, online only) using the Minnesota EPC systematic review. Although the EPC review had a wider scope that included radiation interventions, the ASCO-specific population, intervention, comparison, outcome elements included:

- Population: Patients with stage I-III anal cancer
- Interventions: Chemotherapy components of CRT, including MMC, FU, and capecitabine; induction chemotherapy; ongoing adjuvant chemotherapy
- Comparisons: Alternative chemotherapy components of CRT
- Outcomes: OS, progression-free survival (PFS), or disease-free survival (DFS), adverse events, quality of life

The Expert Panel for this guideline met one time via teleconference, and members were asked to provide ongoing input on the guideline development protocol, quality and assessment of the evidence, generation of recommendations, draft content, as well as review and approve drafts during the entire development of the guideline. ASCO staff met routinely with the expert panel cochairs and corresponded with the panel via e-mail to coordinate the process to completion.

Evidence Quality Assessment

AHRQ methodology was used to rate the evidence included in the systematic review.[9] This methodology is similar to the GRADE system that is used by ASCO; however, AHRQ uses the term "insufficient" to describe evidence that would be given a "very low quality" rating using GRADE. To be consistent with GRADE, ASCO has converted AHRQ's "insufficient" label to "very low quality" or "no studies found" for the purposes of this guideline. Otherwise, quality ratings have been adopted as assigned in the AHRQ systematic review. The risk of bias domain of GRADE was assessed using the Cochrane Risk of Bias II tool.[10] The overall quality of evidence was assessed by outcome of interest. This rating includes factors such as study design, consistency of results, directness of evidence, precision, publication bias, and magnitude of effect (Appendix Table A2).[11]

Guideline Review and Approval

The draft recommendations were released to the public for open comment from June 17, 2024, through July 1, 2024. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation with six written comments received. A total of 100% of the six respondents either agreed or agreed with slight modifications to the recommendations. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions.

The draft was submitted to two external reviewers with content expertise. Review comments, such as clarification that the use of capecitabine could be recommended as an alternative to FU, were reviewed by the Expert Panel and integrated into the manuscript. Additionally, a guideline implementability review was conducted. No edits to the guideline were recommended through the implementability review.

All changes were incorporated into the final manuscript prior to ASCO Evidence Based Medicine Committee (EBMC) review and approval. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO EBMC before submission to the *Journal of Clinical Oncology* for editorial review and consideration for publication.

Guideline Updating

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

RESULTS

Characteristics of Studies Identified in the Literature Search

The Minnesota EPC systematic review provided the evidence base to inform this ASCO guideline, and an ASTRO guideline

on radiation therapy interventions for anal cancer. A PRISMA flow diagram of studies included in that review can be found in the systematic review, which has been published separately.[12] Studies from the systematic review that were relevant to the ASCO guideline population, interventions, comparisons, and outcomes included two phase III RCTs of 682 patients (RTOG 98-11)[13] and 940 patients (ACT II) [14] that were conducted in the United Kingdom and the United States, respectively. The baseline median age was 55 and 60 years, 37% and 50% of patients were male, 26% and 32% of patients had positive nodal status, and 14% and 20% had anal margin involvement in the RTOG 98-11 and ACT-II trials, respectively. In addition, the ACT II RCT excluded patients with HIV, did not report patients' race, and 10% had T1 disease. The RTOG 98-11 RCT included a relatively more advanced-stage population, with no patients having T1 disease, and 22% with stage IV-A disease; patients with advanced HIV were excluded. Three nonrandomized studies of interventions (NRSIs) comprising at total of 554 patients, which were conducted in the United States, the United Kingdom, and Canada, respectively, were also included.[15-17] In the NRSIs, the median patient age was approximately 58 to 60 years, 27% to 35% were male, and fewer than 10% had HIV. One NRSI (N = 107) reported that the study population was >80% White,[16] whereas the other two NRSIs did not report patients' race. Further details regarding patient characteristics are included in the published Minnesota EPC systematic review. [12] Evidence quality assessment results from the systematic review conducted by the EPC are summarized in the footnotes to evidence tables (Data Supplement, online only). Characteristics of the final included study, the 307-patient phase III ACCORD 03 study that looked at induction chemotherapy with FU and cisplatin before CRT, compared with CRT with no induction chemotherapy, are outlined in the *Literature Review and Clinical Interpretation* section.[18]

RECOMMENDATIONS

All recommendations are available in Table 1 and presented as an algorithm in Figure 1.

RADIOSENSITIZING CHEMOTHERAPY

Literature Review and Analysis

Two randomized controlled trials investigated radiosensitizing chemotherapy with FU and cisplatin versus FU and MMC.[13,14] Initial results for the RTOG 98-11 trial showed that, after a median follow-up of 2.5 years, there was no significant difference in OS; however, the survival curves did not remain proportional and began to separate after approximately 1.5 years; a follow-up analysis showed that there was a significant difference in OS at 5 years post-treatment (Data Supplement, Table S2). There was also a significant benefit in DFS, and nonsignificant differences favoring MMC for colostomy-free survival, colostomy failure, and locoregional failure (LRF). There was a significantly higher rate of acute hematologic toxicity with MMC versus cisplatin in RTOG 98-11 and in ACT II, but no significant differences in acute overall, dermatologic, GI, or genitourinary toxicities (Data Supplement, Table S3). In ACT II, after a median follow-up of 5.1 years, there was no significant difference in the primary study outcome complete response, or OS, indicating that CRT with FU and cisplatin was not more effective than CRT with FU and MMC. The complete response rates were approximately 90% in both groups in the ACT II trial. A post hoc analysis of RTOG 98-11 found that initial tumor volume >5 cm and/or node positivity were associated with reduced OS, DFS, and LRF.[21]

The comparison of CRT with MMC and capecitabine versus CRT with MMC and FU was investigated in two retrospective cohort studies and one prospective cohort study, comprising 554 patients in total.[15-17] Both of the studies that reported harms found that there was a significantly higher rate of grade 3 or higher hematological toxicity with FU compared to capecitabine.[15,16] The prospective study, which included 107 patients, found that grade 3 or greater neutropenia and leukopenia, as well as treatment breaks, were more common in the FU group, compared to capecitabine, and a higher rate of hematologic grade 3 or four toxicity was found at 6 weeks after completion of CRT with FU versus capecitabine.[16] There were no other significant differences found in efficacy or harms for the comparison of capecitabine versus FU.

Clinical Interpretation

Based on historical trials, FU and MMC remain the recommended standard-of-care combination of radiosensitizing chemotherapy because no newer studies have been published that demonstrate superiority of newer regimens over this established combination. However, due to the increased risk of myelosuppression with MMC compared to cisplatin, the latter option may be recommended, especially for patients who are immunosuppressed or for transplant recipients. The options for dose and frequency of the recommended treatment options are the consensus of the Expert Panel based on the intervention and comparison arms of the two keys RCTs that are included in the evidence base: RTOG 98-11 and ACT II. Finally, although the evidence base is limited, capecitabine, which is administered orally rather than by infusion, is recommended as a potentially more convenient option for patients than FU. The subsequent sections outline some further considerations regarding MMC dosing and capecitabine as an alternative to FU.

MMC Dosing Options

Variability in the dose of MMC as a radiosensitizer in the treatment of anal cancer has remained for several decades. In RTOG 98-11, two cycles of MMC were dosed at 10 mg/m^2, weeks 1 and 5, resulting in grade 3-4 acute hematologic toxicity in 61% of patients.[13] In ACT II, the largest phase III

TABLE 1. Summary of All Recommendations

Clinical Question	Recommendation
General note. The following recommendations (strong or conditional) and terminology (Appendix Table A2.) represent reasonable options for patients depending on clinical circumstances and in the context of individual patient preferences. Recommended care should be accessible to patients whenever possible.	
Clinical question 1: What are the recommended radiosensitizing chemotherapy agents for patients with stage I-III anal cancer?	1.1. MMC with a fluoropyrimidine (FU or capecitabine) is recommended as the radiosensitizing component of chemoradiation for anal cancer. (Evidence quality: Moderate; Strength of recommendation: Strong)
	Qualifying statements Due to an increased risk of myelosuppression, patients who are immunosuppressed should avoid treatment with MMC. The preferable regimen is cisplatin and FU (Recommendation 1.2). While there have been no RCTs of the MMC and capecitabine combination, the Expert Panel recognizes that this agent is often used as an orally administered alternative to FU and is currently being used in ongoing clinical trials. A prospective nonrandomized study of this intervention found that there was a higher rate of hematologic grade 3 or 4 toxicity at 6 weeks after completion of CRT with FU *v* capecitabine.[16]
	1.2. Cisplatin with FU is an additional chemotherapy combination that may be recommended as the radiosensitizing component of chemoradiation. (Evidence quality: Moderate; Strength of recommendation: Strong)
	Qualifying statements This recommendation is based on the noninferiority of cisplatin and FU compared to MMC and FU in the ACT-II RCT.[14] In this trial, there was a lower risk of myelosuppression with cisplatin and FU compared to MMC and a fluoropyrimidine. Cisplatin is not recommended for patients with renal dysfunction, significant neuropathy, or hearing loss. There is no evidence to support substituting carboplatin for cisplatin.
Clinical question 2: What are the recommended dose and schedule for the chemotherapy options included in Recommendations 1.1 and 1.2?	1.3. Recommended dosing and schedules for the chemotherapy options included in Recommendations 1.1 and 1.2 include (Evidence quality: Moderate; Strength of recommendation: Conditional)
	Chemotherapy agent(s) — Dose and frequency
	MMC and FU — MMC: 10 mg/m^2 (max 20 mg) once per day on day 1 and day 29,[a] or 12 mg/m^2 (max 20 mg) once on day 1 only. FU: 1,000 mg/m^2 (continuous infusion) once per day on days 1-4 (week 1) and 29-32 (week 5).
	[a]*Qualifying statement:* The second dose of mitomycin, as used in week 5 (day 29) in RTOG 98-11,[13] is associated with additional toxicity and should be used with caution. Please see *MMC Dosing Options* in the full guideline text for further discussion on this topic.
	MMC and capecitabine as an alternative to FU — In combination with MMC, the recommended dose of capecitabine is 825 mg/m^2 twice per day, orally administered on days of radiation.
	Cisplatin and FU — Cisplatin: 60 mg/m^2 once per day on days 1 and 29 with a maximum surface area of 2.0 m^2 (ie, max. single dose of 120 mg) with FU (1,000 mg/m^2 [continuous infusion]) once per day on days 1-4 (week 1) and 29-32 (week 5).
	Qualifying statements Patients who are immunosuppressed and treated with the recommended dose and frequency of cisplatin and FU should be monitored closely. 20 mg/m^2 intravenously once per week with FU (300 mg/m^2) infused continuously on days of radiation is also a recommended alternative, based on a lower level of evidence.[19,20]
	1.4. Where combination chemotherapy is not indicated, for example, in patients with poor ECOG performance status, radiosensitizing with single agent FU may be offered. (Evidence quality: Low; Strength of recommendation: Conditional)
Clinical question 3: Is induction chemotherapy recommended for patients with stage I-III anal cancer?	2.1. Routine induction chemotherapy prior to CRT is not recommended for patients with localized anal cancer. (Evidence quality: Moderate; Strength of recommendation: Strong)
Clinical question 4: Is ongoing adjuvant chemotherapy recommended for patients with stage I-III anal cancer?	3.1. Additional chemotherapy following CRT is not recommended for patients with localized anal cancer. (Evidence quality: Moderate; Strength of recommendation: Strong)

NOTE. The strength of the recommendation is defined as follows: Strong: In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention. Conditional/Weak: In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.

Abbreviations: CRT, chemoradiation; ECOG, Eastern Cooperative Oncology Group; FU, fluorouracil; MMC, mitomycin-C; RCT, randomized clinical trial.

trial conducted to date, one cycle of MMC was provided at 12 mg/m², week 1 only, resulting in lower acute hematologic toxicity (25% of patients).[14] In turn, grade 3-4 hematologic toxicity can lead to radiation treatment breaks. Indeed, there was a higher rate of breaks in RT delivery in RTOG 98-11 compared to ACT II of 58% versus 26%. The goal is to avoid >4-day break in a 28-fraction course of CRT, which was associated with inferior outcomes in ACT II.[22]

Due to the significant hematologic toxicity associated with CRT with MMC at 10 mg/m² and FU for two cycles, only 50% of patients are able to complete the regimen without a chemotherapy dose reduction and 38% do not receive a second cycle of MMC because of grade ≥3 neutropenia associated with the first cycle.[23] Some oncologists have altered their practices to give two cycles of FU, but only one cycle of MMC 10 mg/m² in order to avoid hematologic toxicity. In two retrospective series from Kaiser Permanente (N = 217) and the two tertiary cancer centers in Alberta, Canada (N = 169),[24,25] outcomes were compared between patients who received one versus two cycles of MMC 10 mg/m². In both studies, there were no specific patient selection criteria for the number of cycles; within the Kaiser system, differential MMC prescription reflected differences in practice patterns among medical oncologists, while in Alberta, they reflected differential practice patterns between two cancer centers. In both experiences, there was no difference in baseline tumor stage between arms, nor was there a difference in outcomes including DFS and OS between patients who received one versus two cycles of MMC. Not surprisingly, toxicities were higher among patients who received two cycles of MMC including grade ≥3 hematologic toxicity, hospitalization rates for febrile neutropenia, and treatment-related deaths.

There are no established criteria to select patients for one versus two doses of MMC. Given the excellent results seen with one cycle of MMC, and the reduced hematologic toxicity and resulting treatment breaks, it is a reasonable option. Special populations, such as patients with anal SCC and HIV, who have a higher risk of leukopenia attributable to chemotherapy,[26] could be more appropriate to select for one cycle of MMC. It is unknown whether there are subgroups of patients with more advanced-stage anal cancer who could benefit from receiving a second dose of MMC.

Capecitabine as an Alternative to FU

IV FU has remained the standard of care in the treatment of locally advanced anal cancer. Capecitabine has been determined to be noninferior in the treatment of locally advanced rectal cancer.[27] To date, the pursuit of a large phase III trial comparing IV FU to capecitabine has not been conducted. However, retrospective and phase II studies report that CRT with capecitabine plus MMC is well tolerated, has promising early outcomes, and may be a reasonable option for patients with stage I-III anal SCC.[16,28,29]

ADDITION OF INDUCTION OR ADJUVANT ONGOING CHEMOTHERAPY TO CRT

Literature Review and Clinical Interpretation

The phase III ACCORD 03 study (N = 307) looked at induction chemotherapy with FU and cisplatin prior to CRT, compared to CRT with no induction chemotherapy.[18] This study was conducted in France, and had a 2 × 2 factorial design, which also included a radiation boost versus no boost comparison in addition to the induction versus no induction comparison. The mean age of patients in this study was 58.8 years, 20% were male, and 33% had poorly differentiated tumors. No information was reported on HIV status or race of participants. The study was downgraded for quality because of attrition in study participants over the course of treatment, which limited the power of the study to detect differences between treatment and control arms. This intervention had no significant effect on colostomy-free survival or OS but did nonsignificantly increase the risk of grade 3 or 4 hematological toxicity. Induction chemotherapy with FU and cisplatin was also included in the RTOG 98-11 trial as part of the FU and cisplatin CRT arm.[13] Outcomes from RTOG 98-11 have been reviewed previously, and indicate that the standard of care should remain FU and MMC, without the addition of induction chemotherapy.

The ACT II trial, which was described previously, had a 2 × 2 factorial design to assess radiosensitizing chemotherapy with FU and cisplatin versus FU and MMC, as well as whether two courses of FU and cisplatin maintenance chemotherapy after CRT would improve PFS. There was no significant difference in 3-year PFS between arms (Data Supplement, Table S1).

As there was no benefit shown with induction or adjuvant ongoing chemotherapy in the respective trials that explored these interventions, they are not routinely recommended.

DISCUSSION

Concurrent CRT with a combination of radiosensitizing chemotherapy agents is recommended within this guideline as a potentially effective treatment option that may allow patients with stage I-III anal cancer to avoid surgery. This guideline relies on a modest evidence base to formulate recommendations, with two included randomized trials to support the long-standing combination of FU and MMC for CRT radiosensitization. Other combination therapy options are recommended as alternatives, based on lower-quality evidence. Given the increasing incidence of anal cancer, there is a growing need for new research to continue to move the field forward in terms of treatment options for this patient population. No studies of immunotherapy were

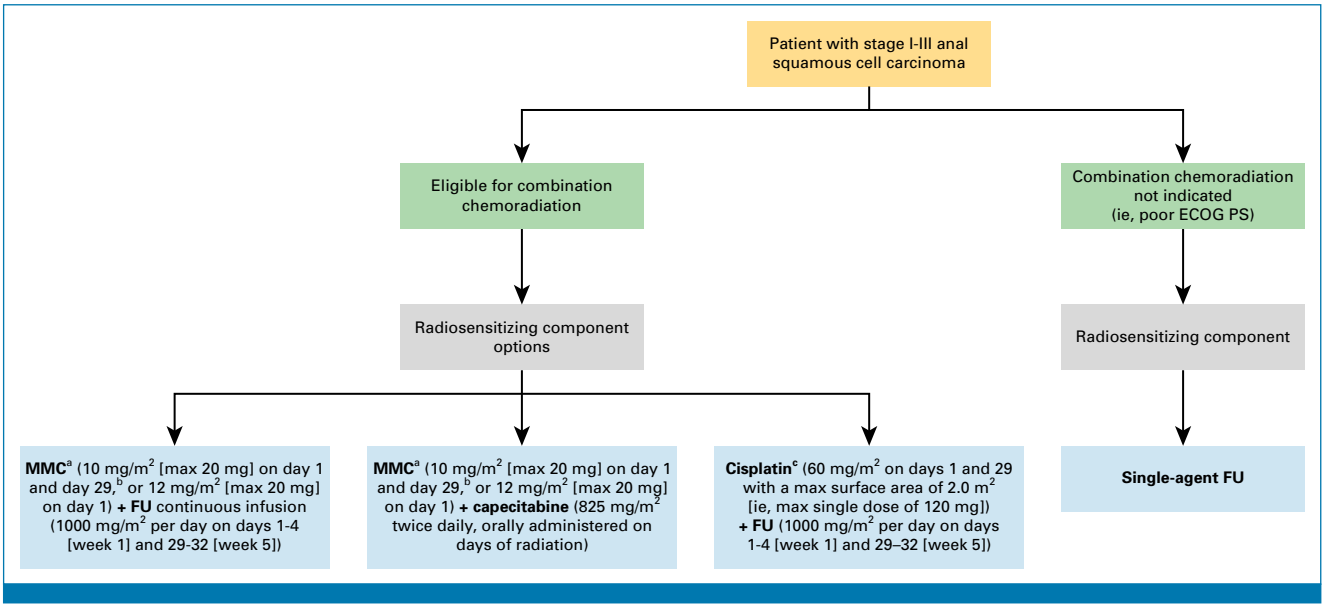

FIG 1. Systemic therapy for stage I-III anal cancer algorithm. [a]Because of an increased risk of myelosuppression, patients who are immunosuppressed should avoid treatment with MMC. The preferable regimen is cisplatin and FU. [b]The second dose of mitomycin in week 5 (day 29) is associated with additional toxicity and should be used with caution. Please see MMC dosing options in the full guideline text for further discussion on this topic. [c]Cisplatin is not recommended for patients with renal dysfunction, significant neuropathy, or hearing loss. ECOG PS, Eastern Cooperative Oncology Group performance status; FU, fluorouracil; MMC, mitomycin-C.

found that apply to the locally advanced population; the current approval of pembrolizumab for patients with metastatic disease applies to a population that falls outside of the scope of this guideline.[30] The Expert Panel is anticipating the results of the ECOG-ACRIN 2165 phase III RCT (ClinicalTrials.gov identifier: NCT03233711) of PD-1 monotherapy nivolumab following combined modality therapy in higher-risk locally advanced anal cancer, which will be incorporated into a future update of this guideline.[31]

LIMITATION OF THE RESEARCH AND FUTURE RESEARCH

As noted previously, there is a limited evidence base of high-quality recent literature to inform the recommendations for chemotherapy for stage I-III anal cancer. One study included in this review reported race, with an 80% White patient population; this is consistent with the general findings of a study that looked at 310 trials published between 2003 and 2016 and found that 83.4% of patients were non-Hispanic White, 5.9% were African American/Black, 5.3% were Asian/Pacific Islander, and 2.6% were Hispanic.[32] Limited diversity of trial populations impedes the generalizability of trial results and inhibits our understanding of safety and efficacy across populations. Key RCTs included in this review excluded patients with HIV, which limits generalizability of these study results. The systematic review that provided the evidence base for this guideline noted that patients with immunocompromised status, older age, and minoritized racial or ethnic identities are underrepresented in research and recommended that future research priorities should focus on these patient subgroups.[12]

PATIENT AND CLINICIAN COMMUNICATION

As CRT can be associated with long-term toxicity, including sexual and anorectal dysfunction that can significantly affect quality of life, preventive and supportive care are needed to manage these side effects.[33] Communication between the patient and clinician should include of the potential for these long-term toxicities and their management. In addition, given the inter-relationship between risk factors outlined subsequently in the Health Equity Considerations section, clinicians are encouraged to discuss the topics of smoking cessation, optimal HIV care, and HPV vaccination with their patients. It is also important that clinicians delivering oncology treatment are coordinated with a patient's HIV care specialist when applicable, to address adherence to HIV medication. For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: ASCO Consensus Guideline.[34]

HEALTH EQUITY CONSIDERATIONS

Social determinants of health, defined by the WHO as the conditions in which an individual is born, grows, lives, works, and ages, can impact the implementation and outcomes associated with ASCO's expert recommendations on best practices for prevention, screening, palliative and supportive care, and disease management for many patients with cancer.[35] Furthermore, many people in the United States and elsewhere do not receive the highest level of cancer care due to the long-term impact of structural racism and the consequential unequal distribution of wealth and health care resources among racial groups.[36] For

patients with anal cancer, significant disparities exist in incidence and prevalence, as 65% of cases occur in women, and Black men (of African or Caribbean ancestry) have an elevated rate of anal cancer compared with White men or Black women.[37] In one study, among the subgroup of gay and bisexual men with HIV, the incidence of anal cancer among Black men was 2.4 times the rate among non-Black men, after controlling for potentially confounding variables.[38] Men who have sex with men (MSM) are approximately 20 times more likely than heterosexual men to develop anal cancer.[39]

People who smoke are also several times more likely to develop anal cancer compared with those who do not smoke.[37] Smoking rates are also higher among certain lower socioeconomic status (SES) groups, and may be widening over time,[40] although this relationship varies by race and/or ethnicity.[41]

More than 90% of anal cancers are caused by one of nine HPV types that are covered under current vaccines.[42] Thus, anal cancer is largely preventable with widespread vaccination. However, HPV vaccine coverage also varies by SES, with significantly fewer uninsured children age 9-17 years (20.7%) being vaccinated compared with those with private insurance (41.5%) in 2022 in the United States.[43] There was also a positive association between parents' education levels and income, and children's rate of vaccination. Taken together, these factors, among others, contribute to inequality of outcomes, including greater severity of anal cancer in patients with lower income levels.[44]

Geographic disparities are intersectional and can also impact disease incidence, prevalence, and quality of care. For anal cancer, the increase in cases over an 18-year period from 2001-2005 to 2014-2018 was most pronounced in the Midwest and Southeast United States, and these regions contributed more than half of anal cancer deaths.[4,45] A recent study showed significant differences in risk of developing anal cancer for people with HIV, with the risk being several times higher in the Midwest of the United States, compared with the Northeast. Women experienced a two-fold increase in rate in this area. MSM in the Midwest have a nearly a 100-fold increase in risk of anal cancer compared with people in the Northeast without HIV.[46] This study also found that for people with HIV, the presence of comorbidities such as opportunistic illnesses and chronic diseases can increase the risk of developing anal cancer. As anal cancer is a relatively rare disease, with a prevalence of approximately 0.2%, accounting for 1.5% of GI cancers,[44] there may be lack of awareness and recognition of anal cancer and treatment options in less populated areas where anal cancer is not commonly diagnosed. Furthermore, radiation therapy, which is a key treatment modality, is less likely to be available within a reasonable geographic distance for more rural or remote patient populations. Although the number of radiation therapy facilities has increased over the past 15 years, this increase has occurred mostly in urban centers, and as of 2020, 5% of the US population was more than 50 miles from the nearest facility offering radiation, which can involve daily treatments lasting for several weeks.[47]

Availability of anal cancer screening programs also vary by geographic location, as screening rates are higher in the Northeast and West, compared to other parts of the United States. Recent consensus guidelines by the International Anal Neoplasia Society call for screening beginning at age 35 years for MSM and transgender women with HIV, at age 45 years for MSM and transgender women without HIV and others with HIV, as well as recommendations for other subpopulations such as organ transplant recipients. Availability of diagnostic procedures, including equipment and expertise to perform anal rectoscopy, is necessary, thus the effectiveness of screening will vary by availability of these follow-up modalities.[48]

These disparities could be improved by more equitable care, including access to screening, prevention, and HIV care, which is not uniformly available across the United States.[49] Historically, HPV-associated diseases have disproportionately affected racial and ethnic minority groups and people with lower incomes. These disparities persist in the post-vaccine era in the United States and may be exacerbated by the historical social stigma that has limited discussion and awareness of anal cancer.[42,44,50] Although this guideline does not include recommendations intended to reduce disparities in access and outcomes, the Expert Panel intends this guideline to improve awareness of the recommended standard-of-care systemic treatment options for anal cancer, and supports improvement in access to HPV vaccination, anal cancer screening, and HIV care.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[51,52] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[53,54]

Discussion of cost can be an important part of shared decision making.[55] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[55]

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any

financial counseling services available to address this complex and heterogeneous landscape.[55]

The estimated 2-year per-patient cost of anal cancer treatment is $127,531 US dollars (USD) for privately insured patients in the United States, with the highest cost of treatment occurring in the first 6 months after diagnosis.[56] Lifetime costs among a Medicare-insured population have been estimated to be $51,200 USD per patient.[57] As of 2022, 56.9% of boys and girls age 15-17 years had received an HPV vaccination in the United States.[58] As anal cancer is largely preventable with vaccination against HPV, significant cost-savings could theoretically be achieved with widespread vaccination. No articles on financial toxicity among patients with anal cancer were found as part of this review. This area of research should be explored, particularly because people with HIV and comorbidities are at significantly higher risk for anal cancer, and the presence of multiple chronic conditions may increase the risk of financial toxicity.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes at least one member with experience in community oncology. The additional role of this community oncology representative on the guideline panel is to assess the suitability of the recommendations to implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and to provide adequate services in the face of limited resources. The guideline recommendations table and accompanying tools (available at http://www.asco.org/gastrointestinal-cancer-guidelines) were designed to facilitate implementation of recommendations. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

For current information, including selected updates, supplements, slide sets, and clinical tools and resources, visit http://www.asco.org/gastrointestinal-cancer-guidelines.

RELATED ASCO GUIDELINES

- Patient-Clinician Communication[34] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

The Data Supplement for this guideline includes GRADE evidence tables and the results of the implementability review. Guideline recommendations and algorithms are also available in the free ASCO Guidelines app (available for download in the Apple App Store and Google Play Store). Listen to key recommendations and insights from panel members on the ASCO Guidelines podcast. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.org.

ASCO welcomes your comments on this guideline, including implementation challenges, new evidence, and how this guideline impacts you. To provide feedback, contact us at guidelines@asco.org. Comments may be incorporated into a future guideline update. To submit new evidence or suggest a topic for guideline development, complete the form available at www.asco.org/guidelines.

GENDER-INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of individuals regardless of sexual orientation or gender identity.[59] Transgender and nonbinary people, in particular, may face multiple barriers to oncology care including stigmatization, invisibility, and exclusiveness. One way exclusiveness or lack of accessibility may be communicated is through gendered language that makes presumptive links between gender and anatomy.[60-63] With the acknowledgment that ASCO guidelines may impact the language used in clinical and research settings, ASCO is committed to creating gender-inclusive guidelines. For this reason, guideline authors use gender-inclusive language whenever possible throughout the guidelines. In instances in which the guideline draws upon data based on gendered research (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.org, is available at http://www.asco.org/gastrointestinal-cancer-guidelines.

EQUAL CONTRIBUTION

V.K.M. and C.E. were Expert Panel co-chairs.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Systemic Therapy for Stage I-III Anal Squamous Cell Carcinoma: ASCO Guideline

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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APPENDIX 1. GUIDELINE DISCLAIMER

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APPENDIX 2. GUIDELINE AND CONFLICTS OF INTEREST

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

TABLE A1. Systemic Therapy for Stage I-III Anal Cancer Guideline Expert Panel Membership

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TABLE A2. Recommendation Rating Definitions

Term	Definitions
Evidence quality	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects All or almost all informed people would make the recommended choice for or against an intervention
Conditional/weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists Most informed people would choose the recommended course of action, but a substantial number would not

NOTE. GRADE Handbook, Schünemann et al 2013.[64]