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SYSTEMATIC REVIEW

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Treatment of Stages I–III Squamous Cell Anal Cancer: A Systematic Review

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Nonfinancial conflict of interest was reported by the investigators as follows: Dr. Paolo Goffredo and Dr. Elliot Arsoniadis are colorectal surgeons who treat patients with anal cancer, prescribe treatments examined in this report, and have published research related to anal cancer; Dr. Elizabeth Ester is a radiation oncologist who treats patients with anal cancer and prescribes treatments examined in this report; Dr. Edward Greeno is a medical oncologist who treats patients with anal cancer and prescribes treatments examined in this report; Dr. Bronwyn Southwell is an anesthesiologist; Dr. Shahnaz Sultan is a gastroenterologist. None of the investigators reported any financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. The Patient-Centered Outcomes Research Institute (PCORI®) requested this report from the EPC Program at AHRQ. AHRQ assigned this report to the Minnesota Evidence-based Practice Center (Contract Number: 75Q80120D00008).

AHRQ EPC reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

The Patient-Centered Outcomes Research Institute was established to fund research that helps patients and caregivers make better informed healthcare choices. To fulfill its authorizing mandate, PCORI partners with AHRQ to generate evidence synthesis products and make comparative effectiveness research more available to patients and providers.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, go to https://effectivehealthcare.ahrq.gov/about/epc/evidence-synthesis.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Treatment of Stages I–III Squamous Cell Anal Cancer: A Systematic Review

Structured Abstract

Objectives. To evaluate the comparative effectiveness and harms of initial treatment and posttreatment surveillance strategies for stages I–III squamous cell anal cancer.

Data sources. MEDLINE®, Embase®, Cochrane Register of Controlled Trials, and ClinicalTrials.gov from January 2000 through March 2024; reference lists of systematic reviews and included studies; and a Federal Register notice.

Review methods. Using predefined criteria and dual review, we selected randomized controlled trials (RCTs) and nonrandomized studies of interventions (NRSIs) comparing strategies for chemotherapy, radiation therapy (RT), and surgery; modalities, doses, volumes, and fractionation schema for RT; dose de-escalation or escalation in chemoradiation (CRT); immunotherapy; and posttreatment surveillance. We evaluated risk of bias (RoB) using the RoB2 tool for RCTs and the ROBINS-I tool for NRSIs and strength of evidence (SOE) using Agency for Healthcare Research and Quality Evidence-based Practice Center Program methods for prespecified outcomes (PROSPERO registration number CRD42023456886).

Results. We included 33 articles from 8 RCTs (6 with low to moderate RoB and 2 with high RoB) and 20 NRSIs (all with serious to critical RoB). Compared with RT alone, doublet CRT with 5-fluorouracil (5FU) plus mitomycin C (MMC) showed lower locoregional failure rate (LRF) and greater disease-specific and colostomy-free survival (CFS) (moderate to low SOE), greater hematologic toxicity (low SOE), greater overall acute harms (moderate SOE), and no difference in late harms (low SOE). Doublet CRT with 5FU plus MMC showed lower LRF (low SOE) and greater CFS and disease-free survival (DFS) (low SOE) than CRT with 5FU, and evidence was insufficient to compare harms. Compared with CRT with 5FU plus MMC, CRT with 5FU plus cisplatin did not improve several effectiveness outcomes up to 5 years, or overall acute or late harms (moderate to low SOE), showed lower hematologic toxicity (moderate SOE), and had conflicting, insufficient evidence for CFS. Triplet CRT with paclitaxel plus capecitabine plus MMC showed greater CFS, DFS, overall survival, and overall acute harms than doublet CRT with capecitabine plus MMC (low SOE). Remaining comparisons had insufficient evidence. Patients with older age, immunocompromised status, or minoritized racial/ethnic identities were underrepresented in included studies.

Conclusions. Doublet CRT is likely more effective but may have greater hematologic toxicity compared with RT alone or CRT with 5FU. Adding paclitaxel to doublet CRT may increase treatment efficacy and toxicity. Evidence is insufficient for optimal posttreatment surveillance strategies, quality of life, and other patient-reported outcomes. Future RCTs should increase inclusion of historically underrepresented patients, and future real-world evidence generation must prioritize methodological rigor.

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Executive Summary

Main Points

- For the initial treatment of stages I–III squamous cell carcinoma of the anus (SCCA), compared with radiation therapy (RT) alone, concurrent doublet chemoradiation (CRT) with 5-fluorouracil (5FU) plus mitomycin (MMC) likely results in greater disease-free survival and lower locoregional failure rate, may result in greater colostomy-free survival, likely increases overall acute harms, may increase hematologic toxicity, and may have no difference in late harms.
- Compared with concurrent CRT with 5FU, CRT with 5FU plus MMC may result in greater disease-free and colostomy-free survival and lower locoregional failure rate but difference in harms remains uncertain.
- Compared with CRT with 5FU plus MMC, CRT with 5FU plus cisplatin likely does not increase overall or progression-free survival and complete response rates, likely does not decrease distant metastasis rate; and may not increase disease-free survival, nor lower locoregional failure rate (up to 5 years of followup), likely decreases the risk of hematologic toxicity, but may not differ in other acute or late harms. Difference in colostomy-free survival remains uncertain.
- Compared with doublet CRT with capecitabine plus MMC, triplet CRT with paclitaxel plus capecitabine plus MMC may increase complete response, overall, disease-free, and colostomy-free survival, and overall acute harms, but may not differ in acute neutropenia, dermatologic, gastrointestinal, or genitourinary toxicity.
- Evidence remains uncertain for other comparisons including local excision versus CRT for stage I cancer; capecitabine versus 5FU; different modalities, doses, volumes, and fractionation schema for RT; dose de-escalation or escalation in CRT; immunotherapy; posttreatment surveillance strategies; and patient-reported outcomes such as bowel, urinary, and sexual function, pain, and quality of life.
- Most of the studies are assessed with high risk of bias. Observational studies should apply advanced methods such as target trial emulation for making causal inferences.
- Patients with immunocompromised status, older age, or minoritized racial/ethnic identities are underrepresented in the available body of evidence.

Background and Purpose

CRT with 5FU plus MMC has remained the standard treatment for stages I–III SCCA for several decades, despite clinical uncertainties and technological advancements. **This systematic review assesses the effectiveness and harms of different strategies for the initial treatment of stages I–III SCCA.** This review, funded by the Patient-Centered Outcomes Research Institute® (PCORI®), will be used by the American Society of Clinical Oncology (ASCO) and the American Society of Radiation Oncology (ASTRO) to develop clinical practice guidelines for the treatment of SCCA.

Methods

We followed the Agency for Healthcare Research and Quality Evidence-based Practice Program methods guidance. Our searches covered publications in MEDLINE®, Embase®, Cochrane Register of Controlled Trials, and ClinicalTrials.gov from January 2000 through March 2024, plus the reference lists of systematic reviews and included studies regardless of publication dates. We included randomized controlled trials (RCTs) and nonrandomized studies of interventions (NRSIs) comparing strategies for initial treatment and posttreatment surveillance. We evaluated risk of bias (RoB) using the Cochrane RoB2 tool for RCTs and the ROBINS-I tool for NRSIs, and strength of evidence (SOE) for prespecified outcomes (PROSPERO registration number CRD42023456886).

Results

We included 33 articles from eight RCTs (six with low to moderate RoB and two with high RoB) and 20 NRSIs (serious to critical RoB). Compared with RT alone, CRT with 5FU plus MMC improved several effectiveness outcomes (moderate to low SOE) but increased overall acute harms (moderate SOE) and resulted in no difference in late harms (low SOE, Table A). Compared with CRT with 5FU, CRT with 5FU plus MMC improved several effectiveness outcomes (low SOE), but evidence was insufficient to compare harms. Compared with CRT with 5FU plus MMC, CRT with 5FU plus cisplatin did not improve several effectiveness outcomes and late harms (moderate to low SOE), lowered acute hematologic toxicity (moderate SOE), and evidence was insufficient and conflicting for colostomy-free survival. Compared with CRT with capecitabine plus MMC, CRT with paclitaxel plus capecitabine plus MMC showed greater overall, disease-free, and colostomy-free survival, and overall acute harms (low SOE). Evidence was insufficient for remaining comparisons (not shown in Table A) including local excision for early-stage cancer, capecitabine versus 5FU, intensity modulated versus three dimensional conformal RT, proton versus photon beam, external beam RT versus brachytherapy boost, different RT doses, volumes, and fractionation schema, induction therapy, maintenance therapy, one versus two cycles of MMC, RT boost versus no boost, immunotherapy, and posttreatment surveillance. Evidence was insufficient for patient-reported outcomes such as bowel, urinary, and sexual function.

Table A. Summary of key findings and strength of evidence

Intervention Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Summary of Individual Study Reported Findings	Strength Of Evidence
CRT with 5FU plus MMC vs. RT alone	Overall survival (up to 5 yrs)	2; RCTs; n=695	No significant difference; precise estimates.	Moderate
	Disease-specific mortality (up to 5 yrs)	1; RCT; n=585	CRT favored over RT alone; rate, 28% vs. 39%, RR of 0.71 (95% CI, 0.53-0.95, median follow up: 42 months and similar in both arms)	Moderate
	CR (6 weeks post treatment)	2; RCTs; n=695	Both RCTs favor CRT over RT alone, rates 80% vs. 54% (p<0.05, n=110); 39% vs.30% (p<0.05, n=585)	Low
	LR failure rate (up to 5 yrs)	2; RCTs; n=695	Both RCTs favor CRT over RT alone, with 5-year rate 32% vs. 50% (p= 0.02, n=110) and 3-year rate 39% vs. 61% (RR, 0.54; 95% CI, 0.42 - 0.69; n=585)	Moderate

Intervention Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Summary of Individual Study Reported Findings	Strength Of Evidence
	Colostomy-free survival (up to 5 yrs)	1; RCT; n=110	CRT favored over RT alone; estimated improvement by 32% at 5yrs (p=0.002); estimates for each arm not reported	Low
	Overall acute harms	1; RCT; n=585	Significantly greater in CRT (48%) vs. RT alone (38.6%).	Moderate
	Acute hematologic toxicity	2; RCTs; n=695	Significantly greater in CRT vs. RT alone, frequency: 1 vs.0 grade 4 events (n=110); or 20 vs.0 overall events (n=585).	Low
	Acute derm and GI toxicity	2; RCTs; n=695	No significant difference, imprecise estimates.	Low
	Acute GU toxicity	1; RCT; n=585	No significant difference, imprecise estimates	Low
	Overall late harms	1; RCT; n=585	No significant difference, imprecise estimates.	Low
	Late derm toxicity	2; RCTs; n=695	No significant difference, imprecise estimates.	Low
	Late GI and GU toxicity	1; RCT; n=585	No significant difference, imprecise estimates.	Low
CRT with 5FU plus MMC vs. CRT with 5FU	Overall survival (at 4 yrs)	1; RCTs; n=310	No significant difference, precise estimates.	Low
	CR (4-6 weeks post treatment)	1; RCTs; n=310	No significant difference, precise estimates.	Low
	DFS (at 4 yrs)	1; RCTs; n=310	Favors 5FU + MMC over 5FU alone, 73% vs. 51% (p<0.001).	Low
	LR failure rate (at 4 yrs)	1; RCTs; n=310	Favors 5FU + MMC over 5FU alone, 16% vs 34% (p<0.001).	Low
	Colostomy-free survival (at 4 yrs)	1; RCTs; n=310	Favors 5FU + MMC over 5FU alone, 71% vs. 59% (p = 0.014).	Low
CRT with 5FU plus MMC vs. CRT with 5FU plus cisplatin	Overall survival (up to 5 yrs)	2; RCT; n=1622	No significant difference, precise estimates.	Moderate
	DM (up to 5 yrs)	1; RCT; n=682	No significant difference, precise estimates.	Moderate
	LR failure and DFS (up to 5 yrs)	1; RCT; n=682	No significant difference, imprecise estimates.	Low
	PFS, CR	1; RCT; n=940	No significant difference, precise estimates.	Moderate
	Overall acute harms	2; RCT; n=1622	No significant difference, precise estimates.	Moderate
	Acute hematologic toxicity	2; RCT; n=1622	Significantly greater with MMC vs. cisplatin, with grade 3+ toxicity frequency of 61% vs. 42% (p<0.001, n=682) and 26% vs. 16% (p<0.001, n=940).	Moderate
	Acute derm, GI, and GU toxicity	2; RCT; n=1622	No significant difference, imprecise estimates.	Low
	Late harms	1; RCT; n=682	No significant difference, imprecise estimates.	Low
CRT with capecitabine plus MMC plus paclitaxel vs.	Overall survival (up to 3 yrs)	1; RCT; n=144	Significantly greater in the paclitaxel arm vs no paclitaxel arm; 95.5% vs 80% (p<0.001).	Low
	Disease-free survival (up to 3 yrs)	1; RCT; n=144	Significantly greater in the paclitaxel arm vs no paclitaxel arm; 87.1% vs 64.4% (p=0.001).	Low

Intervention Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Summary of Individual Study Reported Findings	Strength Of Evidence
CRT with capecitabine plus MMC	Colostomy-free survival (up to 3 yrs)	1; RCT; n=144	Significantly greater in the paclitaxel arm vs no paclitaxel arm; 83.2% vs 67.5% (p=0.029).	Low
	CR (at 26 weeks posttreatment)	1; RCT; n=144	Significantly greater in the paclitaxel arm vs no paclitaxel arm; 88.9% vs 75% (p=0.049).	Low
	Overall acute harms	1; RCT; n=144	Significantly greater in the paclitaxel arm vs no paclitaxel arm; 56.9% vs 26.4% (p<0.001).	Low
	Neutropenia (grade 3 or 4)	1; RCT; n=144	No significant difference, imprecise estimates.	Low
	Acute derm, GI, GU harms	1; RCT; n=144	No significant difference, imprecise estimates.	Low

Note: Remaining comparisons not mentioned in the table received an insufficient grade. All harms are grade 3 or 4 unless specified otherwise.

Abbreviations: CI- confidence interval; CRT- chemoradiation; LR- locoregional; CR- complete response;; DFS- disease-free survival; PFS- progression-free survival; DM- distant metastasis; 5FU- 5 fluorouracil, MMC- mitomycin C; RT- radiation therapy; derm-dermatologic; GI-gastrointestinal; GU-genitourinary; RCT- randomized controlled trial; yrs- years; vs.- versus; RR- relative risk.

Strengths and Limitations

Our review focused on the highest-quality evidence for benefits and harms of initial treatment strategies from four large databases.

Our review and the evidence itself had limitations. We based our SOE assessment on statistical rather than clinical significance due to the lack of established thresholds for minimal clinically important differences and lack of prioritization of outcomes in this field. RCTs were limited by inconsistency in outcome definitions and measurement between trials, inadequately addressing attrition, multiple comparisons testing, and competing risks over a longer followup period, and inadequate power to compare acute and late harms. Included NRSIs had serious to critical RoB, making it impossible to draw causal inferences. Common limitations of the NRSIs included poorly defined interventions and comparators, lack of power calculations, and inadequately addressing missing data, competing risks, confounding, and potential selection bias. Patients with immunocompromised status, older age, or minoritized racial/ethnic identities were underrepresented, making applicability of findings to these groups challenging.

Implications and Conclusions

For the initial treatment of nonmetastatic SCCA, CRT with 5FU plus MMC is likely more effective but may increase hematologic toxicity compared with RT alone or CRT with 5FU. Compared with CRT with 5FU plus MMC, CRT with 5FU plus cisplatin likely does not improve effectiveness outcomes but likely decreases hematologic toxicity. The addition of paclitaxel as a third cytotoxic chemotherapy drug to CRT with capecitabine plus MMC may increase treatment efficacy and toxicity. Optimal posttreatment surveillance strategies remain uncertain. Future research should prioritize methodological rigor through well-designed RCTs or real-world evidence generation from NRSIs using appropriate methodology such as “target trial emulation” for drawing causal inferences, include patient-reported outcomes such as bowel, urinary, and

sexual function, pain, and quality of life, and increase representation of historically underrepresented patients.

1. Introduction

1.1 Background

Anal cancer is a rare disease, representing only 1to 2 percent of all gastrointestinal malignancies.[1] However, its incidence has risen steadily by two to three percent a year over the past decade. Squamous cell carcinoma of the anus (SCCA) is by far the most common histology, accounting for over 90 percent of anal malignancies,[2-4] risk factors include female sex, Black race, and men who have sex with men.[2,5] Treatment of SCCA of the anal canal includes chemotherapy, radiation, and/or surgical intervention. Depending on the initial staging, treatment may yield a sphincter preservation rate near 80 percent and 5-year survival up to 89 percent.[6]

Treatment, survival, and quality of life vary with stage of disease and tumor location. Table 1 reports SCCA staging based on tumor size/extent.[4,7]

Table 1. The American Joint Committee on Cancer Staging system for anal cancer: version 9

Stage	Definition
I	T1 (tumor ≤2 cm in greatest dimension), no nodal involvement (N0), and no distant metastases (M0)
II	T1-T2 (tumor >2cm in greatest dimension without invasion of adjacent organs), N0- N1 (tumor invading perirectal, inguinal, internal iliac, or obturator nodes, and/or external iliac nodes), and M0
III	T3-T4 (tumor >5cm in greatest dimension or tumor of any size invading adjacent organs, such as the vagina, urethra, or bladder), N0-1 (tumor invading perirectal, inguinal, internal iliac, or obturator nodes, and/or external iliac nodes), and M0
IV	Distant metastases (M1)

Historically, nonmetastatic SCCA was treated with large, radical, and highly morbid surgery. However, after Nigro et al. (1974) published a case series describing the success of concurrent chemoradiation (CRT) with 5 fluorouracil (5FU) and Mitomycin-C (MMC) as an organ preserving treatment strategy with reduced harms compared to conventional surgical treatment at the time,[4] concurrent CRT with 5FU and MMC developed into the standard of care for nonmetastatic SCCA and remained so for several decades based on three Phase III trials.[8-10] The chemotherapeutic agents typically used are 5FU, in which the dose is calculated from the patient's body surface area and is given on days 1-4 and again on days 29-32, and MMC, administered as a bolus on days 1 and 29.[11] These regimens present significant toxicity, which has led to increasing interest in alternative treatments to balance benefits and harms.[8,12-14] Indeed, standard treatment is so difficult to tolerate that up to 55 percent of patients take treatment breaks.[6] Ultimately, the toxicity of chemotherapy, radiation, and extended surgical resections lower adherence to prescribed protocols and potentially reduce their effectiveness.[6,15,16]

Potentially less toxic protocols include local excision alone, capecitabine, immunotherapy, proton beam radiotherapy, and de-escalation of radiation dosing for appropriate stages.[6] More advanced tumors are less likely to respond to existing therapeutic approaches. Thus, dose escalation remains a topic of investigation in patients with more advanced disease.[6] In addition, few studies have examined long-term side effects of treatment that significantly impact patient quality of life, such as sexual and bowel dysfunction. Therefore, a rigorous comparative effectiveness evaluation is needed for these emerging therapies and de-escalation strategies, the goal being to identify the optimal management strategy for reducing toxicity without compromising long-term oncologic outcomes, and to provide patients with the best information

to support improved chances of survival and better quality of life. Furthermore, little is known about the comparative effectiveness of different frequencies and modalities of posttreatment surveillance strategies. Similar to the unvalidated schedule implemented in the RTOG 9811 trial, the current standard of care is to follow patients after the completion of their treatment at 3-month intervals the first 2 years, 6-month intervals in years 3 to 5, then yearly thereafter, mostly using clinical examination and diagnostic imaging.[11,17] Uncertainty persists whether surveillance frequency could be decreased after the first two years post treatment, as well as about the comparative validity of different surveillance techniques.[18] A rigorous systematic review will help clinicians, patients, and other stakeholders to make informed decisions about initial treatment and posttreatment surveillance.

1.2 Purpose of This Review

This systematic review assesses the effectiveness and harms of treatment strategies for stages I–III SCCA. Funded by the Patient-Centered Outcomes Research Institute® (PCORI®), the review will be used by the American Society of Clinical Oncology (ASCO) and the American Society of Radiation Oncology (ASTRO) to develop clinical practice guidelines for the treatment of SCCA.

2. Methods

2.1 Review Approach

The methods for this systematic review followed the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[19] This systematic review also reports in accordance with the Preferred Items for Reporting in Systematic Reviews and Meta-Analyses (PRISMA),[20] A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2),[21] and the Patient Centered Outcomes Research Institute (PCORI®) Methodology Standards checklist. The final protocol is registered on PROSPERO (CRD42023456886) and posted on the AHRQ Effective Health Care website at https://effectivehealthcare.ahrq.gov/products/anal-cancer-treatment/protocol.

2.1.1 Key Questions

The Evidence-based Practice Center drafted the following Key Questions (KQs) with input from public comments, Key Informants, and a panel of Technical Experts.

KQ 1. What are the effectiveness and harms of different modalities of initial treatment for stages I–III squamous cell anal cancer?
KQ 2. What are the effectiveness and harms of different modalities of radiation therapy for initial treatment of stages I–III squamous cell anal cancer?
KQ 3. What are the effectiveness and harms of different radiation therapy doses, volumes, and fractionation schema for initial treatment of stage I–III squamous cell anal cancer?
KQ 4. What are the effectiveness and harms of different combinations of chemotherapy and radiation therapy, and dose de-escalation or dose escalation for initial treatment of stages I–III squamous cell anal cancer?
KQ 5. What are the effectiveness and harms of immunotherapy for initial treatment of stages I–III squamous cell anal cancer?
KQ 6. What are the effectiveness and harms of different frequencies and modalities for posttreatment surveillance strategies after initial treatment of stages I–III squamous cell anal cancer?

For all KQs, do the outcomes differ by patient characteristics such as age, sex, immunocompromised status, or other characteristics associated with health inequities (such as race/ethnicity)?

2.2 Study Selection

We conducted a comprehensive literature search May 25–30, 2023, searching in MEDLINE®, Embase®, Cochrane Central Register of Controlled Trials (CENTRAL), and clinicaltrials.gov, from January 1, 2000, through current date (Appendix A). The draft report underwent sequential peer review and public comment. We conducted an updated search during the public comment period, through March 4, 2024. In our search strategy, we included vocabulary and natural language terms, along with free-text words, relevant to each KQ. We supplemented our bibliographic database searches with citation searching of relevant systematic reviews and original research, from which we included all eligible studies regardless of

publication date. All searches were conducted by a medical librarian and were peer reviewed (see Methods, Appendix A). Studies excluded at full-text screening are listed in Appendix B

We uploaded citations into a Web-based online citation and article screening tool, PICO Portal™ (www.picoportal.net), designed for systematic reviews, and removed duplicate citations using the PICO Portal™ software. PICO Portal uses machine learning to sort and present first those citations most likely to be eligible. Initially, two independent reviewers screened titles and abstracts for potential relevance to the KQs using prespecified inclusion and exclusion criteria (Table 2). Any disagreement was resolved through group discussions with the review team. After the machine learning algorithm had been sufficiently trained, using a priori criteria of 90 percent recall rate of eligible citations, we switched to one independent reviewer until we reached a 100 percent recall rate of all eligible articles, and the machine learning algorithm had a zero false negative rate (see review protocol: https://effectivehealthcare.ahrq.gov/products/anal-cancer-treatment/protocol). Two independent reviewers screened each article at the full-text level on PICO Portal™ using the same criteria (Table 2).

Selection criteria for all KQs are presented in Table 2. We included all randomized controlled trials (RCTs) for each unique comparison when available. For other comparisons, we relied on well-designed nonrandomized studies of interventions (NRSIs) as described in Table 2. We searched ClinicalTrials.gov to identify relevant completed studies that did not report outcomes and analyses in the published literature to help assess publication and reporting bias, and to identify and track ongoing studies that might help address the Key Questions in the future. We did not receive any responses to a Federal Register notice requesting Supplemental Evidence and Data for Systematic review (SEADS).

Table 2. Study eligibility criteria

PICOTS; KQ	Inclusion Criteria	Exclusion Criteria
Population; All KQs	Adults with stages I–III squamous cell anal cancer (anal canal and anal margin) Inclusive of all patient characteristics such as age, sex, immunocompromised status, or other characteristics associated with health inequities (such as race/ ethnicity)	Adults with stage IV anal cancer, lower rectal cancer that has spread to the anal canal, nonsquamous cell anal cancer (e.g., adenocarcinomas, undifferentiated cancer) Studies including mixed populations with Stages I-IV squamous cell anal cancer which contain 20% or greater proportion of stage IV squamous cell anal cancer
Interventions; KQ 1	Surgery, radiation therapy, or chemotherapy, alone or in combination as neoadjuvant/ adjuvant or as induction/ maintenance	Reconstructive surgery, palliative therapy (includes chemotherapy with palliative intent), or treatment for premalignant lesions
Comparison; KQ 1	Surgery, radiation therapy, or chemotherapy, alone or in combination as neoadjuvant/ adjuvant or as induction/ maintenance	Reconstructive surgery, palliative therapy (includes chemotherapy with palliative intent), or treatment for premalignant lesions
Interventions; KQ 2	Different modalities of radiation therapy such as, but not limited to, IMRT, proton radiation therapy, and brachytherapy boost.	Palliative therapy
Comparison; KQ 2	Comparators for different modalities of radiation therapy such as, but not limited to, 3DCRT, photon or electron radiation therapy, and external beam radiation therapy boost.	Palliative therapy
Interventions; KQ 3	Radiation therapy**:** varying doses, target (primary and nodal) volumes, and fractionation schema	Palliative therapy

2. Methods

PICOTS; KQ	Inclusion Criteria	Exclusion Criteria
Comparison; KQ 3	Radiation therapy**:** varying doses, target (primary and nodal) volumes, and fractionation schema	Palliative therapy
Interventions; KQ 4	Chemotherapy and radiation therapy combinations (e.g., 5-Fluorouracil, Mitomycin-C, Cisplatin)**:** variations in dose of chemotherapy or radiation therapy	Palliative therapy
Comparison; KQ 4	Chemotherapy and radiation therapy combinations (e.g., 5-Fluorouracil, Mitomycin-C, Cisplatin): variations in dose of chemotherapy or radiation therapy	Palliative therapy
Interventions; KQ 5	Immunotherapy (e.g., pembrolizumab, nivolumab)	None
Comparison; KQ 5	Other treatment (e.g., chemotherapy, radiation therapy, chemotherapy + radiation therapy)	None
Interventions; KQ 6	Posttreatment surveillance strategies**:** variations in frequency and in modalities (e.g., CT, MRI, PET scans, biopsy, DRE, anoscopy, flexible sigmoidoscopy)	Screening for primary prevention, initial cancer staging, strategies for surveillance post noninitial curative treatment
Comparison; KQ 6	Posttreatment surveillance strategies**:** variations in frequency and in modalities (e.g., CT, MRI, PET scans, biopsy, digital rectal exam, anoscopy, flexible sigmoidoscopy)	Screening for primary prevention, initial cancer staging, strategies for surveillance post noninitial curative treatment
Outcomes; All KQs	Overall survival, disease-specific survival, disease-free survival (including persistence, recurrence, or relapse), colostomy-free survival, local control, complete clinical response, salvage rate, sphincter preservation, health-related quality of life, treatment breaks frequency or duration), treatment discontinuation, interruptions, or median treatment days, bleeding per rectum, functional outcomes (e.g., fecal or urinary incontinence, erectile dysfunction, sexual dysfunction, use of vaginal dilators), harms of treatment including acute and late toxicity (e.g., myelosuppression, gastrointestinal toxicity, such as diarrhea, vomiting, and bowel obstruction, secondary malignancy, radiation dermatitis, radiation proctitis, radiation cystitis, pelvic insufficiency fractures, vaginal stenosis)	None
Timing; All KQs	No restrictions on duration of treatments or followup.	None
Setting; All KQs	Cancer care settings	None
Study Design; All KQs	Randomized controlled trials, nonrandomized controlled trials, observational cohort with concurrent comparator, interrupted time-series, and other quasi-experimental designs using appropriate analytic techniques.	Case reports, case series, commentaries, cross-sectional studies, reviews, qualitative studies, studies with sample size less than 30 patients (or less than 15 per treatment group/arm), nonrandomized studies with unspecified or poorly defined intervention/ treatment protocol (e.g., lack of names of chemotherapy agents used), nonrandomized studies with analytic techniques that don't allow drawing causal inferences.

Abbreviations: 3DCRT = three-dimensional conformal radiation therapy; DRE = digital rectal exam; IMRT = intensity-modulated radiation therapy; KQ = Key Question; MRI = magnetic resonance imaging; PET = positron emission tomography; CT = computed tomography.

2.3 Assessment of Risk of Bias

We evaluated each study for risk of bias (RoB) using the Cochrane Risk of Bias Tool 2.0 (RoB 2)[22] for RCTs and the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I)[23] for NRSI. Components of the RoB 2 include participant group assignment (random sequence generation, allocation concealment), blinding (performance and detection bias), completeness of followup (attrition bias), analyses and outcome reporting consistent with predefined protocols (selective reporting bias), and other issues (such as appropriateness of analytic approach). We assessed RCT RoB for each domain mentioned above, and assigned a summary RoB rating for each study as low, moderate, or high. Components of the ROBINS-I include assessing bias due to confounding, classification of interventions, selection of participants (into the study, or into the analysis), deviations from intended interventions, missing data, measurement of the outcome, and selection of the reported results. We assessed the RoB for NRSI for each domain mentioned above, and assigned a summary RoB rating as low, moderate, serious, or critical. One investigator assessed RoB and a second reviewed; discrepancies were reconciled via consensus.

2.4 Data Extraction and Data Management

We extracted the data using standardized extraction form in Microsoft Excel for all included studies. We extracted data elements such as author, year of publication, funding source, setting, subject inclusion and exclusion criteria, intervention and control characteristics, sample size, followup duration, participant baseline age, race/ethnicity, sex, immunocompromised status, clinical characteristics including cancer stage and outcome timing, and results of outcomes and adverse effects outlined in Table 2 (frequency of events, risk difference, risk ratio, odds ratio, or hazard ratio). One reviewer extracted the data, and a second reviewer verified the extracted data for accuracy by comparing it directly with the data source. Any discrepancies were resolved by full team discussions. Definitions for acute versus late harms varied between studies; we extracted data for harms using author reported definitions for each study.

2.5 Data Synthesis

We organized all included studies by KQ. Within each KQ, we further organized studies by unique comparisons, outcomes, and outcome timing. Because of heterogeneity in interventions across studies and the small number of studies for each comparison, we were not able to pool data from multiple studies for any outcomes under any unique comparison; therefore, we synthesized the data qualitatively.

2.6 Grading the Strength of the Body of Evidence

We evaluated the strength of evidence (SOE) of outcome-intervention pairs in accordance with AHRQ methods.[24] We briefly summarize the process of grading the SOE below and provide additional details in Methods Appendix A. Outcomes are listed in Table 2, above.

We assigned the SOE an overall grade of high, moderate, low, or insufficient (Table 3) by evaluating and weighing the combined results of the following five domains: study limitations, consistency, directness, precision, and reporting bias. For more details regarding individual domains, please see Appendix A.

Table 3. Interpretations of overall rating in strength of evidence assessment

Strength of Evidence Rating	Interpretation
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions).
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of the effect for this outcome. No evidence is available, or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

RCT evidence was initially considered high, with possible downgrades for any of these domains. For NRSIs, the strength started at moderate for harms outcomes, and low for benefit outcomes. While AHRQ guidance allows for upgrading NRSI evidence in certain circumstances, we did not upgrade any NRSI because none of the included studies merited doing so. When both RCTs and post hoc secondary analyses of RCTs were included for an outcome, we followed AHRQ guidance for consideration of consistency and weighing of primary RCTs over post hoc studies. For bodies of evidence with only a single study, we rated consistency as not applicable. We downgraded SoE when there was no replication (only one study). In other words, if only one study existed for a comparison, SoE could not be rated as high. In cases of RCTs where there was more than one publication evaluating the same outcome, to avoid double counting that RCT population, we chose to assess findings from the main report of the RCT instead of the post hoc, secondary analyses which were assessed at high RoB. We derived SOE rating based on statistical rather than clinical significance because validated measures of clinical significance (minimal clinically important differences) were not available and there is a lack of prioritization among outcomes frequently evaluated in the literature. For interpreting SOE ratings, as per AHRQ guidance, we used the qualifiers “likely” for statements with moderate SOE, “may” for statements with low SOE, and “uncertain” for statements with insufficient SOE.

2.7 Applicability Assessment

Applicability was evaluated following the AHRQ Methods Guide. We identified several factors that could influence applicability a priori, including patient characteristics, interventions, comparisons, outcomes, and settings (see details in Appendix A). This information was used to determine the relevance of the evidence to real-world clinical practice in typical U.S. settings and to qualitatively summarize applicability assessments. The findings are discussed in the review.

2.8 Peer Review and Public Commentary

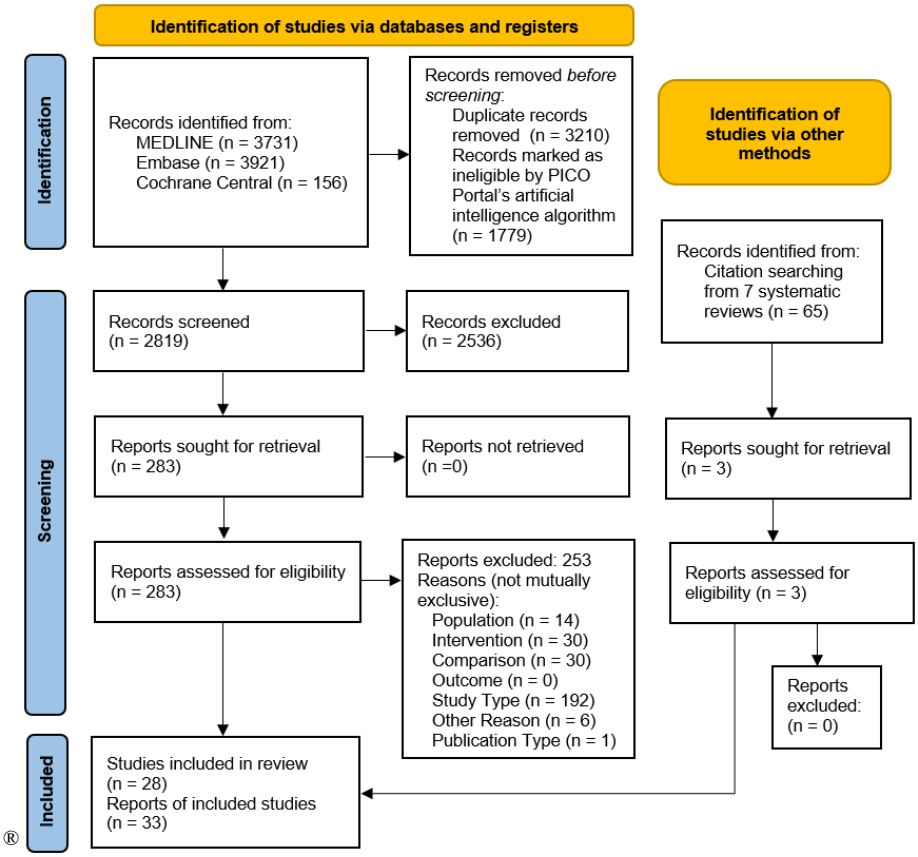
The report was reviewed by nine peer-reviewers including clinician scientists and content experts in radiation oncology, medical oncology, and surgical oncology, and an independent patient advocate with expertise in patient-reported outcomes. An updated report was then posted on the AHRQ website for public commentary. It remained open for public comment for 45 days. The disposition of comments document will be posted approximately three months after the final report is posted.

3. Results

3.1 Overview

From 4,598 unique search results, we identified 33 eligible publications consisting of 28 unique studies. Of the 33 eligible publications, 16 were related to Key Question (KQ) 1, seven were related to KQ2, eight were related to KQ3, six were related to KQ4, and one was related to KQ6. We found no studies related to KQ5 on the effectiveness and harms of immunotherapy versus other treatment modalities for squamous cell carcinoma of the anus (SCCA). The flow of the systematic review is described in Figure 1, adapted from the Preferred Items for Reporting in Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[20]

Figure 1. Literature flow in systematic review



The results section is organized by KQ. The literature within each KQ is further organized by intervention comparisons, and for each comparison we provide a description of included literature, a summary of the risk of bias (RoB), and key findings. For KQ1, we identified moderate to insufficient strength of evidence (SOE) for four comparisons. We found insufficient SOE due to a high RoB for all outcomes in all remaining comparisons, including two comparisons in KQ1 (comparing chemoradiation [CRT] with mitomycin C [MMC] and 5 fluorouracil [5FU] versus MMC and capecitabine; and comparing CRT with MMC and 5FU versus MMC and cisplatin) and all comparisons in KQs 2 through 6. Therefore, for comparisons with insufficient SOE, we do not provide estimates in the summary of findings tables; instead we provide them in the Appendix C, Appendix Table C.6.2. Detailed trial characteristics, participants, and RoB assessments for studies can be found in Appendix Tables C.1.1 to C.1.5,

C.2.1 to C.2.5, and C.4.1 and C.4.2, respectively. Appendix Tables C.5.1 to C.5.5 details the key findings and Appendix Tables C.6.1 to C.6.5 details SOE assessment for KQs 1 through 4 and 6. Unpublished RCTs are listed in Appendix D and the PCORI Methodology Standards Checklist is presented in Appendix E.

3.2 Findings for Key Question 1: Initial Treatment Strategies

Key Question 1. What are the effectiveness and harms of different modalities of initial treatment for stages I–III squamous cell anal cancer?

3.2.1 Key Points

- **For local excision (LE) versus CRT in initial treatment of early stage (T1N0) SCCA:**
  - evidence was insufficient to inform benefits and
  - no evidence addressed harms.
- **Compared with radiation therapy (RT) alone, doublet CRT with 5FU plus MMC:**
  - likely results in greater rate of disease-free survival (DFS, moderate SOE),
  - likely results in lower locoregional failure rate (LRF, moderate SOE),
  - likely results in no difference for overall survival (OS, moderate SOE),
  - may result in greater rates of colostomy-free survival (CFS, low SOE),
  - may result in greater complete response rates (CR, low SOE),
  - likely results in greater rates of acute overall harms (moderate SOE),
  - may result in greater rates of acute hematologic toxicity (low SOE),
  - may result in no significant difference in other acute harms (low SOE), and
  - may result in no significant difference in late harms (low SOE).
- **Compared with singlet CRT with 5FU, doublet CRT with 5FU plus MMC:**
  - may result in a greater rate of DFS (low SOE),
  - may result in a greater rate of CFS (low SOE),
  - may result in a lower rate of LRF rate (low SOE),
  - may result in no significant difference in CR (low SOE), and
  - may result in no significant difference for OS (low SOE).
  - Evidence was insufficient to compare any harms.
- **Compared with CRT with 5FU plus MMC, CRT with 5FU plus cisplatin:**
  - likely does not result in a higher CR rate (moderate SOE),
  - likely does not result in a higher progression-free survival rate (moderate SOE),
  - likely does not result in a lower rate of distant metastasis (moderate SOE),
  - likely does not result in greater OS (moderate SOE),
  - may not result in lower LRF rate (low SOE),
  - may not result in lower DFS (low SOE),
  - has insufficient evidence on rates of CFS,
  - likely does not result in lower rate of acute overall harms (moderate SOE),
  - likely results in lower rates of acute hematologic toxicity (moderate SOE),
  - may not result in lower acute dermatologic, gastrointestinal, and genitourinary toxicity rates (low SOE), and
  - may not result in lower late harms (low SOE).
- **Compared with CRT with capecitabine plus MMC, CRT with capecitabine plus MMC plus paclitaxel:**
  - may result in a higher OS, DFS, CFS, and CR rate (low SOE)

  - may result in greater overall acute harms (low SOE)
  - may result in no significant difference in acute neutropenia, dermatologic, gastrointestinal, or genitourinary harms (low SOE)
- **Comparing CRT with MMC and cisplatin versus CRT with MMC and 5FU:**
  - evidence was insufficient to compare effectiveness and harms.
- **Comparing CRT with MMC and capecitabine versus CRT with MMC and 5FU:**
  - evidence was insufficient to compare effectiveness and harms.

3.2.2 Local Excision Versus CRT for Stage I Cancer

3.2.2.1 Description of Included Evidence

Three nonrandomized studies of interventions (NRSIs) (n=3316) compared the efficacy of LE versus CRT in adult patients with early-stage cancer (T1N0 disease, Table 4).[25-27] Two NRSIs (n=3126) drew data from the National Cancer Database (year 2004 to 2012, n=2243)[25] and the Surveillance, Epidemiology, and End Results Program (SEER) database (year 2004 to 2015, n=883).[27] In contrast, one NRSI (n=190) applied several selection criteria to SEER-Medicare linked data (year 1992 to 2000), restricting its sample to a small and highly specific group of patients.[26] Two NRSIs had serious RoB[25,27] and one NRSI had critical RoB.[26] One NRSI (n=2243)[25] was at risk of misclassifying treatment assignment, two NRSIs (n=1073)[26,27] provided insufficient to no information regarding missing data in their analyses, and one small sized NRSI (n=190)[26] had critical risk of selection bias and did not provide power calculations.

Table 4. Study characteristics for local excision (LE) versus CRT

Characteristic	Information
Number of studies	3 NRSIs (n=3316)
Study population	2 NRSIs (n=3126): Mean age, 55-60 years, >80% White, 32 to 48% male, HIV status not reported, 8 to 10% with histologically poor or undifferentiated cancer, and about 30% with tumor size up to 1 cm. 1 NRSI (n=190): Mean age, 75 years, sex, race, HIV status, and tumor histologic grade and size not reported.
Intervention	Local excision
Comparator	CRT (3 NRSIs), RT alone (1 NRSI)
Setting and funding	3 NRSIs (n=3316): US; funded by federal agency.
Risk of bias	2 NRSIs (n=3126): Serious risk of bias 1 NRSI (n=190): Critical risk of bias

Abbreviations: HIV = human immunodeficiency virus; n = number of study participants; NRSI = nonrandomized study of intervention; CRT = chemoradiation; RT = radiation therapy.

3.2.2.2 Summary of Findings

3.2.2.2.1 Summary of Findings for Effectiveness

Evidence was insufficient to compare LE versus CRT (Table 5) for OS in two NRSIs, (n=2433,[25,26] imprecise estimates) including analyses stratified by tumor size (≤1 cm and >1 cm to ≤2 cm, one NRSI, n=2243), and for 5-year cause-specific survival rate in one NRSI (n=883, imprecise estimate).[27]

3.2.2.2.2 Summary of Findings for Harms

None of the three NRSIs reported data on harms of treatment or toxicity outcomes.

Table 5. Summary of findings for LE versus CRT

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	SOE
LE vs CRT, early stage	Overall survival	2; NRSIs; n=2433;	Inconclusive. No significant difference.	Insufficient
	Cause-specific survival	1; NRSI; n=883;	Inconclusive No significant difference.	Insufficient

Abbreviations: NRSI = nonrandomized study of intervention; vs. = versus; LE = local excision; n = number; CRT = chemoradiation; SOE = strength of evidence.

3.2.3 RT Alone Versus CRT With 5FU + MMC

3.2.3.1 Description of Included Evidence

Three studies comparing RT alone versus CRT were included (Table 6); two were randomized controlled trials (RCTs) (n=695)[8,9] and one (n=577)[28] reported post hoc analyses of an included RCT, with a longer followup period after the parent trial concluded. The larger RCT (n=585)[9] included a few cases of stage IV cancer at baseline (metastasis in <4 percent of total sample), whereas the smaller RCT (n=110)[8] reported no cases of stage IV cancer at baseline. The larger RCT (n=585)[9] allowed a higher total and per fraction dose of radiation and a higher dose of 5FU and MMC compared with the other RCT (n=110, Appendix Table C.1.1), but modalities of delivering RT were similar in both RCTs. The study entailing post hoc analysis of an RCT (n=585)[28] had high RoB because it was not a pre-specified analysis and evaluated multiple outcomes over multiple timepoints without sufficiently accounting for competing risks or multiple comparisons testing. One RCT (n=110)[8] raised concerns for bias because it did not describe how randomization was conducted or present power calculations.

Table 6. Study characteristics for RT alone versus CRT with 5FU + MMC

Characteristic	Information
Number of studies	2 RCTs (n=695); 1 *post hoc* analysis of an RCT (n=577)
Study population	Mean age, >60 years, 30 to 45% male, HIV status and race not reported, 23 to 45% with positive nodal status, and a similar mix of T1 to T4 disease.
Intervention	RT alone; RT schema: 45 Gy in 25 fractions + EBRT-Boost with 15-20 Gy
Comparator	CRT with 5FU and MMC; RT: 45 Gy in 25 fractions + EBRT-Boost with 15-20 Gy
Setting and funding	1 RCT (n=110): European Union; funding source not reported. 1 RCT (n=585): United Kingdom; funding source not reported.
Risk of bias	1 RCT (n=110): moderate risk of bias; 1 RCT (n=585): low risk of bias 1 post hoc analysis of RCT: high risk of bias

Abbreviations: 5FU = 5 fluorouracil; CRT = chemoradiation; EBRT =external beam radiation therapy; HIV = human immunodeficiency virus; Gy = gray; MMC = mitomycin C; n = number; RCT = randomized controlled trial; RT = radiation therapy.

3.2.3.2 Summary of Findings

3.2.3.2.1 Summary of Findings for Effectiveness

Findings are summarized in Table 7. Compared with RT alone, CRT resulted in a significantly higher CR rate at six weeks posttreatment (low SOE in two RCTs, same direction but inconsistent magnitude of effect) and significantly lower locoregional (LR) failure rates for up to 5 years of followup (moderate SOE in 2 RCTs, with consistent estimates), which persisted up to 12 years according to the post hoc analyses of the larger RCT (hazard ratio, 0.61 favoring

CRT over RT alone, 95% confidence interval [CI], 0.49 – 0.76). Both RCTs reported no significant difference in OS rate between CRT versus RT alone (moderate SOE in 2 RCTs, with imprecise estimates). However, the larger RCT (n=585)[9] reported that anal cancer-related mortality was significantly lower after CRT than with RT alone at five years (moderate SOE in 1 RCTs, with a precise estimate) and up to 12 years of followup (HR, 0.67 favoring CRT over RT alone, 95% CI, 0.51 – 0.88). The post hoc analysis of an RCT (n=585) was not prespecified, did not adjust for multiple comparisons, had a high RoB and was not included for SOE analyses to avoid double counting the population.

3.2.3.2.2 Summary of Findings for Harms

Acute harms or toxicity events occurring during treatment are summarized in Table 7. One RCT (n= 585) reported significantly higher frequency of acute harms during CRT versus RT alone. Another RCT (n=110) found marginally higher frequency of acute harms during CRT versus RT alone, which was not statistically significant but likely lacked power to test meaningful differences between treatment groups.

Late harms or toxicity events that occurred posttreatment are summarized in Table 7. None of the studies showed any significant difference between CRT versus RT.

Table 7. Summary of findings for RT alone versus CRT with 5FU + MMC

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	SOE
RT alone vs. CRT with 5FU and MMC	Overall survival (up to 5 years of followup)	2; RCTs; n=695	No difference. One RCT (n=110) reported a 5 year-overall survival rate of 54% with RT alone vs. 58% with CRT; p = 0.17. One RCT (n=585) reported a 3 year- overall survival rate of 58% with RT alone vs. 65% with CRT, (RR=0·86, 95% CI 0·67–1·11, p=0·25).	Moderate
	Disease-specific mortality (up to 5 years of followup)	1; RCT; n=585	CRT favored over RT alone. One study reported a frequency of 28% with CRT vs. 39% with RT alone, RR of 0.71 for CRT (95% CI, 0.53 - 0.95, ref-RT) over median followup of 42 months	Moderate
	Complete response (at 6 weeks posttreatment)	2; RCTs; n=695	CRT favored over RT alone. One RCT reported a complete response of 54% in RT alone vs. 80% in CRT at 6 weeks posttreatment (p<0.05). One RCT reported a complete response of 30% with RT alone vs. 39% with CRT at 6 weeks post treatment (p<0.05).	Low
	Local failure rate (up to 5 years followup)	2; RCTs; n=695	CRT favored over RT alone. One RCT reported a frequency of 50% with RT vs. 32% with CRT at 5 years (p = 0.02). One RCT reported a frequency of 61% with RT alone vs. 39% with CRT at 3 years (RR, 0.54; 95% CI, 0.42 - 0.69; ref-RT alone)	Moderate
	Colostomy-free survival (up to 5 years followup)	1; RCT; n=110	CRT favored over RT alone. One RCT reported improvement in CRT arm vs. RT arm by 32% at 5yrs (p=0.002); individual estimates by arm not reported.	Low

3. Results, Findings for Key Question 1: Initial Treatment Strategies, RT Alone Versus CRT With 5FU + MMC

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	SOE
	Overall acute harms	1; RCT; n=585	Significantly greater in CRT vs. RT alone. One RCT (n=585) reported significant greater (p=0.03) overall acute toxicity with RT alone (n=110 out of 285 patients with vs. CRT (n=140 out of 292 patients).	Moderate
	Acute hematologic toxicity	2; RCTs; n=695	Significantly greater in CRT vs. RT alone. One RCT (n=110) reported one grade 4 event in CRT vs zero grade 4 events in RT alone. One RCT (n=585) reported greater toxicity with CRT (n=20) vs. RT alone (n=0).	Low
	Acute dermatologic toxicity	2; RCTs; n=695	No significant difference. One RCT (n=110) reported no significant difference (p>0.05) in acute grade 3+ toxicity in CRT (n=26) vs. RT alone (n=29). Another RCT (n=585) reported no significant difference in overall (p>0.05, n=76 with RT alone vs. n=93 with CRT) or severe toxicity (n=39 with RT alone vs. n=50 with CRT).	Low
	Acute gastrointestinal toxicity	2; RCTs; n=695	No significant difference. One RCT (n=110) reported no significant difference (p>0.05) in acute grade 3+ diarrhea with CRT (n=10) vs. RT alone (n=4). Another RCT (n=585) reported no significant difference (p>0.05) in overall (n=39 with RT alone vs. n=46 with CRT) or severe gastrointestinal toxicity (n=5 with RT alone vs. n=14 with CRT).	Low
	Acute genitourinary toxicity	1; RCT; n=585	No significant difference. One RCT (n=585) reported no significant difference (p>0.05) in overall (n=13 with RT alone vs. n=20 with CRT) or severe toxicity (n=1 with RT alone vs. n=3 with CRT).	Low
	Overall late harms	1; RCT; n=585	No significant difference. One RCT (n=585) reported no significant difference (p=0.39) in overall late toxicity (n=108 out of 285 patients with RT alone vs. n=122 out of 292 patients with CRT).	Low
	Late dermatologic toxicity	2; RCTs; n=695	No significant difference. One RCT (n=110) reported no significant difference (p>0.05) with CRT (n=3) vs. RT alone (n=2). Another RCT (n=585) reported no significant difference (p>0.05) with a frequency of 47 events with RT alone vs. 59 events with CRT reported after 2 months from the end of treatment.	Low

3. Results, Findings for Key Question 1: Initial Treatment Strategies, RT Alone Versus CRT With 5FU + MMC

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	SOE
	Late gastrointestinal toxicity	1; RCT; n=585	No significant difference. Another RCT (n=585) reported no significant difference (p>0.05) in overall events (n=77 in RT vs. n=84 in CRT) reported after 2 months posttreatment.	Low
	Late genitourinary toxicity	1; RCT; n=585	No significant difference. One RCT (n=585) reported no significant difference (p>0.05) with a total of 19 events in RT arm vs. 18 events in CRT arm reported after 2 months from the end of treatment.	Low

Abbreviations: 5FU = 5 fluorouracil; CI = confidence interval; CRT = chemoradiation; MMC = mitomycin C; RCT = randomized controlled trial; RT = radiation therapy; RR = relative risk ratio; SOE = strength of evidence; vs.= versus.
Note: One RCT (n = 585) defined acute harms as up to 2 months posttreatment and late harms as beyond 2 months posttreatment. One RCT (n = 110) did not define acute vs late harms.

3.2.4 CRT With 5FU Versus CRT With 5FU + MMC

3.2.4.1 Description of Included Evidence

One RCT (n=310)[10] compared CRT with 5FU versus CRT with 5FU + MMC (Table 8). In this RCT, RT was delivered by electron or photon beams, with a dose of 1.8Gy per day, 5 days per week for 5 weeks, with a boost of 5.4 Gy for positive inguinal nodes. Chemotherapy was delivered in two cycles, at the start and the end of initial RT. A third cycle of salvage CRT (5FU + cisplatin) was offered to all nonresponders at four to six weeks after initial CRT, before considering surgery (Appendix Table C.1.1). Several issues in this RCT raise concerns for RoB for effectiveness outcomes, such as 310 patients from 104 institutions randomized without description of the randomization process and variability in total dose of RT administered. Outcomes related to harms had a high RoB due to a third cycle of CRT (5FU and cisplatin) for salvage, provided to those who did not respond to initial treatment.

Table 8. Study characteristics for CRT with 5FU versus CRT with 5FU + MMC

Characteristic	Information
Number of studies	1 RCTs (n=310)
Study population	median age, 60 years, 35% male, HIV status and race not reported, 61% with tumor size <5cm, and 17% with nodal positivity
Intervention	Single agent CRT with 5FU, RT dose 1.8 Gy 5 times per week for 5 weeks
Comparator	CRT with 5FU and MMC; RT dose 1.8 Gy 5 times per week for 5 weeks
Setting and funding	United States of America; funding source not reported.
Risk of bias	Moderate risk of bias for effectiveness outcomes, high risk of bias for harms.

Abbreviations: 5FU = 5 fluorouracil; CRT = chemoradiation; Gy = gray; HIV = human immunodeficiency virus; MMC = mitomycin C; n =number; RCT = randomized controlled trial; RT = radiation therapy.

3.2.4.2 Summary of Findings

3.2.4.2.1 Summary of Findings for Effectiveness

Compared with doublet CRT with 5FU and MMC, singlet CRT with 5FU may increase LR failure rate, may decrease DFS and CFS rates, and may not increase OS and CR rates over 4 years of followup (low SOE, Table 9).

3.2.4.2.2 Summary of Findings for Harms

Evidence was insufficient to compare harms of initial treatment with doublet versus single agent CRT regimens due to high RoB from salvage CRT and imprecise estimates (Table 9).

Table 9. Summary of findings for CRT with 5FU versus CRT with 5FU + MMC

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	SOE
CRT with 5FU vs. CRT with 5FU and MMC	Overall survival	1; RCTs; n=310	No significant difference. 71% with 5FU vs. 78.1% with 5FU/MMC (p=0.31) at 4 years	Low
	Complete response	1; RCTs; n=310	No significant difference. 86% with 5FU vs. 92.2% with 5FU/MMC (p=0.14), 4 to 6 weeks posttreatment	Low
	Disease-free survival	1; RCTs; n=310	Favors 5FU + MMC over 5FU alone. 51% 5FU vs. 73% with 5FU/ MMC (p<0.001) at 4 years	Low
	Local failure rate	1; RCTs; n=310	Favors 5FU + MMC over 5FU alone. 34% 5FU vs. 16% with 5FU/ MMC (p<0.001) at 4 years	Low
	Colostomy-free survival	1; RCTs; n=310	Favors 5FU + MMC over 5FU alone. 59% with 5FU vs. 71% with 5FU/MMC (p = 0.01) at 4 years	Low
	Overall acute harms	1; RCTs; n=310	Inconclusive. Significantly favors 5FU arm	Insufficient
	Acute hematologic toxicity	1; RCTs; n=310	Inconclusive. Significantly favors 5FU arm	Insufficient
	Overall late harms	1; RCTs; n=310	Inconclusive. No significant difference	Insufficient

Abbreviations: 5FU = 5 fluorouracil; CRT = chemoradiation; MMC = mitomycin C; RCT = randomized controlled trial; vs. = versus; SOE = strength of evidence.
Note: Acute harms were defined as up to 90 days from starting the treatment and late harms as beyond the 90-day cut-off. For outcomes with insufficient SOE, we present details in the appendix Table C.5.1.

3.2.5 CRT With 5FU + Cisplatin Versus CRT With 5FU + MMC

3.2.5.1 Description of Included Evidence

Four reports of two RCTs (n=1622)[17,29-31] compared doublet CRT comprising 5FU paired with MMC versus cisplatin (Table 10). Two reports (n=1533)[30,31] were post hoc analyses of the two RCTs[17,29]. One RCT (n=940)[29] excluded patients with HIV positive status, while the other RCT (n=682)[17] did not report the immune status of patients and excluded patients with acquired immunodeficiency syndrome (Appendix Table C.3.1). One RCT (n=682)[17] allowed higher doses of MMC and cisplatin and included an induction phase in the cisplatin arm only (Appendix Table C.1.1). The two publications with post hoc analyses of RCTs had high RoB because they were not pre-specified and evaluated outcomes at multiple time points without accounting for competing risks or multiple comparisons testing.

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Table 10. Study characteristics for CRT with 5FU + cisplatin versus CRT with 5FU + MMC

Characteristic	Information
Number of studies	4 publications (n=1622); 2 RCTs (n=1622); 2 post hoc analyses of RCTs (n=1533)
Study population	2 RCTs: median age, 55 to 60 years, 37 to 50% male, 26 to 32% with positive nodal status, 14 to 20% patients with anal margin involvement. 1 RCT (n=940) excluded HIV positive patients, did not report patients' race, and included 10% with T1 disease and no patients with stage IV cancer. 1 RCT (n=682) did not report HIV status and race and included 0% with T1 diseases and 22% with stage IV cancer.
Intervention	1 RCT (n=940): CRT with 2 cycles of 5FU and 2 cycles of 60 mg/m^2 cisplatin over one month with 50% receiving maintenance chemotherapy with cisplatin in a 2x2 factorial design; conventional RT with dose 50.4 Gy in 28 fractions. 1 RCT (n=682): Induction chemotherapy with 2 cycles of 5FU and 2 cycles of 75 mg/m^2 cisplatin over two months followed by CRT with 2 cycles of 5FU and 2 cycles- 75 mg/m^2 cisplatin over one month, and conventional RT (dose 45-59 Gy).
Comparator	1 RCT (n=940): CRT with 2 cycles of 5FU and 1 cycle of 12 mg/m^2 MMC over one month with 50% receiving maintenance chemotherapy with cisplatin in a 2x2 factorial design; conventional RT with dose 50.4 Gy in 28 fractions. 1 RCT (n=682): CRT with 2 cycles of 5FU and 2 cycles of 12 mg/m^2 MMC over one month, and conventional RT with dose 45-59 Gy.
Setting and funding	1 RCT (n=940): United Kingdom; nonprofit organization 1 RCT (n=682): US; funded by a federal agency.
Risk of bias	2 RCTs: Low risk of bias for comparison of MMC versus cisplatin 2 post hoc analyses of RCTs: high risk of bias

Table Note: 5FU = 5 fluorouracil; CRT = chemoradiation; Gy = gray; HIV = human immunodeficiency virus; MMC = mitomycin C; n = number; RCT = randomized controlled trial; RT = radiation therapy.

3.2.5.2 Summary of Findings

3.2.5.2.1 Summary of Findings for Effectiveness

Findings are summarized in Table 11. We did not grade SOE from the second publications (high RoB) with post hoc, secondary analyses of RCT data to avoid double counting populations for similar set of 5-year outcomes.[30,31] MMC versus cisplatin up to 5 years of followup showed no significant difference in OS in both RCTs[17,29] (n=1622, moderate SOE) and DFS in one RCT[17] (n=682, low SOE). However, a post hoc analyses of one RCT (Appendix Table C.5.1) showed significant benefit in overall and DFS, favoring MMC over cisplatin over a longer followup (up to 8 years).[31] One RCT[29] (n=940, moderate SOE), showed no difference in CR rate at 26 weeks or progression-free survival between MMC versus cisplatin over a median followup of 5 years. One RCT (n=682)[17] and its post hoc analyses[31] (Appendix Table C.5.1) with longer followup time, both reported no significant difference in LR failure (1 RCT, low SOE) or distant metastasis rates (1 RCT, moderate SOE) between MMC versus cisplatin. One RCT (n=940)[29] and its *post hoc* analysis[30] (Appendix Table C.5.1) reported no significant difference in CFS between MMC versus cisplatin. Another RCT[17] (n=682) reported a significantly higher CFS rate favoring MMC over cisplatin; however, this benefit was attenuated and nonsignificant over a longer followup time in post hoc analyses[31] (Appendix Table C.5.1).

3.2.5.2.2 Summary of Findings for Harms

Both RCTs showed significantly greater severe (grade 3 or grade 4) acute hematologic toxicity rate in patients receiving MMC versus cisplatin (moderate SOE). Neither study found a difference in acute nonhematologic toxicity and late toxicity (low SOE, Table 11).

3. Results, Findings for Key Question 1: Initial Treatment Strategies, CRT With 5FU + Cisplatin Versus CRT With 5FU + MMC

Table 11. Summary of findings for CRT with 5FU + cisplatin versus CRT with 5FU + MMC

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	SOE
CRT with 5FU and MMC vs. CRT with 5FU and cisplatin	Overall survival (up to 5 years followup)	2; RCTs; n=1622	No difference. One RCT reported an HR of 1.28 for MMC (95% CI, 0.90 - 1.84, p=0.17, ref- cisplatin) over a median followup of 2.5 years. One RCT reported an HR of 1.05 (95% CI, 0.80 - 1.38) over median followup of 5.1 years.	Moderate
	Distant metastasis (up to 5 years followup)	1; RCT; n=682	No significant difference. Frequency 15% (95% CI, 10 - 20) with MMC arm vs. 19% (95% CI, 14 - 24) with cisplatin over median followup 2.5 years (p=0.14).	Moderate
	Locoregional failure (up to 5 years followup)	1; RCT; n=682	No significant difference. One RCT reported an HR of 1.32 for MMC (95% CI, 0.98 - 1.78, p=0.07, ref- cisplatin) over a median followup of 2.5 years	Low
	Colostomy-free survival to 5 years followup)	2; RCTs; n=1622	Inconclusive. Mixed (conflicting) findings. One RCT reported a significant difference favoring MMC over cisplatin. One RCT reported no significant difference.	Insufficient
	Cumulative colostomy rate (at 5 years)	1; RCT; n=682	Inconclusive. One RCT reported a significant difference favoring MMC over cisplatin.	Insufficient
	Disease-free survival (up to 5 years followup)	1; RCT; n=682	No significant difference. Frequency of 60% (95% CI, 53%-67%) with MMC vs. 54% (95% CI, 46%-60%) with cisplatin, and an HR of 1.20 for MMC (95% CI, 0.93 - 1.55), median followup 2.5 years.	Low
	Progression-free survival	1; RCT; n=940	No difference. One RCT reported an HR 0.95 (95% CI, 0.75 - 1.19) over a median followup of 5.1 years.	Moderate
	Complete response	1; RCT; n=940	No difference. One RCT reported a complete response frequency of 90.5% with MMC vs 89.6% with cisplatin.	Moderate
	Overall acute harms	2; RCTs; n=1622	No significant difference. One RCT (n=682) reported overall grade 3 toxicity 87% with MMC vs. 83% with cisplatin (p=0.13). One RCT (n=940) reported overall grade 3+ toxicity 71% with MMC vs. 72% with cisplatin (p>0.05).	Moderate
	Acute hematologic toxicity	2; RCTs; n=1622	Significantly greater with MMC vs. cisplatin. One RCT (n=682) reported grade 3+ toxicity 61% with MMC vs. 42% with cisplatin (p<0.001). One RCT (n=940) reported grade 3+ toxicity 26% with MMC vs. 16% with cisplatin (p<0.001).	Moderate

3. Results, Findings for Key Question 1: Initial Treatment Strategies, CRT With 5FU + Cisplatin Versus CRT With 5FU + MMC

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	SOE
	Acute dermatologic toxicity	2; RCTs; n=1622	No significant difference. One RCT (n=682) reported grade 3+ toxicity 48% in MMC arm vs. 41% in cisplatin arm (difference, 7%, 95% CI, -1% to 14%, p=0.09). One RCT (n=940) reported overall grade 3+ toxicity 48% in MMC arm vs. 47% in cisplatin arm (p>0.05)	Low
	Acute gastrointestinal toxicity	2; RCTs; n=1622	No significant difference. One RCT (n=682) reported grade 3 toxicity 30% with MMC vs. 40% with cisplatin and grade 4 toxicity frequency of 4% with MMC vs. 2% with cisplatin. One RCT (n=940) reported overall grade 3+ toxicity 16% with MMC vs. 18% with cisplatin (p>0.05)	Low
	Acute genitourinary toxicity	2; RCTs; n=1622	No significant difference. One RCT (n=682) reported grade 3 toxicity frequency of 10 events in MMC arm vs. 1 event in cisplatin arm and grade 4 toxicity frequency of 11 events in MMC arm vs. 0 events in cisplatin arm. One RCT (n=940) reported grade 3+ toxicity 1% in MMC arm vs. 2% in cisplatin arm (p>0.05)	Low
	Overall late harms	1; RCT; n=682	No significant difference. One RCT (n=682) reported grade 3 toxicity 8% in MMC arm vs. 6% in cisplatin arm and grade 4 toxicity 3% in MMC arm vs. 4% in cisplatin arm.	Low
	Late dermatologic toxicity	1; RCT; n=682	No significant difference. One RCT (n=682) reported grade 3 toxicity frequency of 5 events in MMC arm vs. 3 events in cisplatin arm and grade 4 toxicity frequency of 5 events in MMC arm vs. 4 events in cisplatin arm.	Low
	Late gastrointestinal toxicity	1; RCT; n=682	No significant difference. One RCT (n=682) reported grade 3 toxicity frequency of 5 events with MMC vs. 5 events with cisplatin and grade 4 toxicity frequency of 5 events with MMC vs. 1 event with cisplatin.	Low
	Late genitourinary toxicity	1; RCT; n=682	No significant difference. One RCT (n=682) reported grade 3 toxicity frequency of 2 events in MMC arm vs. 1 event in cisplatin arm and grade 4 toxicity frequency of 0 events in MMC arm vs. 0 events in cisplatin arm.	Low

Abbreviations: 5FU = 5 fluorouracil; CI = confidence interval; CRT = chemoradiation; HR = hazard ratio; MMC = mitomycin C; RCT = randomized controlled trial; RT = radiation therapy; vs. = versus; SOE = strength of evidence.
Note: Timepoint cutoff for acute vs late harms not defined. For outcomes with insufficient SOE, we present details in the appendix Table C.5.1.

3.2.6 CRT With MMC + Cisplatin Versus MMC + 5FU

3.2.6.1 Description of Included Evidence

One RCT[32] (n=88) compared doublet CRT consisting of MMC paired with 5FU versus cisplatin (Table 12). This pilot RCT had high RoB because several participants were found ineligible after randomization, randomization process was not described in detail, the trial could not analyze its target sample size based on power calculations, treatment protocol varied widely, and missing data was not explained.

Table 12. Study characteristics for CRT with MMC + cisplatin versus MMC + 5FU

Characteristic	Information
Number of studies	1 RCT (n=88)
Study population	Median age, 55 years, 30% male, median tumor size 5 cm, and 49% with positive nodal status; HIV status and race not reported.
Intervention	Chemoradiation with cisplatin and MMC
Comparator	Chemoradiation with 5FU and MMC
Setting and funding	European Union; funded by a federal agency.
Risk of bias	High risk of bias

Abbreviations: CRT = chemoradiation; 5FU = 5 fluorouracil; HIV = human immunodeficiency virus; MMC = mitomycin C; n = number; RCT = randomized controlled trial.

3.2.6.2 Summary of Findings

3.2.6.2.1 Summary of Findings for Effectiveness

Evidence was insufficient (Table 13) due to high RoB and imprecision in estimates. No significant difference was found in CR, progression-free or event-free survival between arms.

3.2.6.2.2 Summary of Findings for Harms

Evidence was insufficient for acute harms. We found no evidence to address late harms.

Table 13. Summary of findings for CRT with MMC + cisplatin versus MMC + 5FU

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	SOE
CRT with MMC and cisplatin vs. CRT with MMC and 5FU	Progression-free and event-free survival, complete response, acute hematologic and gastrointestinal toxicity	1; RCTs; n=88	Inconclusive. No significant difference.	Insufficient

Abbreviations: 5FU = 5 fluorouracil; CRT = chemoradiation; MMC = mitomycin C; RCT = randomized controlled trial; SOE = strength of evidence; vs. = versus.

3.2.7 CRT With MMC + Capecitabine Versus MMC + 5FU

3.2.7.1 Description of Included Evidence

Three NRSIs[16,33,34] (n=554) compared CRT with MMC plus 5FU versus capecitabine (Table 14). All three reported similar protocols (Appendix Table C.1.1). In two NRSIs[33,34] (n=407), a significantly greater proportion of patients in the 5FU arm received <2 cycles of MMC, but the third NRSI[16] (n=147) administered only one cycle of MMC per protocol, and the rate of treatment completion was higher in the 5FU arm versus the capecitabine arm. All three NRSIs had a serious RoB; they did not report power calculations or information about missing data; two

NRSIs[16,33] (n=254) did not adjust for confounding, and two NRSIs[33,34] (n=407) reported a shorter total followup for capecitabine than for 5FU arm not fully explained by health-related events.

Table 14. Study characteristics for CRT with MMC + capecitabine versus MMC + 5FU

Characteristic	Information
Number of studies	3 NRSIs (n=554)
Study population	3 NRSIs: Median age about 58 to 60 years, 27% to 35% male, <10% HIV positive, and a similar distribution of cancer stage. One NRSI (n=107) reported that their sample was >80% White, whereas other 2 NRSIs did not report patient's race.
Intervention	Doublet CRT with capecitabine and MMC
Comparator	Doublet CRT with 5FU and MMC
Setting and funding	1 NRSI (n=107): US; funding source not reported. 1 NRSI (n=147): United Kingdom; funded by government and nonprofit agencies. 1 NRSI (n=300): Canada; funded by a federal agency.mrt
Risk of bias	3 NRSIs: Serious risk of bias

Abbreviations: 5FU = 5 fluorouracil; CRT = chemoradiation; HIV = human immunodeficiency virus; MMC = mitomycin C; n = number; nonrandomized study of intervention = NRSI.

3.2.7.2 Summary of Findings

3.2.7.2.1 Summary of Findings for Effectiveness

Evidence was insufficient because of serious RoB (Table 15). All three NRSIs (n=554) reported no significant differences in CFS rate between 5FU versus capecitabine, with imprecise estimates. One NRSI[33] (n=107) reported no significant differences in OS, distant metastasis, and local failure rate between 5FU versus capecitabine, with very imprecise estimates. One NRSI (n=147)[16] reported no significant difference in progression-free survival and another NRSI (n=300)[34] reported an imprecise estimate suggesting no significant difference in disease-specific survival between 5FU versus capecitabine.

3.2.7.2.2 Summary of Findings for Harms

Evidence was insufficient because of serious RoB (Table 15). Two[16,33] out of three NRSIs (n=254) reported harms, and both reported a significantly greater acute grade 3 or higher hematologic toxicity for patients receiving 5FU versus capecitabine. One NRSI (n=107)[33] reported no significant difference in acute grade 3 nonhematologic toxicity rate. One NRSI (n=147)[16] reported no significant difference in acute grade 3 nonhematologic toxicity and overall acute harms in patients receiving 5FU compared with capecitabine. For both NRSIs, comparisons for toxicity likely lacked optimal information size (statistical power) to draw reliable conclusions. None of these NRSIs reported late toxicity events.

Table 15. Summary of findings for CRT with MMC + capecitabine versus MMC + 5FU

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	SOE
CRT with MMC and capecitabine vs. CRT with MMC and 5FU	Overall and colostomy-free survival, distant metastasis, and locoregional failure	1; NRSI; n=107	Inconclusive. No significant difference at 2 years.	Insufficient
	Colostomy-free survival	3; NRSIs; n=507	Inconclusive. No significant difference up to 2 yrs.	Insufficient
	Disease-free survival	2; NRSIs; n=397	Inconclusive. No significant difference up to 2 yrs.	Insufficient

3. Results, Findings for Key Question 1: Initial Treatment Strategies, CRT With Capecitabine + MMC Versus Capecitabine + MMC + Paclitaxel

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	SOE
	Complete response	1; NRSI; n=100	Inconclusive. No significant difference at 6 months	Insufficient
	Disease-specific survival	1; NRSI; n=300	Inconclusive. No significant difference at 5 years	Insufficient
	Overall acute harms	1; NRSI; n=118	Inconclusive. No significant difference.	Insufficient
	Treatment break due to toxicity	1; NRSI; n=107	Inconclusive. Favors capecitabine.	Insufficient
	Acute hematologic toxicity	2; NRSIs; n=225	Inconclusive. Favors capecitabine.	Insufficient
	Acute dermatologic and gastrointestinal toxicity	2; NRSIs; n=225	Inconclusive. No significant difference.	Insufficient

Abbreviations: 5FU = 5 fluorouracil; CRT = chemoradiation; MMC = mitomycin C; vs. = versus; SOE = strength of evidence; NRSI = nonrandomized study of intervention.

3.2.8 CRT With Capecitabine + MMC Versus Capecitabine + MMC + Paclitaxel

3.2.8.1 Description of Included Evidence

One RCT[35] (n=144) evaluated whether addition of paclitaxel to the regimen of CRT with capecitabine plus MMC increases treatment efficacy in nonmetastatic SCCA (Table 16). To accommodate paclitaxel as a third chemotherapy drug, this RCT reduced the dose of capecitabine and MMC in the intervention arm. Additionally, this RCT delivered RT using intensity-modulated radiation therapy (IMRT). This RCT could enroll only half of its target sample size; however, the authors reported no postrandomization attrition. More than three quarters of the patients had stage III SCCA. This RCT was assessed as having a low RoB.

Table 16. Study characteristics: CRT with capecitabine + MMC versus capecitabine + MMC + paclitaxel

Characteristic	Information
Number of studies	1 RCT (n=144)
Study population	Median age 56.5 years, 10% male, 0% HIV positive, and 78% with Stage III SCCA.
Intervention	CRT with capecitabine (625 mg/m^2), plus MMC (10 mg/m^2 on day 1), plus paclitaxel (45 mg/m^2 intravenous weekly); using IMRT
Comparator	CRT with capecitabine (825 mg/m^2) and MMC (12 mg/m^2 on day 1); using IMRT
Setting and funding	Russia; source of funding not reported
Risk of bias	Low risk of bias

Abbreviations: CRT = chemoradiation; HIV = human immunodeficiency virus; MMC = mitomycin C; n = number; RCT = randomized controlled trial; RT = radiation therapy; IMRT = intensity modulated RT; SCCA = squamous cell carcinoma of the anus.

3.2.8.2 Summary of Findings

3.2.8.2.1 Summary of Findings for Effectiveness

Compared with CRT with capecitabine plus MMC, CRT with capecitabine plus MMC plus paclitaxel may result in greater OS, DFS, CFS, and CR rates (low SOE, Table 17). The authors did not report confidence intervals for estimates or number of events which made it challenging to evaluate the precision of estimates.

3.2.8.2.2 Summary of Findings for Harms

Compared with CRT with capecitabine plus MMC, CRT with capecitabine plus MMC plus paclitaxel may result in greater overall acute harms and no significant difference in acute neutropenia, dermatologic, gastrointestinal, or genitourinary toxicity (low SOE); due to low event rates, the estimates are assessed as being imprecise (Table 17).

Table 17. Summary of findings for CRT with capecitabine + MMC versus capecitabine + MMC + paclitaxel

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	SOE
CRT with capecitabine plus MMC plus paclitaxel vs. CRT with capecitabine plus MMC	Overall survival (up to 3 yrs)	1; RCT; n=144	Favors paclitaxel arm. Significantly greater in the paclitaxel arm vs no paclitaxel arm; 95.5% vs 80% (p<0.001).	Low
	Disease-free survival (up to 3 yrs)	1; RCT; n=144	Favors paclitaxel arm. Significantly greater in the paclitaxel arm vs no paclitaxel arm; 87.1% vs 64.4% (p=0.001).	Low
	Colostomy-free survival (up to 3 yrs)	1; RCT; n=144	Favors paclitaxel arm. Significantly greater in the paclitaxel arm vs no paclitaxel arm; 83.2% vs 67.5% (p=0.029).	Low
	CR (at 26 weeks posttreatment)	1; RCT; n=144	Favors paclitaxel arm. Significantly greater in the paclitaxel arm vs no paclitaxel arm; 88.9% vs 75% (p=0.049).	Low
	Overall acute harms	1; RCT; n=144	Significantly greater in paclitaxel arm. 56.9% in paclitaxel arm vs 26.4% in no paclitaxel arm; difference 30.5% (95% CI, 14.5% to 44.4%, p < 0.001).	Low
	Neutropenia (grade 3 or 4)	1; RCT; n=144	No significant difference. 12 (16.7%) in paclitaxel arm vs 7 (9.7%) patients in no paclitaxel arm; absolute difference 7% (95% CI, - 4.3% to 18.4%, p=0.22)	Low
	Acute dermatologic toxicity	1; RCT; n=144	No significant difference. 7 patients in each arm	Low
	Acute gastrointestinal toxicity	1; RCT; n=144	No significant difference. Paclitaxel arm vs no paclitaxel arm; grade 3-4 diarrhea: 10 (13.9%) vs 5 (6.9%) patients with absolute difference 7% (95% CI, -3.3% to 17.6%, p=0.17); grade 3-4 proctitis: 9 (12.5%) vs 4 (5.6%) patients with absolute difference 6.9% (95% CI, -2.9% to 17.1%, p=0.15)	Low
	Acute genitourinary toxicity	1; RCT; n=144	No significant difference. 1 patient per arm had grade 3 cystitis and no patients had grade 3-4 vaginitis	Low

Abbreviations: CI = confidence interval; CRT = chemoradiation; CR = complete response; RCT = randomized controlled trial; MMC = mitomycin C; vs. = versus; SOE = strength of evidence.

3.3 Findings for Key Question 2: RT Modalities

Key Question 2. What are the effectiveness and harms of different modalities of radiation therapy for initial treatment of stages I–III squamous cell anal cancer?

3.3.1 Key Points

- Comparing intensity modulated RT (IMRT) with three-dimensional conformal RT (3DCRT) or other RT modalities:
  - evidence was insufficient to compare effectiveness and harms.
- Comparing proton IMRT with photon IMRT:
  - evidence was insufficient to compare effectiveness and harms.
- Comparing external beam RT (EBRT) with brachytherapy (BT):
  - evidence was insufficient to compare effectiveness and harms.

3.3.2 Intensity Modulated RT Versus Conventional Modalities

3.3.2.1 Description of Included Evidence

Two NRSIs[36,37] (n=1944) compared IMRT with non-IMRT (Table 18). One NRSI (n=1165)[36] included participants from SEER-Medicare database, and the other NRSI[37] (n=779) included participants from Veterans Affairs database. In both NRSIs, the comparator "non-IMRT" group could be treated with either two- or three-dimensional conformal RT, and patients receiving IMRT were significantly more likely to be treated with MMC as a part of their CRT regimen and have a positron emission tomography (PET)-scan at the time of diagnosis. In one NRSI[37] (n=779), patients receiving IMRT were significantly more likely to receive MMC. Both NRSIs used advanced statistical techniques to address confounding. Both NRSIs had serious RoB due to missing details for chemotherapy agents used, inadequate adjustments for confounding by different chemotherapy regimens, and insufficient information about missing data (Table 18).

Table 18. Study characteristics for IMRT versus non-IMRT

Characteristic	Information
Number of studies	2 NRSIs (n=1944)
Study population	1 NRSI (n=1165): median age, 70 years, 35% male, 89% White, and 8% with HIV. 1 NRSI (n=779): mean age, 61 years, 92% male, 84% White, and 20% with HIV.
Intervention	IMRT
Comparator	Conventional RT (2D or 3DCRT)
Setting; funding	1 NRSI (n=1165): US; funding from federal agency. 1 NRSI (n=779): US; funding source not reported.
Risk of bias	2 NRSIs: Serious risk of bias

Abbreviations: 3DCRT = three-dimensional conformal radiation therapy; HIV = human immunodeficiency virus; IMRT = intensity modulated radiation therapy; n = number; NRSI = nonrandomized study of intervention; RT = radiation therapy.

3.3.2.2 Summary of Findings

3.3.2.2.1 Summary of Findings for Effectiveness

Evidence was insufficient due to high RoB (Table 19).

3.3.2.2.2 Summary of Findings for Harms

Evidence was insufficient due to high RoB (Table 19).

Table 19. Summary of findings for IMRT versus non-IMRT

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	Strength Of Evidence
IMRT vs. non-IMRT	Overall and disease-specific survival	2; NRSI; n=1944	Inconclusive. No significant difference.	Insufficient
	Tumor related colostomy-free survival	1; NRSI; n=779	Inconclusive. Favors IMRT	Insufficient
	Acute grade 3+ hematologic toxicity	1; NRSIs; n=312	Inconclusive. No significant difference.	Insufficient
	Acute grade 3+ bone marrow suppression	1; NRSIs; n=1165	Inconclusive. No significant difference.	Insufficient

Abbreviations: IMRT = intensity modulated radiation therapy; NRSI = nonrandomized study of intervention; vs. = versus.

3.3.3 Intensity Modulated Versus Three-Dimensional Conformal RT

3.3.3.1 Description of Included Evidence

Two NRSIs[38,39] (n=7037) compared IMRT versus 3DCRT (Table 20). One NRSI[39] (n=6814) leveraged the National Cancer Database and another NRSI (n=223)[38] was a single center retrospective chart review. One NRSI (n=6814)[39] had critical RoB; it did not provide sufficient information about chemotherapy agents, variations in radiation therapy protocols, or missing data. One NRSI (n=223)[38] had critical RoB because of inadequate adjustment for confounding, small sample size, lack of information about statistical power calculations, and heterogeneity in CRT protocols (for example, all patients receiving IMRT [n=45] received 5FU + MMC whereas only 80 percent of the 178 patients receiving 3DCRT also received 5FU + MMC.

Table 20. Study characteristics for IMRT versus 3DCRT

Characteristic	Information
Number of studies	2 NRSIs (n=7037)
Study population	1 NRSI (n=6814): median age, 59 years, 30% male, 88% White, HIV status unreported. 1 NRSI (n=223): median age, 59 years, 34% male, 83% White, and 10% with HIV.
Intervention	IMRT
Comparator	3DCRT
Setting and funding	1 NRSI (n=6814): US; funding from university. 1 NRSI (n=223): US; funding source not reported.
Risk of bias	2 NRSIs: Critical risk of bias

Abbreviations: 3DCRT = three-dimensional conformal radiation therapy; HIV = human immunodeficiency virus; IMRT = intensity modulated radiation therapy; n = number; NRSI = nonrandomized study of intervention.

3.3.3.2 Summary of Findings

3.3.3.2.1 Summary of Findings for Effectiveness

Evidence was insufficient for comparing IMRT with 3DCRT (Table 21).

3.3.3.2.2 Summary of Findings for Harms

Neither NRSI reported on toxicity outcomes.

Table 21. Summary of findings for IMRT versus 3DCRT

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	Strength Of Evidence
IMRT vs. 3DCRT	Overall survival	2; NRSI; n=7037	Inconclusive. Mixed (conflicting) evidence.	Insufficient
IMRT vs. 3DCRT	Locoregional recurrence-free, distant metastasis-free, and colostomy-free survival	1; NRSI; n=223	Inconclusive. No significant difference over 5 years	Insufficient

Abbreviations: 3DCRT = three-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; NRSI = nonrandomized study of intervention; vs. = versus.

3.3.4 Proton Versus Photon Intensity Modulated RT

3.3.4.1 Description of Included Evidence

One NRSI[40] (n= 208) compared proton- versus photon-IMRT (Table 22). This was a multi-centric retrospective study. Patients treated with proton- (vs. photon-) IMRT were significantly more likely to have negative nodal status. Chemotherapy protocols varied, with 87 percent receiving 5FU and MMC combination and 2 percent receiving no chemotherapy, and RT boost techniques varied between integrated versus sequential boost. This NRSI had a serious RoB because of a sample size for proton-IMRT group (n=58), heterogeneity in CRT protocols that could not have been sufficiently addressed by adjustment, no power calculation, and no information regarding missing data.

Table 22. Study characteristics for IMRT with proton versus photon

Characteristic	Information
Number of studies	1 NRSI (n=208)
Study population	Mean age of 62 years, 27% male, 12% HIV positive, 50% with positive nodal status, and race not reported.
Intervention	Proton IMRT
Comparator	Photon IMRT
Setting and funding	United States of America; funding source not reported.
Risk of bias	Serious risk of bias

Abbreviations: HIV = human immunodeficiency virus; IMRT = intensity modulated radiation therapy; n = number; NRSI = nonrandomized study of intervention.

3.3.4.2 Summary of Findings

3.3.4.2.1 Summary of Findings for Effectiveness

Evidence was insufficient for comparing effectiveness of proton- versus photon-IMRT (Table 23).

3.3.4.2.2 Summary of Findings for Harms

Evidence was insufficient for comparing harms of proton- versus photon-IMRT (Table 23).

Table 23. Summary of findings for IMRT with protons versus photons

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	Strength Of Evidence
IMRT with protons vs. photons	Local control and progression-free survival, acute grade 3+ hematologic and acute and late grade 3+ overall, dermatologic, gastrointestinal, or genitourinary toxicity	1; NRSI; n=208	Inconclusive. No significant difference.	Insufficient

Abbreviations: NRSI = nonrandomized study of intervention; IMRT = intensity modulated radiation therapy; vs. = versus.

3.3.5 External Beam RT Versus Brachytherapy Boost

3.3.5.1 Description of Included Evidence

Three publications[41-43] of two NRSIs (n=586) compared RT boost with EBRT versus BT (Table 24). Two publications[41,42] of one NRSI (n=162) leveraged data from a prospective cohort. The third NRSI[43] (n=424) was a secondary analysis of a subset of patients from an RCT who responded to initial treatment (CRT or RT alone); this NRSI did not report characteristics for its included patient sample. All three NRSIs had serious RoB; they provided no power calculations or information regarding missing data. Two publications[41,42] of one NSRIs (n=162) allowed variable chemotherapy protocols (although no significant imbalance between EBRT vs. BT arms were noted), and selected some centers where brachytherapy was not provided. The third NRSI[43] (n=424) had serious RoB due to the lack of information regarding variations in initial treatment protocols and other characteristics between EBRT versus BT groups.

Table 24. Study characteristics for RT boost with EBRT versus BT

Characteristic	Information
Number of studies	3 publications of 2 NRSIs (n=586)
Study population	2 publications of 1 NRSI (n=162): mean age, 60 to 65 years, and <30% male. 1 publication noted <6% with HIV positive status. Race was not reported 1 NRSI (n=424) did not evaluate participant characteristics at baseline across the intervention and comparison groups.
Intervention	EBRT boost
Comparator	BT boost
Setting and funding	Two publications of 1 NRSI (n=162): France; funding source not reported. One NRSI (n=424): United Kingdom; funding source not reported
Risk of bias	All three publications: serious risk of bias

Abbreviations: BT = brachytherapy; EBRT = external beam radiation therapy; HIV = human immunodeficiency virus; n = number; NRSI = nonrandomized study of intervention; RT = radiation therapy.

3.3.5.2 Summary of Findings

3.3.5.2.1 Summary of Findings for Effectiveness

Evidence was insufficient for comparing RT boost with EBRT versus BT (Table 25).

3.3.5.2.2 Summary of Findings for Harms

Evidence was insufficient for comparing harms of RT boost with EBRT versus BT.

Table 25. Summary of findings for RT boost with EBRT versus BT

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	Strength Of Evidence
RT boost with EBRT vs. BT	Overall and colostomy-free survival and local control	1 NRSI (2 publications); n=162	Inconclusive. No significant difference, up to 5 yrs.	Insufficient
	Overall, disease-specific, disease-free, and relapse-free survival	1; NRSI; n=424	Inconclusive. No significant difference over 13 yrs.	Insufficient
	Late ulcers/ radionecrosis	1; NRSI; n=424	Inconclusive. Favors EBRT	Insufficient

Abbreviations: BT = brachytherapy; EBRT = external beam radiation therapy; NRSI = nonrandomized study of intervention; RT = radiation therapy; vs. = versus; yrs. = years.

3.4 Findings for Key Question 3: RT Doses, Volumes, and Fractionation Schema

Key Question 3. What are the effectiveness and harms of different radiation therapy doses, volumes, and fractionation schema for initial treatment of stage I–III squamous cell anal cancer?

3.4.1 Key Points

- Comparing different RT doses for initial treatment:
  - evidence was insufficient to compare effectiveness and harms.
- Comparing different dosimetric (dose-volume) parameters:
  - evidence was insufficient to compare effectiveness and harms.
- Comparing different fractionation schema for initial treatment:
  - evidence was insufficient to compare effectiveness and harms.

3.4.2 Different Doses for RT

3.4.2.1 Description of Included Evidence

Two publications[44,45] from one RCT (n= 307) and two NRSIs[46,47] (n=8723) compared different total doses for RT (Table 26). The RCT (n= 307) compared a total dose of 60 Gy ("Standard dose") versus 65 to 70 Gy ("High dose"). Among the two NRSIs[46,47] (n=8723), one NRSI[46] (n=7792 patients) leveraged data from the National Cancer Database to compare 45 to 54 Gy with >54 Gy, and the other NRSI[47] (n=931) was a secondary analysis of data collected for an RCT and compared 50.4 Gy in 38 to 42 days (reference group) with 5 other groups; namely, ≤40 Gy, >40 Gy to <48.6 Gy, 50.4 Gy in <38 days, 50.4 Gy in >42 days, and >52.2 Gy. The two publications of RCT[44,45] (n=307) had high RoB because of considerable attrition leaving fewer analyzable patients than the required sample size, boost modality varied across arms, and quality of life outcomes were available in only 119 patients. The two NRSIs[46,47] had critical RoB for not sufficiently capturing or accounting for heterogeneity in CRT protocols.

3. Results: Findings for Key Question 3: RT Doses, Volumes, and Fractionation Schema, Different Doses for RT

Table 26. Study characteristics for comparing different doses of RT

Characteristic	Information
Number of studies	2 publications from 1 RCT (n=307) and 2 NRSIs (n=8723)
Study population	2 publications of 1 RCT: mean age, 57 to 60 years, about 20% male, and up to 33% with poorly differentiated tumor. HIV status and race not reported. 1 NRSI (n=7792): median age, 61 to 70 years, 30% male, 89% White, 40% with positive nodal status, 29% with poorly differentiated/undifferentiated tumor, and HIV status not reported. 1 NRSI (n=931): median age, 60 to 65 years, 38% male, 32% with positive nodal status, 45% with poorly differentiated/undifferentiated tumor, and race and HIV status not reported.
Intervention vs. Comparator	2 publications from one RCT: standard (60 Gy) vs. high (65-70 Gy) dose 1 NRSI (n=7792): 45 to 54 Gy vs. >54 Gy 1 NRSI (n=931): 50.4 Gy in 38 to 42 days (reference group) with 5 other groups: ≤40 Gy, >40 Gy to <48.6 Gy, 50.4 Gy in <38 days, 50.4 Gy in >42 days, and >52.2 Gy.
Setting and funding	2 publications of 1 RCT: France; funding from government and nonprofit agencies. 1 NRSI (n=7792): US; funding from university. 1 NRSI (n=931): United Kingdom; funding source not reported
Risk of bias	2 publications from one RCT: high risk of bias 2 NRSIs: critical risk of bias

Abbreviations: RCT = randomized controlled trial; Gy = gray; NRSI = nonrandomized study of intervention; RT = radiation therapy; EBRT = external beam radiation therapy; BT = brachytherapy; HIV = human immunodeficiency virus; vs. = versus.

3.4.2.2 Summary of Findings

3.4.2.2.1 Summary of Findings for Effectiveness

Evidence was insufficient for comparing effectiveness of different doses of RT (Table 27).

3.4.2.2.2 Summary of Findings for Harms

Evidence from one RCT (n=357) was insufficient for comparing harms (Table 27).

Table 27. Summary of findings for comparing different doses of RT

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	Strength Of Evidence
Standard boost (15 Gy; total dose, 60 Gy) vs. high-dose boost (20-25 Gy; total dose, 65-70 Gy)	Overall, disease-free, colostomy-free, and disease-specific survival, LRF, QoL Questionnaire- C30, ASCT questionnaire, and overall acute & late grade 3+ toxicity.	1; RCT; n=307	Inconclusive. No significant difference.	Insufficient
Dose, 45-54Gy vs. >54Gy	Overall survival (up to 5 years)	1; NRSI; n=7792	Inconclusive. Favors 45-54 Gy	Insufficient
RT regimens: group 1) 50.4Gy, 38-42 days (reference group) vs. group 2) ≤40Gy; group 3) >40Gy to <48.60Gy; group 4) 50.4Gy, <38 days; group 5) 50.4Gy, >42 days; group 6) >52.2Gy	Overall and progression-free survival	1; NRSI; n=931	Inconclusive. Favors 50.4 Gy in 38-42 days over greater overall treatment time or lower total dose.	Insufficient

Abbreviations: ASCT = Anal Sphincter Conservative Treatment; Gy = gray; NRSI = nonrandomized study of intervention; LRF = locoregional failure rate; QoL = quality of life; RCT = randomized controlled trial; RT = radiation therapy; vs.= versus.

3.4.3 Dose-Volume Predictors of Toxicity

3.4.3.1 Description of Included Evidence

Two NRSIs[48,49] (n= 215) evaluated dosimetry-based predictors of acute and late toxicity (Table 28). Both had critical RoB because they had a high potential for selection bias and derived dosimetry-based predictors using a lowest p-value approach from the same population in which they further evaluated these selected parameters in multivariable regression models, adjusting for limited confounders, without any external validation. In one NRSI[48] (n=101), CRT protocols varied which was not sufficiently accounted for in the analyses. In the other NRSI[49] (n=114), all patients received doublet CRT with 5FU and MMC; however, chemotherapy dose and modality of RT delivery varied, which was not accounted for in analysis.

Table 28. Study characteristics for dosimetry studies

Characteristic	Information
Number of studies	2 NRSIs (n=215)
Study population	1 NRSI (n=101): median age, 57 years, 51% male, 25% with HIV, 36% with positive nodal status, and race not reported. 1 NRSI (n=114): median age, 64 years, 22% male, 65% with positive nodal status, 45% with poorly differentiated/undifferentiated tumor, 1% with HIV, and race not reported.
Intervention vs. Comparator	1 NRSI (n=101): Dose-volume predictors of acute and late toxicity. 1 NRSI (n=114): Dose-volume predictors of acute and late gastrointestinal toxicity
Setting and funding	1 NRSI (n=101): US; funding source-none. 1 NRSI (n=114): Sweden; funding from government agency.
Risk of bias	2 NRSIs: critical risk of bias

Abbreviations: HIV = human immunodeficiency virus; n = number; NRSI = nonrandomized study of intervention; vs. = versus.

3.4.3.2 Summary of Findings

3.4.3.2.1 Summary of Findings for Effectiveness

Neither of the two NRSIs reported any effectiveness-related outcomes.

3.4.3.2.2 Summary of Findings for Harms

Evidence from two NRSI was insufficient to evaluate toxicity (Table 29).

Table 29. Summary of findings for significant predictors of toxicity in dosimetry studies

Dose-Volume Parameter	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	Strength Of Evidence
Small bowel V35Gy	Grade 2+ acute diarrhea	1; NRSI; n=101	Inconclusive. Significant predictor.	Insufficient
Bladder D0.5cc	Grade 2+ acute genitourinary toxicity	1; NRSI; n=101	Inconclusive. Significant predictor.	Insufficient
Anterior skin V35Gy	Grade 2+ inguino-genital skin toxicity	1; NRSI; n=101	Inconclusive. Significant predictor.	Insufficient
Posterior skin V15Gy	Grade 2+ perianal skin toxicity	1; NRSI; n=101	Inconclusive. Significant predictor.	Insufficient
Lower pelvis bone V45Gy	Grade 2+ anemia	1; NRSI; n=101	Inconclusive. Significant predictor.	Insufficient
Large bowel V20Gy	Grade 2+ late gastrointestinal toxicity	1; NRSI; n=114	Inconclusive. Significant predictor.	Insufficient

Abbreviations: Gy = gray; n = number; NRSI = nonrandomized study of intervention.

3.4.4 Fractionation Schema for RT

3.4.4.1 Description of Included Evidence

One NRSI[50] (n= 6429) compared >4.7 vs. ≤4.2 fractions per week; albeit as a surrogate for prolonged overall treatment time (Table 30). This NRSI analyzed the National Cancer Database (years 2004 to 2014). Specifications for chemotherapy protocols could not be ascertained, except 86.5 percent of patients received multi-agent chemotherapy. Proton-IMRT was administered to 46.2 percent of patients. This NRSI was at a critical RoB. Considering variations in CRT protocols, the regression model evaluating >4.7 vs. ≤4.7 fractions per week did not adjust for total dose or chemotherapy; and lacked information on missing data.

Table 30. Study characteristics for comparing fractionation schema for RT

Characteristic	Information
Number of studies	1 NRSIs (n=6429)
Study population	40% of patients were >60 years of age, 80.6% White, 30% male, 82.6% with comorbidity score of 0, 37% with positive nodal status, and 28.7% with poorly differentiated tumor. HIV status was not reported.
Intervention vs. Comparator	>4.7 fractions per week versus ≤4.7 fractions per week
Setting and funding	US; funding from university.
Risk of bias	Critical risk of bias

Abbreviations: HIV = human immunodeficiency virus; n = number; NRSI = nonrandomized study of intervention; RT = radiation therapy; vs. = versus.

3.4.4.2 Summary of Findings

3.4.4.2.1 Summary of Findings for Effectiveness

Evidence was insufficient for comparing >4.7 versus ≤4.7 fractions per week (Table 31).

3.4.4.2.2 Summary of Findings for Harms

This NRSI reported no data on harms or toxicity-related events.

Table 31. Summary of findings for comparing fractionation schema for RT

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	Strength Of Evidence
≤4.7 fractions/week vs. >4.7 fractions/week	Overall survival	1; NRSI; n=6429	Inconclusive. Favors >4.7 fractions/week, significantly	Insufficient

Abbreviations: n = number; NRSI = nonrandomized study of intervention; RT = radiation therapy; vs. = versus.

3.5 Findings for Key Question 4: Dose De-Escalation and Escalation in CRT

Key Question 4. What are the effectiveness and harms of different combinations of chemotherapy and radiation therapy, and dose de-escalation or dose escalation for initial treatment of stages I–III squamous cell anal cancer?

3.5.1 Key Points

- Comparing induction versus no induction chemotherapy before doublet CRT:

  - evidence was insufficient to compare effectiveness and harms.
- Comparing maintenance versus no maintenance chemotherapy after doublet CRT:
  - evidence was insufficient to compare effectiveness and harms.
- Comparing one versus two cycles of MMC in doublet CRT:
  - evidence was insufficient to compare effectiveness and harms.
- Comparing receiving RT boost versus not receiving RT boost after doublet CRT:
  - evidence was insufficient to compare effectiveness and harms.

3.5.2 Induction Versus No Induction Therapy

3.5.2.1 Description of Included Evidence

Two publications[44,45] from one RCT (n= 307) compared induction chemotherapy with 5FU and cisplatin versus no induction chemotherapy (Table 32). The RCT had high RoB because of considerable attrition over the course of treatment, yielding a sample size less than required by power calculations; additionally, quality of life outcome was available in only 39 percent of all patients[45] and boost modality (EBRT or BT) varied across arms.

Table 32. Study characteristics for induction chemotherapy versus none

Characteristic	Information
Number of studies	2 publications from 1 Randomized Controlled Trial (n=307)
Study population	Mean age, 57 to 60 years, 20% male, and up to 33% with poorly differentiated tumor. HIV status and race was not reported.
Intervention vs. Comparator	Induction chemotherapy with 5FU and cisplatin versus no induction chemotherapy
Setting and funding	France; funding from government and nonprofit agencies.
Risk of bias	High risk of bias

Abbreviations: 5FU= 5 fluorouracil; HIV= human immunodeficiency virus; n=number; vs. = versus.

3.5.2.2 Summary of Findings

3.5.2.2.1 Summary of Findings for Effectiveness

Evidence was insufficient for comparing effectiveness of induction versus no induction before doublet CRT (Table 33).

3.5.2.2.2 Summary of Findings for Harms

Evidence from one RCT (n=307) was insufficient for comparing the harms of induction versus no induction chemotherapy.

Table 33. Summary of findings for induction chemotherapy versus none

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	Strength Of Evidence
Induction vs. no induction	Overall, disease-free, colostomy-free, and disease-specific survival, Quality of Life Questionnaire- C30, Anal Sphincter- Conservative Treatment questionnaire and overall acute and late grade 3+ toxicity.	1; RCT; n=307	Inconclusive. No significant difference.	Insufficient
	Acute grade 3+ hematologic toxicity	1; RCT; n=307	Favors no induction over induction.	Insufficient

Abbreviations: RCT = randomized controlled trial; SOE = strength of evidence; vs. = versus.

3.5.3 Maintenance Versus No Maintenance Chemotherapy

3.5.3.1 Description of Included Evidence

One RCT[12] (n=940) compared maintenance therapy with 5FU and cisplatin versus no maintenance (Table 34). This RCT excluded HIV positive patients. It had a high RoB due to considerable attrition in the maintenance arm alone, after randomization.

Table 34. Study characteristics for maintenance chemotherapy versus none

Characteristic	Information
Number of studies	1 RCT (n=940): 2 by 2 factorial design also testing MMC vs. cisplatin
Study population	Median age of 58 years, 38% male, 52% with tumor size of 5 cm or less, 32% with positive lymph nodes, and about 30% with poorly differentiated tumor. HIV positive patients were excluded, and race was not reported.
Intervention vs. Comparator	Maintenance chemotherapy with 5FU and cisplatin versus no maintenance chemotherapy
Setting and funding	United Kingdom; funding from nonprofit organization.
Risk of bias	High risk of bias

Abbreviations: 5FU = 5 fluorouracil; HIV = human immunodeficiency virus; MMC = mitomycin C; n = number; RCT = randomized controlled trial; vs. = versus.

3.5.3.2 Summary of Findings

3.5.3.2.1 Summary of Findings for Effectiveness

Evidence was insufficient for comparing effectiveness of maintenance chemotherapy with no maintenance chemotherapy after doublet CRT (Table 35).

3.5.3.2.2 Summary of Findings for Harms

No evidence directly compared the harms (Table 35).

Table 35. Summary of findings for maintenance chemotherapy versus none

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	Strength Of Evidence
Maintenance chemotherapy vs. none	Overall, progression-free, colostomy-free, and disease-specific survival	1; RCT; n=940	Inconclusive. No significant difference.	Insufficient

Abbreviations: RCT = randomized controlled trial; vs. = versus.

3.5.4 One Versus Two Cycles of MMC

3.5.4.1 Description of Included Evidence

One NRSI[51] (n=217) compared one versus two cycles of MMC in a doublet CRT regimen with 5FU and MMC (Table 36). CRT protocols were mostly similar in all patients except that patients receiving two cycles of MMC were significantly more likely to also receive IMRT (however, the study adjusted for receipt of IMRT in the analysis). This retrospective study had serious RoB due to lack of power calculations, insufficient information regarding missing data, and potential selection bias because in at least some patients, receipt of only one cycle of MMC could potentially have been due to omission of the second cycle of MMC based on patient's health status and provider discretion, and not necessarily based on an institutional protocol.

3. Results, Findings for Key Question 4: Dose De-Escalation and Escalation in CRT, One Versus Two Cycles of MMC

Table 36. Study characteristics for 1 versus 2 cycles of MMC

Characteristic	Information
Number of studies	1 NRSIs (n=217)
Study population	Median age, 60 years, 70% female, 10% with HIV, 52% with tumor size >5cm, and 40% with positive nodal status. Race not reported.
Intervention vs. Comparator	1 versus 2 cycles of MMC in doublet CRT with 5FU and MMC
Setting and funding	US; funding source not reported.
Risk of bias	Serious risk of bias

Abbreviations: 5FU = 5 fluorouracil; CRT = chemoradiation; HIV = human immunodeficiency virus; MMC = mitomycin C; n = number; NRSI = nonrandomized study of intervention; vs. = versus.

3.5.4.2 Summary of Findings

3.5.4.2.1 Summary of Findings for Effectiveness

Evidence was insufficient for comparing effectiveness (Table 37; very imprecise estimates).

3.5.4.2.2 Summary of Findings for Harms

Evidence was insufficient for comparing acute or late toxicity (Table 37).

Table 37. Summary of findings for 1 versus 2 cycles of MMC

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	Strength Of Evidence
1 vs. 2 cycles of MMC	Overall, progression-free, colostomy-free, and disease-specific survival, and overall acute and late grade 3+ toxicity.	1; NRSI; n=217	Inconclusive. No significant difference.	Insufficient

Table Note: NRSI = nonrandomized study of intervention; MMC = mitomycin C; vs. = versus; vs. = versus.

3.5.5 RT Boost Versus No Boost

3.5.5.1 Description of Included Evidence

One NRSI[43] (n=490) compared patients receiving RT boost versus no RT boost (Table 38). This NRSI was a secondary analysis of a subgroup of patients from an RCT[9] (n=585) who responded to initial treatment (either CRT or RT alone); this NRSI did not report characteristics for its included patient sample. It had serious RoB due to the lack of information regarding treatment protocol differences and characteristics between groups receiving RT boost versus no RT boost, no power calculations, competing risks, and lack of information for missing data.

Table 38. Study characteristics for comparing RT boost versus no boost

Characteristic	Information
Number of studies	1 NRSIs (n=490)
Study population	Not reported.
Intervention vs. Comparator	RT boost versus no RT boost
Setting and funding	United Kingdom; funding source not reported.
Risk of bias	Serious risk of bias

Abbreviations: NRSI = nonrandomized study of intervention; RT = radiation therapy; vs. = versus.

3.5.5.2 Summary of Findings

3.5.5.2.1 Summary of Findings for Effectiveness

Evidence was insufficient for comparing effectiveness of receiving versus not receiving RT boost after doublet CRT (Table 39).

3.5.5.2.2 Summary of Findings for Harms

Evidence was insufficient for comparing the harms of receiving versus not receiving RT boost based solely on reporting of late anorectal ulceration/radionecrosis at 6 months.

Table 39. Summary of findings for comparing RT boost versus no boost

Intervention Vs. Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	Strength Of Evidence
Boost vs. no boost	Overall, disease-specific, and relapse-free survival, and locoregional control	1; NRSI; n=490	Inconclusive. No significant difference.	Insufficient
	Late anorectal ulceration/ radionecrosis	1; NRSI; n=490	Inconclusive. Favors no boost over boost.	Insufficient

Abbreviations: NRSI = nonrandomized study of intervention; vs. = versus.

3.6 Findings for Key Question 5: Immunotherapy

Key Question 5. What are the effectiveness and harms of immunotherapy for initial treatment of stages I–III squamous cell anal cancer?

3.6.1 Key Points

- Comparing immunotherapy with other modalities of initial treatment for stages SCCA:
  - no evidence was found to inform the effectiveness and harms.

3.7 Findings for Key Question 6: Post-Treatment Surveillance

Key Question 6. What are the effectiveness and harms of different frequencies and modalities for post-treatment surveillance strategies after initial treatment of stages I–III squamous cell anal cancer?

3.7.1 Key Points

- Comparing different surveillance strategies after initial treatment with doublet CRT:
  - evidence was insufficient to compare effectiveness and harms.

3.7.2 Description of Included Evidence

One NRSI[18] (n=138) compared different frequencies of surveillance after initial treatment (Table 40). This single-institution NRSI included patients with biopsy-proven, nonmetastatic cancer, treated with CRT using IMRT. Patients were followed posttreatment every three months for two years, every six months in year three to year five, then yearly thereafter. This NRSI had critical RoB due to the variable followup time (median, 27 months), selection bias from its retrospective design, no adjustment for confounding, lack of formal statistical hypothesis testing, and insufficient information regarding missing data.

3. Results, Findings for Key Question 6: Posttreatment Surveillance, Description of Included Evidence

Table 40. Study characteristics for comparing posttreatment surveillance strategies

Characteristic	Information
Number of studies	1 NRSIs (n=138)
Study population	Median age of 58 years, 29% male, 14% HIV positive, and race not reported. High risk group (n=61): T4N0 or T1 to T4N+ disease. Low-risk group (n=77): T1-3N0 disease
Comparison	Posttreatment event frequency within year 1 vs within year 2 vs. years 3 to 5; to justify reducing frequency of screening beyond 2nd year.
Setting and funding	United States of America; funding source not reported.
Risk of bias	Critical risk of bias

Abbreviations: HIV= human immunodeficiency virus; n = number; NRSI = nonrandomized study of intervention.

3.7.3 Summary of Findings

3.7.3.1 Summary of Findings for Effectiveness

Evidence is insufficient for comparing effectiveness of different surveillance strategies after initial treatment with doublet CRT (Table 41).

3.7.3.2 Summary of Findings for Harms

This NRSI did not report any data on harms of surveillance.

Table 41. Summary of findings for comparing posttreatment surveillance strategies

Intervention Vs. Comparison	Outcomes	Number of Studies; Study Design; Participants (n)	Conclusions. Summary of Individual Study Findings.	Strength Of Evidence
Event frequency: within 1yr vs. within 2 yrs vs. year 3 to 5	Frequency of total events, late grade 3+ toxicity, local recurrence, and distant metastasis	1; NRSI; n=138	Inconclusive. No significant difference between annual versus twice a year frequency of surveillance beyond 2 years after initial treatment.	Insufficient

Table Note: NRSI = nonrandomized study of intervention; vs.= versus; yrs. = years.

4. Discussion

4.1 Overview

Using exclusively comparative effectiveness studies, our findings aimed to help identify optimal strategies for initial treatment of nonmetastatic squamous cell carcinoma of the anus (SCCA) including local excision (LE) in early-stage disease; the optimal chemotherapy regimen; ideal radiation therapy (RT) technique and dose fractionation scheme; potential roles for immunotherapy; and effective posttreatment surveillance. The review covered a diverse set of interventions intended to maximize tumor response while limiting recurrence and treatment-related toxicities. However, due to challenges with high risk of bias (RoB) precluding the ability to draw causal inferences, we relied on findings from only six randomized controlled trials (RCTs).[8-10,17,29] We identified moderate- to low- strength evidence to support optimal chemoradiation (CRT) regimens. We found little to no information on various RT dosing regimens or modalities, or posttreatment surveillance. Furthermore, many studies were conducted before the widespread implementation of intensity modulated RT (IMRT), making the findings less applicable to current practice.

We found low- and moderate-strength evidence in two RCTs[8,9] indicating that compared with CRT, RT alone resulted in greater locoregional failure rate and disease-specific mortality rates and lower complete response (CR) and colostomy-free survival (CFS) rates while also incurring lower acute hematologic and overall harms. But low-strength evidence also showed that no other acute or late toxicities differed between CRT and RT alone. Moderate- to low- strength evidence from two RCTs[17,29] showed that compared with CRT with 5 fluorouracil (5FU) and mitomycin C (MMC), CRT with 5FU and cisplatin was not superior for oncological outcomes but resulted in lower hematologic toxicity. We found low-strength evidence from one RCT indicating that adding paclitaxel as a third cytotoxic agent to doublet CRT with capecitabine plus MMC may improve several effectiveness outcomes and increase treatment related acute toxicity.[35] For all other interventions and outcomes, we found the evidence insufficient. This does not mean that none of the individual interventions described are potentially useful for patients, practitioners, and the healthcare system. Rather, it means that current available evidence cannot yet provide clear answers about which, if any, interventions offer consistently greater benefits on a relative scale. At present, the uncertainty of the evidence is too high for us to draw many conclusions. Further, when studies with inadequate power, no power calculations, or other serious methodological limitations report no significant differences between interventions, it is inappropriate to conclude non-inferiority of any interventions.

4.2 Key Findings in Relation to Clinical Dilemmas

4.2.1 Systemic Therapy

CRT is the standard of care for nonmetastatic SCCA; but treatment approaches vary widely, as do reported outcomes, making between-study comparisons difficult. Treatment-related morbidity is considerable, yet poorly captured, with inconsistent definitions delineating acute versus late toxicities and infrequent study of long-term toxicities. In addition, we found little data regarding optimal posttreatment surveillance and a complete lack of published data describing the current role of immunotherapy. Despite these gaps in knowledge, we sought to critically appraise the available literature to help address specific questions related to individualized

treatment approaches. Though various RCTs and nonrandomized studies of interventions (NSRIs) have established concurrent doublet CRT as the primary treatment, the optimal regimen has yet to be established. Current recommendations support the use of concurrent doublet CRT with infusional 5FU or its oral prodrug capecitabine, along with MMC or cisplatin.[11,52]

Our review confirmed that overall, doublet CRT with 5FU and MMC resulted in better effectiveness outcomes than singlet CRT using 5FU or RT alone.[8-10] Of note, in the three RCTs supporting these comparisons, the outcomes overall survival (OS) and CR rates should be interpreted cautiously. In these three RCTs, CR was assessed between four to six weeks posttreatment which might be premature, leading to fewer events (low power) and imprecision in estimates. A post hoc study of the ACT II trial, which was conducted several years after these RCTs, suggests that the optimal time to assess may be 26 weeks after CRT initiation.[53] Additionally, these three RCTs were conducted in the era of older, outdated RT methods which carried a much greater risk of toxicity. Therefore, the null findings for OS might be explained by death from other causes such as treatment-related toxicity. Cisplatin, when compared with MMC in a doublet chemotherapy regimen with 5FU, resulted in lower acute hematologic toxicity but no significant difference in overall acute harms and several effectiveness outcomes. Despite this, MMC has historically been favored over cisplatin based mainly on long-term results[31] of the RTOG 98-11 trial, a preference that merits a more nuanced discussion. The long-term followup of RTOG 98-11 was a retrospective post hoc analysis of the same 5-year outcomes analyzed in the parent trial report, these analyses were not prespecified in the trial protocol, and it had a high RoB for reasons such as long-term outcome ascertainment was inadequately described and likely retrospective and it lacked a thorough competing risks analysis and adjustment for multiple comparisons testing.[31] In addition, the parent study[17] and the long-term followup study[31] showed conflicting results, with 5-year colostomy-free survival improving significantly with MMC in the parent trial but not in the long-term followup study and vice versa for 5-year overall and disease-free survival. Moreover, in RTOG 9811, only the cisplatin arm had an additional induction phase delivered before concurrent CRT, which could have played a dominant role on the outcomes in this study and limits the ability to draw inferences for an exclusively concurrent CRT regimen.[17] The subsequent ACT-II trial was deemed null; it failed to demonstrate an oncologic benefit for cisplatin over MMC, with similar toxicity profiles.[29] Thus, the difference between MMC and cisplatin appears to be driven by MMC's worse hematologic toxicity profile. Upon detailed examination, we feel these oncologic outcomes should be questioned at best. Contextual factors might also influence clinical decision making (for example, the ease of administering MMC vs cisplatin). Subsequent cisplatin-based treatment options for progressive disease may also influence initial treatment choice. One RCT reported that the addition of paclitaxel to CRT with capecitabine plus MMC may increase treatment efficacy and toxicity.[35] Following the InterAAct trial, paclitaxel is used to treat metastatic SCCA.[54] However, it is not specifically recommended in guidelines for stages I–III SCCA (our population of interest). Of note, the InterAAct trial included 10% population with nonmetastatic SCCA; furthermore, there was a case series from Wisconsin, presented as a poster at a scientific meeting which reported that in 9 patients with localized anal cancer who were ineligible for 5FU + MMC CRT regimen, a carboplatin + paclitaxel CRT regimen resulted in 100% complete clinical response.[55]

Another comparison of interest is capecitabine (an orally administered prodrug of 5FU) versus 5FU (administered as continuous intravenous infusion for 4 days in weeks 1 and 5).[33] Capecitabine might be more convenient, pragmatic, and a cheaper alternative to infusional 5FU. Our review did not find sufficient direct evidence comparing the effectiveness and harms of

these two drugs. However, some evidence in advanced gastric and colorectal cancers suggests that capecitabine is noninferior to infusional 5FU;[56,57] and international guidelines recommend either capecitabine or 5FU in the treatment of nonmetastatic SCCA[11]. Multiple ongoing clinical trials are assessing immunotherapy as a component of initial treatment strategies (for example, NCT04230759, NCT03233711; Appendix D), but without reportable data yet.

For maintenance chemotherapy, compared with no maintenance chemotherapy, we found insufficient evidence for its impact on effectiveness outcomes. In the ACT II RCT, which evaluated maintenance chemotherapy versus none, only 44 percent of the patients randomized to the maintenance chemotherapy arm completed the regimen, reportedly due to toxicity events or patient preferences.[29] The high rate of differential attrition in the ACT II trial induces a very high RoB in its evaluation of the impact of maintenance chemotherapy on the RCT endpoints. However, given the poor feasibility of completing maintenance chemotherapy due to greater toxicity in ACT-II trial as well as the lack of evidence of any additional benefits of maintenance chemotherapy, international guidelines recommend against providing maintenance chemotherapy for the initial treatment of stages I–III SCCA.[52]

Therefore, despite the vast amount of low to moderate quality data available, no choice of doublet cytotoxic chemotherapy selection has clearly emerged as superior in terms of maximizing oncologic outcomes while minimizing treatment-related toxicities. As clinicians counsel patients on their individualized treatment approach, consideration must be given to co-morbid conditions, compliance, cost, drug availability, and implications for quality of life.

4.2.2 Radiation Therapy

Advances in RT have depended on the fundamental concept that targeted delivery to diseased tissue maximizes response while limiting morbidity to nearby organs at risk. This thought process has led to increased use of IMRT.[46] Despite these potential benefits, our review found insufficient evidence to compare the effectiveness and harms of IMRT and 3 dimensional conformal radiation therapy (3DCRT). The Phase II, single arm RTOG 0529 study was among the first to report clinically acceptable effectiveness and favorable toxicity outcomes in support of the feasibility of IMRT.[57] However, due to methodological limitations, including the lack of a concurrent control arm or a historical control group by applying requisite statistical weighting/matching techniques, this study was not included in our analyses. Notably, the contouring protocols developed in the RTOG 0529 have been frequently cited in the literature in this field. In one pilot RCT (n=20), compared with 3DCRT arm (n=10), patients in the IMRT arm (n=10) were able to receive a lesser radiation dose to bowel, bladder, and bone marrow, and had a lower frequency of gastrointestinal toxicity.[58] Based on this pilot RCT and the NRSIs assessed in this review, some clinical experts recommend the use of IMRT over 3DCRT.[52] Further efforts to reduce radiation doses to nearby organ systems led to the comparison of IMRT with proton beam (IMPT) and traditional IMRT (using photon beam) after a feasibility study showed similar toxicity rates of IMPT to historical controls in the RTOG 0529 trial.[59] In line with the prior feasibility study, the one NSRI in this review comparing IMPT to IMRT found no differences in acute or late toxicity outcomes.

Other modifications to radiation therapy delivery have been tested. In Europe, conventional RT practices include split-course therapy, consisting of an initial total dose of 45 Gy to the pelvis, followed by a boost dose of 15-20 Gy to the anal canal (after a 6- to 8-week gap) delivered via either EBRT or brachytherapy.[60] A pivotal principle of radiation therapy lies in the delivery of a high total fractionated dose without prolongation of overall treatment time, since extended treatment time has a detrimental impact on local control. Evidence was insufficient to

compare EBRT versus brachytherapy, although brachytherapy had a higher incidence of late ulcers/radionecrosis in one NSRI.[43] Similarly, no differences were observed in survival outcomes or quality of life when comparing standard-dose boost (15 Gy) versus high-dose boost (20-25 Gy).[45] Finally, locoregional control or overall survival did not differ between patients who received a boost versus those that did not. In addition to boost therapy, varying dose fractionation schemes were assessed regarding whether de-escalation was appropriate in achieving similar survival rates. Two NRSIs found that total radiation doses <48.60 Gy, 50.40 Gy delivered over > 42 days, and ≤4.72 fractions per week (a surrogate for prolonged overall treatment time), were associated with lower overall survival.[47,50] However, we found that the NRSIs had a very high RoB making it impossible to draw causal inferences.

Thus, current evidence is insufficient for assessing methods of radiation delivery, presence or absence of a boost, or fractionation schema. Furthermore, evidence concerning patient-reported outcomes is insufficient. Patient-reported outcomes such as persistently poor quality of life, pain, and worsening bowel and sexual function are potential adverse effects of chemoradiation.[61,62] One RCT included in this review evaluated quality of life, but outcome data were missing in about two-thirds of the patients included in the RCT leading to a very high RoB and insufficient evidence.[45] None of the included studies evaluated sexual function as an outcome of interest.

4.2.3 Posttreatment Surveillance

Alongside improving CRT strategies, optimizing a posttreatment surveillance schedule bridges the gap between therapeutic innovation and healthcare implementation. Timely detection of local recurrence or distant metastases allows for appropriate next steps in management, such as salvage treatment. Risk stratifying tumor characteristics and determining posttreatment relapse patterns could further improve already favorable long-term outcomes. One NSRI[18] included in this review found that 89 percent of local recurrences occurred by year 2, with the majority being found due to symptoms of anal pain, bleeding, and persistent ulceration, while the remaining were found by a 3-month posttreatment positron emission tomography (PET) scan. Although the evidence is very limited, this suggests that strict adherence to surveillance regimens in the first two years is paramount, with the potential for a reduction in surveillance frequency thereafter.

4.3 Strengths and Limitations

4.3.1 Strengths of the Review Process

We adopted a review scope intended to limit bias on interventions and posttreatment surveillance for nonmetastatic SCCA. We included studies with an active comparator to determine direct effects of the described interventions. While this constraint may have led to studies being overlooked, it allowed a very high-level assessment of the state of the science in this domain while attempting to maintain data quality. Because ours was a targeted systematic review, we took a rigorous approach to assessing for RoB and based our decisions on the highly variable studies included in this review as well as the complexity of care in this disease process. Studies not rising to the needed level of scientific rigor were determined to be at higher RoB, and, although we did include potentially valuable evidence from higher-RoB studies in our review, caution must be used in applying these conclusions to clinical practice.

4.3.2 Limitations of the Review Process

We excluded studies with fewer than 15 participants per study arm as well as single arm studies, preventing us from evaluating several interventions of interest; but such studies had very high RoB, making it impossible to draw causal inferences and inclusion of such studies would

not have changed the conclusions of this review. We only reviewed publications available in English language in the four large databases mentioned before. Therefore, we may have missed relevant publications published in other languages or available only in other databases. We started our search from January 2000 and relied on published systematic reviews and reference lists of included studies to cover literature published before this date. Based on feedback from peer reviewers, key informants, technical experts, and content experts in our team, a federal register notice, and public comments, we did not identify any additional relevant studies which we may have missed; nonetheless, the potential for missing older relevant studies remains. We based our SOE assessment on statistical rather than clinical significance because established thresholds of clinically meaningful effects for individual outcomes do not exist. This would likely not change the conclusions of this review. We prioritized clinical outcomes based on feedback from key informants, technical experts, partners, and content experts on our team; other process outcomes such as convenience and costs might influence clinical decision making.

4.3.3 Limitations of the Evidence Base

We found no more than four studies per unique intervention-outcome comparison and most of the studies had a high RoB. Large prospective research studies are difficult to conduct in developed countries where nonmetastatic SCCA is a rare disease. Clinical experts can make treatment recommendations based on clinical experience, pragmatism, and extrapolation of findings from other cancers; however, from a systematic review perspective, we can only critique available evidence. RCTs were limited by lack of consistency in outcome definitions and measurement between trials,[63] inadequately addressing attrition, multiple comparisons testing, and competing risks over a longer followup period, and inadequate power to compare acute and late harms. One study attempted to establish a core outcome set for SCCA research with the help of a Delphi study including healthcare professionals and patients;[64,65] however, its uptake in the research community is unclear. Common limitations of the NRSIs included selection bias, poorly defined interventions and comparators, lack of power calculations, and inadequately addressing missing data, competing risks, and potential confounding. Our conclusions largely reflect weaknesses of the evidence base. Patients with immunocompromised status, older age, and minoritized racial/ethnic identities were underrepresented in research, making applicability of findings to these subgroups challenging.

4.4. Implications for Clinical Practice and Policy

The lack of sufficient evidence to support widespread dissemination of several interventions analyzed in this review leaves patients, their families, and practitioners without clear answers. Owing to under-representation in the available body of evidence, decision making for patients with immunocompromised status, older age, and minoritized racial/ethnic identities, who face disproportionately worse treatment outcomes, remains challenging.[66,67] When deciding on treatment approaches, institutions and providers will continue to depend on limited, best available evidence along with subjective observations and clinical gestalt till more evidence becomes available; while taking individual patient characteristics and preferences into consideration. Future RCTs should consider implementing policies to intentionally increase representation of historically underrepresented patient subgroups.

4.5 Implications for Future Research

A search on October 31, 2023, in the ClinicalTrials.gov registry identified eight potentially relevant records and one record by hand search (Appendix D), one trial comparing photon RT (IMRT, volumetric modulated arc therapy, helical tomotherapy) to IMPT, several studies looking

at the role of immunotherapy (nivolumab, sintilimab, and durvalumab) + CRT versus CRT alone, and, finally, one trial examining the role of circulating tumor DNA in followup.

This review identified major evidence gaps for initial treatment and post treatment surveillance of nonmetastatic SCCA which merit the focus of future research, such as:

- Replication study to confirm whether addition of paclitaxel as a third cytotoxic agent to the standard doublet CRT regimen increases treatment effectiveness.
- Long-term comparative effectiveness of CRT strategies for non-metastatic SCCA in terms of oncologic outcomes, toxicities, and patient-reported outcomes using advanced causal inference methods to analyze meticulously curated real-world data.
- Comparative effectiveness of LE versus CRT in the treatment of stage I SCCA.
- Comparative effectiveness, harms, and costs of different RT modalities, optimal dose and fractionation schema for RT, and optimal dose for chemotherapy agents.
- Well-designed NRSIs to evaluate applicability of RCT findings in real world settings such as rural or low volume cancer care centers and evaluate long-term outcomes and harms such as sexual and bowel dysfunction.
- Immunotherapy for the initial treatment of nonmetastatic SCCA, noting that ongoing RCTs (Appendix D) are attempting to address this issue.
- Enhancing the data quality of large databases, with details for each component of CRT and toxicity data to complete more robust and methodologically sound comparisons.
- Focusing on underrepresented populations (older age, immunocompromised status, and racial/ethnic minorities), because we found only scarce, low-quality data.
- Evaluating patient-reported outcomes such as bowel function (fecal incontinence, urgency, proctitis, anal stenosis, anal sphincter control), bladder function, sexual function (dyspareunia, vaginal stenosis, penile impotence), pain, and quality of life, as well as studying the social impact on the patient's life.[68]
- Evaluating best approaches for mitigating harms and optimizing quality of life posttreatment (e.g., pelvic muscle training, preventing anal and vaginal stenosis).

Some evidence gaps are under investigation in ongoing trials (Appendix D). One example is the PLATO (PersonaLising Anal cancer radioTherapy dOse protocol) which includes three anal cancer trials (ACT) known as ACT3, ACT4 and ACT5. These trials will evaluate RT dose escalation and de-escalation strategies in specific clinical scenarios for personalizing treatment strategies. In a prespecified pilot phase analysis of ACT5 RCT, comparing standard dose vs dose-escalated concurrent CRT in advanced nonmetastatic SCCA, investigators reported that RT dose intensification appeared to be safe with acceptable compliance, acute toxicity, and patient-reported outcomes (quality of life, pain, and bowel toxicity) at 6 months.[68] However, these findings were presented at a scientific conference and not yet published as a full length report; therefore, we did not formally included them in our analyses; although they appear promising.

4.6 Conclusions

Concurrent CRT with 5FU plus MMC is more effective but has greater hematologic toxicity than RT alone or CRT with 5FU for the initial treatment of stages I–III SCCA. The addition of paclitaxel to doublet CRT with capecitabine plus MMC may increase treatment efficacy and toxicity. Evidence is insufficient for optimal posttreatment surveillance strategies, quality of life, and other patient-reported outcomes. Future RCTs should be more inclusive of historically underrepresented patient subgroups. Future real world evidence generation must prioritize methodologic rigor, using methods like target trial emulation for making causal inferences.

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6. Abbreviations and Acronyms

3DCRT	Three-dimensional conformal radiation therapy
5FU	5-Fluorouracil
AHRQ	Agency for Healthcare Research and Quality
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
ASCO	American Society of Clinical Oncology
ASTRO	American Society of Radiation [i]Oncology
BT	Brachytherapy
CR	Complete response
CFS	Colostomy-free survival
CI	Confidence interval
CRT	Chemoradiation
DFS	Disease-free survival
DRE	Digital rectal exam
EBRT	External beam radiation therapy
EPC	Evidence-based practice center
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
Gy	Gray (unit of radiation dose)
HIV	Human immunodeficiency virus
HR	Hazard ratio
IMRT	Intensity-modulated radiation therapy
KM	Kaplan Meier
KQ	Key Question
LFR	Locoregional failure rate
LE	Local excision
MMC	Mitomycin C
MRI	Magnetic resonance imaging
NCDB	National Cancer Database
NRSI	Nonrandomized study of interventions
NSD	No significant difference
PET	Positron emission tomography
PCORI	Patient-Centered Outcomes Research Institute
PICOTS	Population, intervention, comparator, outcomes, timing, and study design/setting
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
OS	Overall survival

6. Abbreviations

RCT	Randomized controlled trial
RoB	Risk of bias
RR	Risk ratio
RT	Radiation therapy
SCCA	Squamous cell carcinoma of the anus
PSEER	Surveillance, Epidemiology, and End Results program
SOE	Strength of evidence
SR	Systematic Review
TOO	Task Order Officer
US	United States
VMAT	Volumetric modulated arc therapy
Vs	Versus
Yrs.	Year

Treatment of Stages I–III Squamous Cell Anal Cancer: A Systematic Review

Appendixes

Appendix A. Methods
Appendix B. References Excluded at Full-Text Screening
Appendix C. Evidence Tables
Appendix D. List of Unpublished Randomized Controlled Trials
Appendix E. PCORI Methodology Standards Checklist

Appendix A. Methods

Search Strategy

The search strategy was designed and conducted by an experienced systematic review/medical reference Librarian with input from the investigators. To find additional relevant studies, reference lists of relevant systematic reviews were manually screened. We applied the following limits or filters to the database searches:

- Date: We considered a literature search starting in 2000 sufficient for the purpose of this review.
- Language. Publications were excluded if they were written in a language other than English. This was due to resource constraints.
- Publication status. We searched for published studies.
- Human or organism. No limits were applied to the search.
- Study design. The search was not restricted by study design.

We conducted a comprehensive literature search in May 2023 and an updated search through March 2024. We searched the following databases:

- MEDLINE (Ovid) All (1946-March 4, 2024). Date searched March 6, 2024.
- Embase (Ovid) (1974 to 2023 May 25). Date searched March 6, 2024.
- Cochrane Central Register of Controlled Trials (Wiley) Issue 2 of 12, February 2024. Date searched: March 6, 2024.

We conducted a grey literature search in September 2023 that included the following resources:

- ClinicalTrials.gov www.clinicaltrials.gov Date search: September 1, 2023.
- Reference lists of systematic reviews and included studies.

Ovid MEDLINE(R) ALL <1946 to May 25, 2023>

1 exp Anus Neoplasms/ or ((anal or anus or perianal) adj3 (cancer* or carcino* or neoplas* or squamous or tumo?r* or SCC)).ti,ab. 9919

2 (anal adj3 (basaloid or cloacogenic or epidermoid or margin or skin or transitional)).ti,ab. 955

3 1 or 2 10456

4 antineoplastic protocols/ or antineoplastic combined chemotherapy protocols/ or brachytherapy/ or chemoprevention/ or chemoradiotherapy/ or chemoradiotherapy, adjuvant/ or chemotherapy, adjuvant/ or combined modality therapy/ or consolidation chemotherapy/ or dose fractionation, radiation/ or Imaging, three-dimensional/ or Immunotherapy/ or Maintenance chemotherapy/ or exp Proton Therapy/ or Neoadjuvant therapy/ or radioimmunotherapy/ or Radiotherapy/ or Radiotherapy, adjuvant/ or Radiotherapy, computer-assisted/ or Radiotherapy, conformal/ or exp Radiotherapy, High-Energy/ or Radiotherapy, intensity-modulated/ or Radiotherapy dosage/ or Radiation dose hypofractionation/ or Radiation, Ionizing/ or Re-Irradiation/ or (antineoplastic protocols or beam radiation therapy or chemoprevention or chemotherapy or chemoradiotherapy or CRT or combined modalit* therap* or dose escalation or dose de-escalation or dose fractionation or dose hypofractionation or dose-volume or electron beam therapy or radioimmunotherapy or radiotherapy or radiation dose or radiation dosage or re-irradiation or treatment modalit* or Intensity-modulated radiation therapy or IMRT or 3-dimensional radiation therapy or 3DCRT or 3D-CRT).ti,ab. 1094578

5 Antibodies, Monoclonal, Humanized/ or Cisplatin/ or Capecitabine/ or Cetuximab/ or docetaxel/ or fluorouracil/ or Immune Checkpoint Inhibitors/ or Mitomycin/ or Nivolumab/ or Paclitaxel/ or Programmed Cell Death 1 Receptor/ or (5-fluorouracil or Capecitabine or Cisplatin or Capecitabine or Cetuximab or Docetaxel or Durvalumab or F-FU or Fluoropyrimidines or Fluorouracil or humanized monoclonal antibodies or immune checkpoint inhibitor* or Mitomycin or Nivolumab or Paclitaxel or Pembrolizumab or programmed cell death 1 receptor or PD-L1).ti,ab. 299275

6 Anal Canal/su or "margins of excision"/ or (surg* adj3 (anal or anus)).ti,ab. 12168

7 or/4-6 1261729

8 Disease management/ or exp disease progression/ or disease resistance/ or Endoscopy/ or Magnetic Resonance Imaging/ or positron emission tomography computed tomography/ or Watchful Waiting/ or (anoscopy or endoscopy or disease management or monitor* or disease progress* or disease resistan* or magnetic resonance imaging or MRI or positron emission tomography or PET or PET-CT or surveillance or surveille or watchful waiting).ti,ab. 2353924

9 Salvage Therapy/ or (salvage adj3 (chemo* or surg* or therap* or treatment?)).ti,ab. 28776

10 Neoplasm grading/ or Neoplasm Invasiveness/ or Neoplasm Metastasis/ or Neoplasm Recurrence, Local/ or Recurrence/ or neoplasm staging/ or Tumor Burden/ or ((neoplasm? or nodal or tumo?r) adj3 (assess* or burden or grade or grading or invasive* or metastas?s or restaging or stage or staging or status or recurrent or recurrence or relapse?)).ti,ab. 791339

11 (tumo?r adj3 (diameter or dimension or size or volume)).ti,ab. 100012

12 algorithms/ or disease-free survival/ or nomograms/ or "predictive value of tests"/ or prognosis/ or progression-free survival/ or treatment failure/ or treatment outcome/ or Time Factors/ or (algorithm? or nomogram? or outcome? or predict* or prognosis or survival).ti,ab. 7012049

13 or/8-12 8897255

14 7 or 13 9426317

15 3 and 14 6358

16 comment/ or editorial/ or letter/ or case reports/ 4270811

17 15 not 16 4984

18 limit 17 to (english language and yr="2000 -Current") 3527

Embase <1974 to 2023 May 25>

1 exp anus carcinoma/ 4036

2 ((anal or anus or perianal) adj3 (cancer* or carcino* or neoplas* or squamous or tumo?r* or SCC)).ti,ab. 11167

3 (anal adj3 (basaloid or cloacogenic or epidermoid or margin or skin or transitional)).ti,ab. 1492

4 or/1-3 13107

5 Adjuvant chemoradiotherapy/ or Adjuvant chemotherapy/ or Adjuvant radiotherapy/ or Brachytherapy/ or Cancer immunotherapy/ or Chemoprophylaxis/ or Chemoradiotherapy/ or Computer assisted radiotherapy/ or Consolidation chemotherapy/ or External beam radiotherapy/ or Induction chemotherapy/ or Ionizing radiation/ or Intensity modulated radiation therapy/ or Maintenance chemotherapy/ or multimodality cancer therapy/ or Neoadjuvant therapy/ or photon therapy/ or Radiation dose escalation/ or Radiation dose fractionation/ or Radiation dose

reduction/ or Radioimmunotherapy/ or Radiotherapy/ or Re-irradiation/ or Three-dimensional imaging/ or (antineoplastic protocols or beam radiation therapy or chemoprophylaxis or chemotherapy or chemoradiotherapy or CRT or combined modalit* therap* or dose escalation or dose de-escalation or dose fractionation or dose hypofractionation or dose-volume or electron beam therapy or radioimmunotherapy or radiotherapy or radiation dose or radiation dosage or re-irradiation or treatment modalit* or Intensity-modulated radiation therapy or IMRT or three-dimensional imaging or 3DCRT or 3D-CRT).ti,ab. 1513593

6 capecitabine/ or cetuximab/ or cisplatin/ or docetaxel/ or fluorouracil/ or immune checkpoint inhibitor/ or mitomycin/ or monoclonal antibody/ or nivolumab/ or paclitaxel/ or pembrolizumab/ or programmed death 1 receptor/ or (capecitabine or cetuximab or cisplatin or docetaxel or fluorouracil or immune checkpoint inhibitor or mitomycin or monoclonal antibody or nivolumab or paclitaxel or pembrolizumab or programmed death 1 receptor).ti,ab. 869604

7 anal canal/su or surgical margin/ or (surg* adj3 (anal or anus)).ti,ab. 26447

8 Salvage Therapy/ or (salvage adj3 (chemo* or surg* or therap* or treatment?)).ti,ab. 47766

9 disease exacerbation/ or disease management/ or disease resistance/ or Endoscopy/ or nuclear magnetic resonance imaging/ or positron emission tomography-computed tomography/ or treatment outcome/ or watchful waiting/ or (anoscopy or disease management or endoscopy or magnetic resonance imaging or MRI or monitor* or positron emission tomography or PET-CT or PET or disease progression or disease resistan* or disease relapse or disease surveillance or disease surveille or watchful waiting).ti,ab. 4039304

10 cancer grading/ or cancer staging/ or metastatic anal cancer/ or tumor invasion/ or tumor recurrence/ or ((neoplasm? or nodal or tumo?r) adj3 (assess* or burden or grade or grading or invasive* or metasta* or restaging or stage or staging or status or recurrent or recurrence or relapse?)).ti,ab. 785812

11 exp tumor volume/ or (tumo?r adj2 (diameter or dimension or size or volume)).ti,ab. 315137

12 algorithm/ or cancer prognosis/ or exp disease free survival/ or nomogram/ or predictive value/ or exp progression free survival/ or time factor/ or treatment failure/ or treatment outcome/ or (algorithm? or nomogram? or outcome? or predict* or prognosis or survival).ti,ab. 8087210

13 or/5-1211579572

14 4 and 13 9273

15 (Books or Chapter or Conference Abstract or Conference Review or Editorial or letter or Note or preprint).pt. 7931656

16 book/ or case report/ or conference paper/ or conference abstract/ or "conference review"/ or editorial/ or letter/ or symposium/ or workshop/ 7132808

17 15 or 16 10997720

18 14 not 17 4805

19 limit 18 to (english language and yr="2000 -Current") 3624

Cochrane Central Register of Controlled Trials, Issue 5 of 12, May 2023

Range: 2000101-20230530

ID Search Hits

#1 MeSH descriptor: [Anus Neoplasms] explode all trees 168

#2 (anal or anus or perianal) near/3 (cancer* or carcino* or neoplasm? or squamous or tumo?r or SCC):ti,ab 524
#3 (anal near/3 (basaloid or cloacogenic or epidermoid or margin or skin or transitional)):ti,ab 114
#4 #1 or #2 or #3 670
#5 journal:pt 1543403
#6 #4 AND #5 397
#7 (Pubmed):an 798737
#8 #6 AND #7 147

Supplemental Evidence and Data for Systematic review (SEADS): Various stakeholders were informed about submitting information relevant to this review using a Federal Register notification. A portal about the opportunity to submit information was made available on the Effective Health Care (EHC) Website. No submissions were received for this report.

Data Extraction and Data Management

After including eligible studies from all sources mentioned above, we extracted data for a prespecified list of data elements following principles from the Template for Intervention Description and Replication (TIDieR) checklist.[1] Using standardized templates, data from included studies were abstracted into categories that include but are not limited to: study design, publication year, setting, country, funding, sample size, patient selection/ eligibility criteria, description of intervention and cointerventions, population and clinical characteristics including key subgroups (sex, age, race, HIV status), cancer stage, duration of followup, effectiveness-related outcomes, as well as treatment-related harms or toxicity events.

Grading the Strength of the Body of Evidence

To ensure consistency and validity of the evaluation, the initial assessment was independently reviewed by at least one other experienced investigator using the following criteria:

- Study limitations (low, moderate, or high level of study limitations): Rated as the degree to which studies for a given outcome are likely to reduce bias based on study design and conduct. The aggregate RoB across studies reporting an outcome is considered.
- Consistency (consistent, inconsistent, or unknown/not applicable): Rated as the degree to which studies find similar magnitude or direction of effect.
- Directness (direct or indirect): Rated as the degree to which the outcome is directly or indirectly related to health outcomes of interest. Patient centered outcomes are considered direct. In this review, all outcomes are patient centered, resulting in a direct rating for all.
- Precision (precise or imprecise): Describes the level of certainty of the estimate of effect for a particular outcome. Precise estimates allow for a clinically useful conclusion. Precision may be based on sufficiency of sample size and number of events, and if these are adequate, the interpretation of the confidence interval. When quantitative synthesis is not possible, sample size and assessment of variance within individual studies should be considered.
- Reporting bias (suspected or undetected): Publication bias, selective outcome reporting, and selective analysis reporting are types of reporting bias. We used ClinicalTrials.gov to

search for unpublished evidence. Although quantitative funnel plot analysis can be done if enough RCTs (>10) are available, we had two or less RCTs per unique intervention comparison set, so we did not make a funnel plot.

Assessing Applicability

Applicability was assessed in accordance with the AHRQ Methods Guide, using the PICOTS framework.[2] Applicability refers to the degree to which outcomes associated with the intervention is likely to be similar across patients and settings relevant to the care of patients, undergoing initial treatment for stages I-III SCCA, based on the populations, interventions, comparisons, and outcomes synthesized across included studies. Multiple factors were identified *a priori* with input from public comment, the Key Informants, and a panel of Technical Experts, that are likely to impact applicability include characteristics of enrolled patient populations (e.g., sex, age, race, HIV status) and cancer stage based on tumor size and nodal involvement. For each study, we examined the population to identify those with narrow eligibility criteria, exclusions for comorbidities, more complex participants than typically found in the community, and run-in periods that excluded non-adherent participants. For interventions, we checked if studies used tests or treatments not recommended or commonly used in practice, medication dosages not reflective of current practice, co-interventions that might alter effectiveness, and highly trained testers or treatment teams. For comparisons, we evaluated whether studies used inadequate interventions or substandard care as comparators, and instances where the comparator was unclear. For outcomes, we assessed whether unqualified assessors were used, if surrogate or composite outcomes had limited applicability, and if follow-ups were too short for effects to manifest. For settings, we examined whether studies were conducted in environments with different care levels, for example, location of care (such as rural, urban, etc.), care facility statistics (such as high volume versus low volume centers, primary versus tertiary care centers). Reviewers could also note additional applicability concerns. This information was used to determine the relevance of the evidence to real-world clinical practice in typical U.S. settings and to qualitatively summarize applicability assessments. The findings are discussed in the review.

References for Appendix A

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2. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: http://www.effectivehealthcare.ahrq.gov

Appendix B. References Excluded at Full-Text Screening

Reasons for exclusion:

P = Population is inappropriate

I = Intervention is inappropriate

C = Comparison is inappropriate

O = Outcome is inappropriate

S = Study Design is inappropriate

1. Abunassar M, Reinders J, Jonker DJ, et al. Review of anal cancer patients at the Ottawa hospital. Eur J Surg Oncol. 2015;41(5):653-8. doi: 10.1016/j.ejso.2015.02.004. PMID: 604947682. S
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Appendix C. Evidence Tables

Study Design Characteristics: Population, Intervention, Comparators, Outcomes, and Followup Duration

Table C.1.1. Study design characteristics for Key Question 1

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs) Follow-Up Duration	Intervention Comparator Cointervention	Primary Outcome(s)	Secondary Outcome(s)	Harms
Chai, 2017 (29049547)[1] **Local excision vs chemoradiotherapy in T1N0 lesions** **Retrospective cohort**	2,243 patients 503 LE 1,740 CRT 5 years	Local excision CRT	Overall survival at 5 years	Overall survival stratified by tumors ≤1cm, and tumors 1-2cm	NR
Deshmukh, 2018 (27755059)[2] **Local excision vs chemoradiotherapy, and local excision vs radiation therapy in T1N0 lesions** **Retrospective cohort**	190 patients 44 LE 96 CRT 50 RT NR	Local excision CRT or RT	Overall survival	NR	NR
Gao, 2020 (32199768)[3] **Local excision vs chemoradiotherapy in T1N0 lesions** **Retrospective cohort**	883 patients 200 LE 683 CRT 5 years	Local excision CRT	Cause-specific survival at 5 years	Cause-specific survival at 5 years stratified by tumors ≤1cm, and tumors 1-2cm	NR
Bartelink, 1997 (9164216)[4] **Radiation therapy vs Chemoradiotherapy** **Randomized controlled trial**	103 patients 52 RT 51 CRT Median 42 months (range 9-88 months)	RT alone CRT with 5FU and MMC	Overall survival	Locoregional control, progression-free survival, colostomy-free survival, event-free survival, severe toxicity-free survival	Acute: Grade 2, 3, and 4 diarrhea Grade 2, 3, and 4 skin reactions Late: Anal ulceration, anal fistula, anal perforation, rectal stenosis requiring surgery, skin ulceration, severe fibrosis

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs) Follow-Up Duration	Intervention Comparator Cointervention	Primary Outcome(s)	Secondary Outcome(s)	Harms
UKCCCR, 1996 (8874455)[5] **Radiation therapy vs Chemoradiotherapy** **Randomized controlled trial**	585 patients 290 RT 295 CRT Median 42 months (interquartile range 28-62 months)	RT alone CRT with 5FU and MMC	Local failure	Overall survival (3 years), deaths from anal cancer	Acute: Overall cohort Skin Gastrointestinal Genitourinary Late: Overall cohort Skin Gastrointestinal Genitourinary
Northover, 2010 (20354531)[6] **Radiation therapy vs Chemoradiotherapy** **Randomized controlled trial**	577 patients 285 RT 292 CRT Median 13.1 years	RT alone CRT with 5FU and MMC	Overall survival at 12 years	Relapse-free survival, colostomy-free survival, locoregional failure rate, anal cancer death rate	Late: Ulceration / radionecrosis Anorectal Genitourinary Skin
Flam, 1996 (8823332)[7] **RT+5FU vs RT+5FU+MMC** **Randomized controlled trial**	291 patients 145 RT+5FU 146 RT+5FU+MMC Median 3.01 years (range 0.07-6.17 years)	CRT with 5FU only CRT with 5FU and MMC	Not specified	Overall survival, disease-free survival, colostomy-free survival, local failure rate, colostomy rate *All reported at 4 years	NR
Goodman, 2017 (28721892)[8] **RT+MMC+Cape vs RT+MMC+5FU** **Retrospective cohort**	107 patients 44 RT+MMC+Cape 63 RT+MMC+5FU Median 33 months	Capecitabine (oral, 2 cycles) 5FU (continuous intravenous infusion over 4 days, 2 cycles) Concurrent CRT with MMC	Not specified	Overall survival, locoregional recurrence rate, incidence of distant metastases, colostomy creation rate *All reported at 2 years	NR

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs) Follow-Up Duration	Intervention Comparator Cointervention	Primary Outcome(s)	Secondary Outcome(s)	Harms
Jones, 2018 (29859793)[9] **RT+MMC+Cape vs RT+MMC+5FU** **Prospective cohort**	147 patients 52 RT+MMC+Cape 95 RT+MMC+5FU 1 year	Capecitabine (oral, 2 cycles) 5FU (continuous intravenous infusion over 4 days, 2 cycles) Concurrent CRT with MMC	Not specified	Colostomy-free survival, relapse-free survival	Grade 3 or 4 toxicity rates: Overall Hematologic Non-hematologic Gastrointestinal Skin Anal pain Cardiac
Peixoto, 2016 (27563458)[10] **RT+MMC+Cape vs RT+MMC+5FU** **Retrospective cohort**	300 patients 106 RT+MMC+Cape 194 RT+MMC+5FU Median 43.9 months	Capecitabine (oral, 2 cycles) 5FU (continuous intravenous infusion over 4 days, 2 cycles) Concurrent CRT with MMC	Disease-free survival at 5 years	Anal cancer-specific survival at 5 years	NR
Matzinger, 2009 (19643599)[11] **RT+MMC+5FU vs RT+MMC+cisplatin** **Randomized controlled trial**	76 patients 39 RT+MMC+5FU 37 RT+MMC+cisplatin Median 2 years	RT+MMC+5FU RT+MMC+cisplatin	Tumor response at week 16 (8 weeks after treatment)	Progression-free survival, event-free survival,	Grade 3 or 4 toxicity rates: Hematologic, Gastrointestinal, Skin
Ajani, 2008 (18430910)[12] **RT+5FU+MMC vs RT+5FU+cisplatin** **Randomized controlled trial**	644 patients 324 RT+5FU+MMC 320 RT+5FU+cisplatin Median 2.51 years	MMC (2 cycles in concurrent CRT Cisplatin (with ICT 2 cycles + concurrent 2 cycles, both phases with 2 cycles of 5FU) Concurrent CRT with 5FU (2 cycles), RT dose 45-59 Gy.	Disease-free survival at 5 years	Overall survival, colostomy creation rate, time to locoregional treatment failure, time to distant metastasis, locoregional recurrence rate, distant metastasis rate	Acute (grade 3 or 4): Hematologic, and Non-hematologic Late (grade 3 or 4): Gastrointestinal, Skin, Bladder, Subcutaneous tissue, Other.

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs) Follow-Up Duration	Intervention Comparator Cointervention	Primary Outcome(s)	Secondary Outcome(s)	Harms
Gunderson, 2012 (23150707)[13] **RT+5FU+MMC vs RT+5FU+cisplatin** ***Post hoc* analyses of RCT**	649 patients 325 RT+5FU+MMC 324 RT+5FU+cisplatin Up to 8 years	MMC (2 cycles in concurrent CRT Cisplatin (with ICT 2 cycles + concurrent 2 cycles, both phases with 2 cycles of 5FU) Concurrent CRT with 5FU (2 cycles), RT dose 45-59 Gy.	Disease-free survival at 5 years	Overall survival, colostomy-free survival, locoregional failure, distant metastasis rate, colostomy failure rate	Late: Skin, Gastrointestinal, Subcutaneous tissue, Other.
James, 2013 (23578724)[14] **Cisplatin vs MMC** **Randomized controlled trial**	940 patients 247 5FU+cisplatin+ no maintenance 222 5FU+cisplatin + maintenance 246 5FU+MMC+ no maintenance 226 5FU+MMC+ maintenance Median 5.1 years (IQR 3.9-6.9 years)	Cisplatin (2 cycles) MMC (1 cycle) Initial concurrent CRT with either 5FU + MMC (1 cycle) or 5FU + cisplatin (2 cycles); RT-50.4 Gy, 28 fractions. About half received maintenance with 5FU + cisplatin	Progression-free survival at 3 years (stratified by <65 years old, ≥65 years old, females, males, T1+T2, T3+T4, node positive, and node negative)	Overall survival at 3 years, colostomy-free survival, anal cancer mortality	Acute: Overall Hematologic Gastrointestinal Genitourinary Skin Pain Cardiac Vascular Other
Glynne-Jones, 2014 (24827136)[15] **Cisplatin vs MMC** **Randomized controlled trial**	884 patients 230 5FU+cisplatin+ no maintenance 210 5FU+cisplatin + maintenance 232 5FU+MMC+ no maintenance 212 5FU+MMC+ maintenance Median 5.1 years (range 6 days to 10.5 years)	Cisplatin (2 cycles) MMC (1 cycle) Initial concurrent CRT with either 5FU + MMC (1 cycle) or 5FU + cisplatin (2 cycles); RT-50.4 Gy, 28 fractions. About half received maintenance with 5FU + cisplatin	Colostomy-free survival	Progression-free survival	NR

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs) Follow-Up Duration	Intervention Comparator Cointervention	Primary Outcome(s)	Secondary Outcome(s)	Harms
Gordeyev, 2022 (Not indexed in PubMed)[33] **IMRT + capecitabine + MMC + paclitaxel Vs IMRT + capecitabine + MMC** **Randomized controlled trial**	144 patients; N=72 patients per arm Median 39.5 months (6.8 to 94.4 months)	CRT with capecitabine (625 mg/m^2), plus MMC (10 mg/m^2 on day 1), plus paclitaxel (45 mg/m^2 intravenous weekly) CRT with capecitabine (825 mg/m^2) and MMC (12 mg/m^2 on day 1) IMRT (consecutive daily fractions of 1.8 to 2.2 Gy. The planned dose for the primary tumor was 52 to 58 Gy [52–54 Gy for T1 — 2 tumors and 56–58 Gy for T3 — 4 tumors], for affected lymph nodes ≤ 3 cm in size — 50–52 Gy, > 3 cm in size — 54 Gy.)	Disease-free survival at 3 years	Overall and colostomy-free survival at 3 years	Overall acute harms, acute hematologic, dermatologic, gastrointestinal, and genitourinary toxicity

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; LE- local excision; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; CRT- chemoradiation; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; NR- not reported.

Table C.1.2. Study design characteristics for Key Question 2

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs) Followup Duration	Intervention	Comparator	Primary Outcome(s)	Secondary Outcome(s)	Harms
Pollom, 2017 (28258896)[16] **IMRT vs non-IMRT** **Retrospective cohort**	1,165 patients 458 IMRT 707 non-IMRT Median 47.4 months	IMRT	Non-IMRT	Time to first hospitalization	Overall survival, cause-specific survival at 2 years	NR

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs) Followup Duration	Intervention	Comparator	Primary Outcome(s)	Secondary Outcome(s)	Harms
Bryant, 2018 (30102186)[17] **IMRT vs non-IMRT** **Retrospective cohort**	779 patients 376 IMRT 403 non-IMRT NR	IMRT	Non-IMRT	Not specified	Radiation treatment delay ≥10 days, *overall mortality, *anal cancer mortality, *non-anal cancer mortality, *tumor-related ostomy placement *All reported at 5 years	Acute Hemat-ologic
Dasgupta, 2013 (23692961)[18] **IMRT vs 3D CRT** **Retrospective cohort**	223 patients 45 IMRT 178 3D CRT Median 59.6 months	IMRT	3D CRT	Not specified	Overall survival, disease-free survival, distant metastasis-free survival, colostomy-free survival *All reported at 2 years	NR
Elson, 2018 (30329160)[19] **IMRT vs 3D CRT** **Retrospective cohort**	4,378 patients 2,189 IMRT 2,189 3D CRT *After propensity matching NR	IMRT	3D CRT	Overall survival at 10 years	NR	NR
Mohiuddin, 2021 (34646965)[20] **Proton IMRT (IMPT) vs photon IMRT** **Prospective cohort**	208 patients 58 proton IMRT (IMPT) 150 photon IMRT Median 30 months	IMPT	IMRT	Overall grade 3+ acute toxicity	Locoregional recurrence-free survival at 2 years, progression-free survival at 2 years	Acute: Overall, grade 3+ Late: Overall, grade 3+

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs) Followup Duration	Intervention	Comparator	Primary Outcome(s)	Secondary Outcome(s)	Harms
Glynne-Jones, 2011 (20934265)[21] **External beam boost (EBRT) vs brachytherapy (BCT) boost** **Post-hoc of randomized controlled trial**	490 patients 436 boost 54 no boost Of 436 boost, 12 excluded 289 EBRT 135 BCT NR	EBRT	BCT	Not specified	Overall survival, relapse-free survival, anal cancer deaths, non-anal cancer deaths	NR
Hannoun-Levi, 2011 (20619552)[22] **EBRT vs BCT** **Prospective, non-randomized controlled trial**	162 patients 76 EBRT 86 BCT Median 62 months (range 2-108 months)	EBRT	BCT	Overall survival at 5 years	Colostomy-free survival, cumulated rate of local recurrence	NR
Moureau-Zabotto, 2013 (23195780)[23] **EBRT vs BCT** **Retrospective cohort**	99 patients 49 EBRT 50 BCT Median 71.5 months (range 1.2-121 months)	EBRT	BCT	Overall survival at 5 years	Cumulated rate of local recurrence, cumulated rate of distant recurrence, colostomy-free survival	NR

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; RT- radiation therapy; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; EBRT- external beam RT; BCT- brachytherapy; NR- not reported.

Table C.1.3. Study design characteristics for Key Question 3

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs) Follow-Up Duration	Intervention Comparator Cointervention	Primary Outcome(s)	Secondary Outcome(s)	Harms
Peiffert, 2012 (22529257)[24] **Standard boost v high-dose boost** **Randomized controlled trial**	307 patients 75 induction chemo + RCT + standard boost 75 induction chemo + RCT + high-dose boost 82 RCT + standard boost 75 RCT + high-dose boost Median 50 months (range 0-102 months)	Standard dose boost (15Gy) High dose boost (20- 25Gy) CRT with 5FU and cisplatin (2 cycles, weeks 1 and 5), RT (45Gy) and boost with EBRT or Bct, about half received induction chemo with 5FU and cisplatin (2 cycles, weeks 1 and 5) before CRT	Colostomy-free survival at 5 years	Local control, specific survival, tumor-free survival at 5 years	Acute: Hematologic, Gastrointestinal, Infection, Cardiac, Bleeding Late: Gastrointestinal Anal pain Incontinence Ulceration/ fistula
Tournier-Rangeard, 2008 (18191265)[25] **Induction chemotherapy v no induction** **Standard boost v high-dose boost** **Subgroup analysis of a randomized controlled trial**	119 patients *The number of patients who filled out both quality of life questionnaires (before treatment and 2 months after completion)	Standard dose boost (15Gy) High dose boost (20- 25Gy) CRT with 5FU and cisplatin (2 cycles, weeks 1 and 5), RT (45Gy) and boost with EBRT or Bct, about half received induction chemo with 5FU and cisplatin (2 cycles, weeks 1 and 5) before CRT	Quality of life questionnaires (QOL-C30 and AS-CT)	NR	NR
Wegner, 2019 (31136369)[26] **45-54Gy vs. >54Gy** **Retrospective cohort**	7792 patients 4269 treated to doses of 45 to 54 Gy and 3163 treated to doses >54 Gy	Standard dose (45-54Gy) High dose (>54Gy) Concurrent CRT with IMRT or non-IMRT	Overall survival	NR	NR

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs) Follow-Up Duration	Intervention Comparator Cointervention	Primary Outcome(s)	Secondary Outcome(s)	Harms
Glynne-Jones, 2020 (32619648)[27] **Radiation therapy regimens** **group 1) 50.40Gy, 38-42 days (reference group)** **group 2) ≤40Gy** **group 3) >40Gy to <48.60Gy** **group 4) 50.40Gy, <38 days** **group 5) 50.40Gy, >42 days** **group 6) >52.20Gy** ***Post hoc* analysis of RCT**	936 patients Median followup 5.1 years	Radiation therapy regimens group 1) 50.40Gy, 38-42 days (reference group) group 2) ≤40Gy group 3) >40Gy to <48.60Gy group 4) 50.40Gy, <38 days group 5) 50.40Gy, >42 days group 6) >52.20Gy Initial concurrent CRT with either 5FU + MMC (1 cycle) or 5FU + cisplatin (2 cycles); RT-50.4 Gy, 28 fractions. About half received maintenance with 5FU + cisplatin	Overall and progression-free survival	NR	NR
Lukovic, 2023 (36455685)[28] **Dosimetric parameters for acute and late toxicities** **Prospective cohort**	101 patients Median 3.4 years (range 2.7-4.7 years)	Dosimetric parameters derived using lowest p-value approach. All patients got image guided-IMRT and concurrent chemo (variable regimens)	NR	NR	grade 2+ acute diarrhea, grade 2+ acute genitourinary toxicity, grade 2+ inguino-genital skin toxicity, grade 2+ perianal skin toxicity; grade 2+ anemia, late toxicity (grade 2+ anal dysfunction, intestinal toxicity, and inguino-genital/ perianal dermatitis)

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs) Follow-Up Duration	Intervention Comparator Cointervention	Primary Outcome(s)	Secondary Outcome(s)	Harms
Nilsson, 2022 (34598844)[29] **Dosimetric predictors of late toxicities** **Retrospective cohort**	114 patients Median 40 months (range 7-110 months)	Dosimetric parameters derived using lowest p-value approach. All patients got IMRT and concurrent 5FU + MMC	NR	NR	Late grade 2 or higher (grade 2+) gastrointestinal toxicity
Mehta, 2020 (32399269)[30] **≤4.72 fractions/week vs >4.72 fractions/week** **Retrospective cohort**	6,429 patients NR	≤4.72 fractions/wk >4.72 fractions/wk Concurrent CRT, RT dose 45-60Gy, 87% doublet chemo, 46% IMPT	Overall survival	NR	NR

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; EBRT- external beam RT; Bct- brachytherapy; wk- week; NR- not reported.

Table C.1.4. Study design characteristics for Key Question 4

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs) Follow-Up Duration	Intervention Comparator Cointervention	Primary Outcome(s)	Secondary Outcome(s)	Harms
Peiffert, 2012 (22529257)[24] **Induction chemo vs no induction** **Randomized controlled trial**	307 patients 75 induction chemo + RCT + standard boost 75 induction chemo + RCT + high-dose boost 82 RCT + standard boost 75 RCT + high-dose boost Median 50 months (range 0-102 months)	Induction chemo with 5FU and cisplatin (2 cycles, weeks 1 and 5) No induction chemo CRT with 5FU and cisplatin (2 cycles, weeks 1 and 5) and RT (45Gy) with standard (15Gy) or high dose (20- 25Gy) boost with EBRT or Bct	Colostomy-free survival at 5 years	Local control, specific survival, tumor-free survival at 5 years	Acute: Hematologic Gastrointestinal Infection Cardiac Bleeding Late: Gastrointestinal Anal pain Incontinence Ulceration/ fistula

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs) Follow-Up Duration	Intervention Comparator Cointervention	Primary Outcome(s)	Secondary Outcome(s)	Harms
Tournier-Rangeard, 2008 (18191265)[25] **Induction chemotherapy v no induction** **Subgroup analysis of a randomized controlled trial**	119 patients *The number of patients who filled out both quality of life questionnaires (before treatment and 2 months after completion)	Induction chemo with 5FU and cisplatin (2 cycles, weeks 1 and 5) No induction chemo CRT with 5FU and cisplatin (2 cycles, weeks 1 and 5) and RT (45Gy) with standard (15Gy) or high dose (20- 25Gy) boost with EBRT or Bct	Quality of life questionnaires (QOL-C30 and AS-CT)	NR	NR
James, 2013 (23578724)[14] **Maintenance chemotherapy v no maintenance** **Randomized controlled trial**	940 patients 247 5FU+cisplatin+ no maintenance 222 5FU+cisplatin + maintenance 246 5FU+MMC+ no maintenance 226 5FU+MMC+ maintenance Median 5.1 years (IQR 3.9-6.9 years)	Maintenance chemo with 5FU and cisplatin (2 courses, in week 11 and 14) No maintenance chemo Initial treatment with concurrent CRT with either 5FU + MMC (1 cycle) or 5FU + cisplatin (2 cycles); RT-50.4 Gy, 28 fractions.	Progression-free survival at 3 years (stratified by <65 years old, ≥65 years old, females, males, T1+T2, T3+T4, node positive, and node negative)	Overall survival at 3 years, colostomy-free survival, anal cancer mortality	Acute: Overall Hematologic Gastrointestinal Genitourinary Skin Pain Cardiac Vascular Other
White, 2015 (26347494)[31] **1 cycle MMC v 2 cycles MMC** **Retrospective cohort**	217 patients 154 One cycle 63 Two cycles Median 26 months (range 3-109 months)	One cycle of MMC Two cycles of MMC CRT with 5FU (2 cycles) + MMC with standard institutional protocol	Not specified	Overall survival, progression-free survival, colostomy-free survival, cancer-specific survival, all reported at 2 years	Acute: Hematologic Skin Gastrointestinal Genitourinary RT treatment break Late: Overall

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs) Follow-Up Duration	Intervention Comparator Cointervention	Primary Outcome(s)	Secondary Outcome(s)	Harms
Glynne-Jones, 2011 (20934265)[21] **Boost v no boost** ***Post hoc* of randomized controlled trial**	490 patients 436 boost 54 no boost Of 436 boost, 12 excluded 289 EBRT 135 BCT NR	Boost No boost Either RT alone or CRT with 5FU and MMC, RT- 45Gy in 20-25 fractions, boost with EBRT (15Gy) or Bct (25Gy)	Not specified	Overall survival, relapse-free survival, anal cancer deaths, non-anal cancer deaths	NR

Abbreviations: CRT-chemoradiation, N0- node negative; N>0- node positive; T1-3- any size tumor not invading adjacent organs; T4- any size tumor invading adjacent organs; RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; RT- radiation therapy; EBRT- external beam RT; Bct- brachytherapy; NR- not reported.

Table C.1.5. Study design characteristics for Key Question 6

Study (PMID) Study Design	Sample Size (Randomized for RCTs or Included in NRSIs) Follow-Up Duration	Comparison	Primary Outcome(s)	Secondary Outcome(s)	Harms
Frazer, 2020 (32028341)[32] **Retrospective cohort**	138 patients Median 27 months (range 3-141 months)	Event frequency: within 1yr vs. within 2 yrs vs. year 3 to 5 Stratified by risk: High risk group (T4N0 or N>0) Low risk group (T1-3N0)	Not specified	Overall survival, local control, distant metastasis-free survival, event-free survival *All reported at 5 years Number of local recurrences, number of distant metastases, number of late grade 3 toxicities *All reported at the following time points: within 1 year, within 2 years, from years 3-5 from years 5-6	Not reported

Abbreviations: N0- node negative; N>0- node positive; T1-3- any size tumor not invading adjacent organs; T4- any size tumor invading adjacent organs; RCT- randomized controlled trials; NRSI- nonrandomized study of interventions.

Study Participant Characteristics

Table C.2.1. Study participant characteristics for Key Question 1

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs)	Mean or Median Age at Baseline	Cancer Staging	Race/ Ethnicity, n, (%) [Majority]	Sex, n (%)	HIV Status or Immuno-compromised, n (%)
Chai, 2017 (29049547)[1] **Local excision vs CRT in T1N0 lesions** **Retrospective cohort**	2,243 patients 503 LE 1,740 CRT	LE: 54.5 years CRT: 57 years	Stage I: all 2,243 patients	LE: White: 419 (83.3%) CRT: White: 1,547 (88.9%)	LE: Male 240 (47.7%) CRT: Male 562 (32.3%)	NR
Deshmukh, 2018 (27755059)[2] **Local excision vs CRT or RT in T1N0 lesions** **Retrospective cohort**	190 patients 44 LE 96 CRT 50 RT	LE: 74 years CRT: 72 years RT: 77 years	Stage I: all 190 patients	NR	NR	NR
Gao, 2020 (32199768) [3] **Local excision vs chemoradiotherapy in T1N0 lesions** **Retrospective cohort**	883 patients 200 LE 683 CRT	LE: 60 years CRT: 60 years	Stage I: all 883 patients	Overall: Whit: 790 (90%); LE: White (85%) CRT: White (91%)	Male: 310 (35%)	NR
Bartelink, 1997 (9164216)[4] **RT vs CRT** **Randomized controlled trial**	103 patients 52 RT 51 CRT	NR	TNM: T1-2 N1-3: 16 T3-4 N0: 48 T3-4 N1-3: 37 Tx Nx: 2	NR	Male: 30 (29%)	NR
UKCCCR, 1996 (8874455)[5] **RT vs CRT** **Randomized controlled trial**	580 patients 285 RT 295 CRT	Median RT: 65 years CRT: 63 years	TNM: T1: 71 T2: 191 T3: 220 T4: 73 N+: 115 M1: 15	NR	Male: 260 (44%)	NR

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs)	Mean or Median Age at Baseline	Cancer Staging	Race/ Ethnicity, n, (%) [Majority]	Sex, n (%)	HIV Status or Immuno-compromised, n (%)
Northover, 2010 (20354531)[6] **Radiation therapy vs CRT** **Follow up to randomized controlled trial**	577 patients 285 RT 292 CRT	Median RT: 65 years CRT: 63 years	TNM: T1: 71 T2: 191 T3: 220 T4: 73 N+: 115 M1: 15	NR	Male: 260 (44%)	NR
Flam, 1996 (8823332)[7] **RT+5FU vs RT+5FU+MMC** **Randomized controlled trial**	291 patients 145 RT+5FU 146 RT+5FU+MMC	Median RT+5FU: 59 years RT+5FU+MMC: 62.5 years	TNM: T1: 44 T2: 111 T3: 109 T4: 27 N0: 240 N1: 50 Nx: 1	NR	Male: 101 (35%)	NR
Goodman, 2017 (28721892) [8] **RT+MMC+Cape vs RT+MMC+5FU** **Retrospective cohort**	107 patients 44 RT+MMC+Cape 63 RT+MMC+5FU	Median RT+MMC+Cape: 60 years RT+MMC+5FU: 59 years	TNM: T1/Tx: 19 T2: 45 T3: 24 T4: 19 N0/Nx: 44 N1: 29 N2: 14 N3: 20	Overall: White: 86 (80%)	Male: 29 (27%)	HIV+: 8 (7%)
Jones, 2018 (29859793) [9] **RT+MMC+Cape vs RT+MMC+5FU** **Prospective cohort**	147 patients 52 RT+MMC+Cape 95 RT+MMC+5FU	NR	TNM: T1: 15 T2: 64 T3: 37 T4: 29 Tx: 2 N0: 71 N+: 76 M0: 140 M1: 4 Mx:3	NR	Male: 43 (29%)	HIV+: 5 (3%)
Peixoto, 2016 (27563458) [10] **RT+MMC+Cape vs RT+MMC+5FU** **Retrospective cohort**	300 patients 106 RT+MMC+Cape 194 RT+MMC+5FU	Median Cape: 59 years 5FU: 58 years	TNM: T≤5cm: 199 T>5cm: 101 N0: 164 N+: 136	NR	Male: 105 (35%)	HIV+: 13 (4%)

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs)	Mean or Median Age at Baseline	Cancer Staging	Race/ Ethnicity, n, (%) [Majority]	Sex, n (%)	HIV Status or Immuno-compromised, n (%)
Matzinger, 2009 (19643599) [11] **RT+MMC+5FU vs RT+MMC+cisplatin** **Randomized controlled trial**	76 patients 39 RT+MMC+5FU 37 RT+MMC+cisplatin	Median 5FU: 54 years Cisplatin: 59 years	TNM: T1: 1 T2: 36 T3: 29 T4: 9 Tx: 1 N0: 39 N1: 18 N2: 13 N3: 6	NR	Male: 23 (30%)	NR
Ajani, 2008 (18430910)[12] **RT+5FU+MMC vs RT+5FU+cisplatin** **Randomized controlled trial**	644 patients 324 RT+5FU+MMC 320 RT+5FU+cisplatin	Median 55 years	Stage I: 302 (47%) II: 115 (18%) III: 57 (9%)	NR	Male: 198 (31%)	NR
Gordeyev, 2022 (Not indexed in PubMed)[33] **IMRT + capecitabine + MMC + paclitaxel Vs IMRT + capecitabine + MMC** **Randomized controlled trial**	144 patients; N=72 patients per arm Median 39.5 months (6.8 to 94.4 months)	Median 56.5 years	Stage I: 10 (6.9%) II: 21 (14.6%) III: 113 (78.5%)	NR	Male: 13.2%	0 (0%) [HIV positive patients excluded]
Gunderson, 2012 (23150707)[13] **RT+5FU+MMC vs RT+5FU+cisplatin** **Long-term update of RCT**	649 patients 325 RT+5FU+MMC 324 RT+5FU+cisplatin	NR (Long-term update to RTOG 98-11 so this study has the same demographic variables)	NR	NR	NR	NR
James, 2013 (23578724) [14] **Cisplatin vs MMC** **Randomized controlled trial**	940 patients 247 5FU+cisplatin+ no maintenance 222 5FU+cisplatin + maintenance 246 5FU+MMC+ no maintenance 226 5FU+MMC+ maintenance	Median: 58 years	T1: 91 T2: 395 T3: 295 T4: 135 Tx: 22 N0: 587 N+: 305 Nx: 44 Missing T or N: 6	NR	Male: 353 (38%)	NR

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs)	Mean or Median Age at Baseline	Cancer Staging	Race/ Ethnicity, n, (%) [Majority]	Sex, n (%)	HIV Status or Immuno-compromised, n (%)
Glynne-Jones, 2014 (24827136) [15] **Cisplatin vs MMC** **Subgroup analysis of randomized controlled trial**	884 patients 230 5FU+cisplatin+ no maintenance 210 5FU+cisplatin + maintenance 232 5FU+MMC+ no maintenance 212 5FU+MMC+ maintenance	Median: 57 years	TNM: T1: 88 T2: 376 T3: 274 T4: 124 Missing: 22 N0: 556 N+: 283 Missing: 45	NR	Male: 323 (36.5%)	NR

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; HIV- human immunodeficiency virus; LE- local excision; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; CRT- chemoradiation; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; N0- node negative; N>0- node positive; T1-3- any size tumor not invading adjacent organs; T4- any size tumor invading adjacent organs; NR- not reported.

Table C.2.2. Study participant characteristics for Key Question 2

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs)	Mean Age at Baseline	Cancer Staging	Race/ Ethnicity, n, (%) [Majority]	Sex, n (%)	HIV Status or Immuno-compromised, n (%)
Dasgupta, 2013 (23692961)[18] **IMRT vs 3D CRT** **Retrospective cohort**	223 patients 45 IMRT 178 3D CRT	Median 59 years	TNM: T1: 42 T2: 107 T3: 57 T4: 14 Tx: 3 N0: 136 N1: 50 N2: 26 N3: 11	White: 185 (83%)	Male: 75 (33.6%)	HIV+: 22 (9.9%)
Elson, 2018 (30329160)[19] **IMRT vs 3D CRT** **Retrospective cohort**	4,378 patients 2,189 IMRT 2,189 3D CRT *After propensity matching NR	IMRT: 59.8 years 3D CRT: 59.1 years	IMRT: Stage I: 352 II: 1,341 III: 1,209 3D CRT: I: 539 II: 1,853 III: 1,520	IMRT: White: 1,937 (88.5%) 3D CRT: White: 1,917 (87.6%)	IMRT: Male 881 (30.4%) 3D CRT: Male 1,126 (28.8%)	NR
Pollom, 2017 (28258896)[16] **IMRT vs non-IMRT** **Retrospective cohort**	1,165 patients 458 IMRT 707 non-IMRT	Median 70 years	Stage I: 156 II: 409 III: 273 Missing: 327	White: 1,036 (89%)	Male: 414 (36%)	HIV+: 95 (8%)

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs)	Mean Age at Baseline	Cancer Staging	Race/ Ethnicity, n, (%) [Majority]	Sex, n (%)	HIV Status or Immuno-compromised, n (%)
Bryant, 2018 (30102186)[17] **IMRT v non-IMRT** **Retrospective cohort**	779 patients 376 IMRT 403 non-IMRT	IMRT: 62 years Non-IMRT: 60 years	IMRT Stage I: 51 II: 173 III: 152 Non-IMRT I: 65 II: 229 III: 109	IMRT: White: 315 (84%) Non-IMRT: White: 333 (83%)	IMRT: Male 340 (90%) Non-IMRT: Male 377 (94%)	IMRT: HIV+ 76 (20%) Non-IMRT: HIV+ 83 (21%)
Mohiuddin, 2021 (34646965)[20] **Proton IMRT (IMPT) vs photon IMRT** **Prospective cohort**	208 patients 58 proton IMRT (IMPT) 150 photon IMRT	Median 62 years	Stage I: 27 II: 74 III: 102 IV: 3	NR	Male: 56 (27%)	HIV+: 25 (12%)
Glynne-Jones, 2011 (20934265)[21] **External beam boost (EBRT) vs brachytherapy (BCT) boost** **Post-hoc of randomized controlled trial**	490 patients 436 boost 54 no boost Of 436 boost, 12 excluded 289 EBRT 135 BCT	NR (post-hoc of ACT I trial)	NR	NR	NR	NR
Hannoun-Levi, 2011 (20619552)[22] **EBRT vs BCT** **Prospective, non-randomized controlled trial**	162 patients 76 EBRT 86 BCT	65 years	Stage I: 28 II: 67 III: 67	NR	Male: 36 (29%)	HIV+: 9 (6%)
Moureau-Zabotto, 2013 (23195780)[23] **EBRT vs BCT** **Retrospective cohort**	99 patients 49 EBRT 50 BCT	63 years	TNM: T1: 4 T2: 16 T3: 49 T4: 16 Missing: 14 N1: 67 N2: 25 N3: 7	NR	Male: 20 (20%)	HIV+: 3 (3%)

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; HIV- human immunodeficiency virus; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; CRT- chemoradiation; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; EBRT-

external beam RT; Bct- brachytherapy; N0- node negative; N>0- node positive; T1-3- any size tumor not invading adjacent organs; T4- any size tumor invading adjacent organs; NR- not reported.

Table C.2.3. Study participant characteristics for Key Question 3

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs)	Mean Age at Baseline	Cancer Staging	Race/ Ethnicity, n, (%) [Majority]	Sex, n (%)	HIV Status or Immuno-compromised, n (%)
Peiffert, 2012 (22529257)[24] **Standard boost vs high-dose boost** **Randomized controlled trial**	307 patients 75 induction chemo + RCT + standard boost 75 induction chemo + RCT + high-dose boost 82 RCT + standard boost 75 RCT + high-dose boost	58.8 years	TNM Modified: T1-2/N0-1: 113 N0-1: 235	NR	Male 59 (19%)	NR
Tournier-Rangeard, 2008 (18191265)[25] **Standard boost vs high-dose boost** **Subgroup analysis of a randomized controlled trial**	119 patients *The number of patients who filled out both quality of life questionnaires (before treatment and 2 months after completion)	NR	NR	NR	Male 21 (18%)	NR
Wegner, 2019 (31136369)[26] **45-54Gy vs >54Gy** **Retrospective cohort**	7,792 patients 4,629 with dose 45-54Gy 3,163 with dose >54 Gy	≤58 years old: 4,021 patients >58 years old: 3,771 patients	Stage I: 933 Stage II: 3,474 Stage III: 3,385	Overall: 6,920 (89%) White	Male: 2,324 (30%)	NR

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs)	Mean Age at Baseline	Cancer Staging	Race/ Ethnicity, n, (%) [Majority]	Sex, n (%)	HIV Status or Immuno-compromised, n (%)
Glynne-Jones, 2020 (32619648)[27] **Radiation therapy regimens** **group 1) 50.40Gy, 38-42 days (reference group)** **group 2) ≤40Gy** **group 3) >40Gy to <48.60Gy** **group 4) 50.40Gy, <38 days** **group 5) 50.40Gy, >42 days** **group 6) >52.20Gy** ***Post hoc* analysis of RCT**	936 patients	NR	TNM: T1: 91 T2: 395 T3: 295 T4: 135 Tx: 24 N0: 587 N+: 305 Nx: 48	NR	Male: 353 (38%)	NR
Lukovic, 2023 (36455685) [28] **Dosimetric parameters on acute and late toxicities** **Prospective cohort**	101 patients	Median 57 years	TNM: T1: 11 T2: 55 T3: 28 T4: 7 N0: 65 N+ 36	NR	Male: 50 (50.5%)	HIV+: 25 (25%)
Nilsson, 2022 (34598844)[29] **Dosimetric predictors of acute and late toxicities** **Retrospective cohort**	114 patients	Median 63.7 years	TNM: T1: 3 T2: 49 T3: 30 T4: 32	NR	Male: 25 (22%)	HIV+: 1 (1%)

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs)	Mean Age at Baseline	Cancer Staging	Race/ Ethnicity, n, (%) [Majority]	Sex, n (%)	HIV Status or Immuno-compromised, n (%)
Mehta, 2020 (32399269)[30] **≤4.72 fractions/week vs >4.72 fractions/week** **Retrospective cohort**	RT duration cohort: 8,948 patients Overall survival cohort: 6,429 patients* *Used OS cohort for the rest of the columns	NR	TNM: T0/is: 4 T1: 961 T2: 3,329 T3: 1,545 T4: 557 Missing: 93 N0: 4,025 N1: 821 N2: 864 N3: 624 Missing: 95	5,179 (80.6%) White	Male: 1,928 (30%)	NR

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; HIV- human immunodeficiency virus; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; CRT- chemoradiation; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; EBRT- external beam RT; Bct- brachytherapy; N0- node negative; N>0- node positive; T1-3- any size tumor not invading adjacent organs; T4- any size tumor invading adjacent organs; NR- not reported.

Table C.2.4. Study participant characteristics for Key Question 4

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs)	Mean Age at Baseline	Cancer Staging	Race/ Ethnicity, n, (%) [Majority]	Sex, n (%)	HIV Status or Immuno-compromised, n (%)
Peiffert, 2012 (22529257)[24] **Induction chemotherapy vs no induction** **Randomized controlled trial**	307 patients 75 induction chemo + RCT + standard boost 75 induction chemo + RCT + high-dose boost 82 RCT + standard boost 75 RCT + high-dose boost	58.8 years	TNM Modified: T1-2/N0-1: 113 N0-1: 235	NR	Male 59 (19%)	NR
Tournier-Rangeard, 2008 (18191265)[25] **Induction chemotherapy vs no induction** **Subgroup analysis of a randomized controlled trial**	119 patients *The number of patients who filled out both quality of life questionnaires (before treatment and 2 months after completion)	NR	NR	NR	Male 21 (18%)	NR

Study (PMID) Comparison Study Design	Sample Size (Randomized for RCTs or Included in NRSIs)	Mean Age at Baseline	Cancer Staging	Race/ Ethnicity, n, (%) [Majority]	Sex, n (%)	HIV Status or Immuno-compromised, n (%)
James, 2013 (23578724)[14] **Maintenance chemotherapy vs no maintenance** **Randomized controlled trial**	940 patients 247 5FU+cisplatin+ no maintenance 222 5FU+cisplatin + maintenance 246 5FU+MMC+ no maintenance 226 5FU+MMC+ maintenance	Median: 58 years	T1: 91 T2: 395 T3: 295 T4: 135 Tx: 22 N0: 587 N+: 305 Nx: 44 Missing T or N: 6	NR	Male: 353 (38%)	NR
White, 2015 (26347494)[31] **1 cycle MMC vs 2 cycles MMC** **Retrospective cohort**	217 patients 154 One cycle 63 Two cycles	Median 60 years	Stage I: 14 II: 108 III: 95	NR	Male: 66 (30%)	HIV+: 23 (11%)
Glynne-Jones, 2011 (20934265)[21] **Boost vs no boost** **Post-hoc of randomized controlled trial**	490 patients 436 boost 54 no boost Of 436 boost, 12 excluded 289 EBRT 135 BCT	NR (post-hoc of ACT I trial)	NR	NR	NR	NR

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; HIV- human immunodeficiency virus; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; CRT- chemoradiation; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; EBRT- external beam RT; Bct- brachytherapy; N0- node negative; N>0- node positive; T1-3- any size tumor not invading adjacent organs; T4- any size tumor invading adjacent organs; NR- not reported.

Table C.2.5. Study participant characteristics for Key Question 6

Study (PMID) Comparison Study Design	Sample Size (Included in NRSI)	Mean Age at Baseline	Cancer Staging	Race/ Ethnicity, n, (%) [Majority]	Sex, n (%)	HIV Status or Immuno-compromised, n (%)
Frazer, 2020 (32028341) [32] **Frequency of events within 1 yr vs. within 2 yrs vs. yr 3-5** **Retrospective cohort**	138 patients 77 Low-risk 61 High-risk	58 years	Stage I: 24 II: 55 III: 61	NR	Male: 40 (29%)	HIV+: 20 (14%)

Abbreviations: NRSI- nonrandomized study of interventions; yr- year; HIV- human immunodeficiency virus.

Study Selection Criteria

Table C.3.1. Study selection criteria for Key Question 1

Study (PMID) Comparison Study Design	Study Participant Selection Criteria
Chai, 2017 (29049547)[1] **Local excision v chemoradiotherapy in T1N0 lesions** **Retrospective cohort**	Included: patients with anal cancer aged 18-80 years, first and only primary tumor, confirmation of histologic subtype, treatment performed at reporting facility, alive beyond 30d after diagnosis, known surgery, radiotherapy, chemotherapy, and treatment sequence, known clinical stage, T1N0 disease. Excluded: prior/subsequent malignant tumor, non-squamous or unknown histology, treatment at other than the reporting facility, death within 30 days of diagnosis, unknown treatment or treatment sequence, unknown clinical stage, or stage other than T1N0.
Deshmukh, 2018 (27755059)[2] **Local excision v chemoradiotherapy, and local excision v radiation therapy in T1N0 lesions** **Retrospective cohort**	Patients diagnosed with T1N0 anal canal cancer between January 1, 1992, and December 31, 2009 using the ICD-O-3 site code of C21.0, C21.1, and C21.8 for anus, anal canal, and anorectum. The patients with anal margin tumor (ICD-O-3 code C44.5) were not included in this study. To identify patients with T1N0 anal cancer, the American Joint Committee on Cancer classification of malignant tumors (i.e., tumor, node, metastasis staging) was not available in the SEER data for the patients diagnosed between 1992 and 2004. A T1N0 stage variable for those patients was created using (1) information on the size of the primary tumor, (2) extent of spread to nearby lymph nodes, and (3) tumor metastasis to other organs of the body. The study population was limited to patients age 66 years or older who had been diagnosed with pathologically confirmed anal cancer between 1992 and 2009 in SEER-linked Medicare database. The data were limited to patients older than 66 years to allow for a one year period after Medicare enrollment (age 65 years) during which comorbidities could be recorded in claims files for the period before cancer diagnosis. Patients with unknown diagnosis months or diagnosis at autopsy or by death certificate only, or death date mismatch by SEER and Medicare datasets were excluded. We also identified noncancer cohort from the SEER-Medicare database, these were the patients identified from a 5% sample of Medicare beneficiaries. These patients were identified to estimate cancer-related costs.
Gao, 2020 (32199768)[3] **Local excision v chemoradiotherapy in T1N0 lesions** **Retrospective cohort**	Patients aged 18 years with histologically confirmed stage I (American Joint Committee on Cancer 6th edition) squamous cell carcinoma (International Classification of Diseases for Oncology-3 codes: 8070-8) of the anal canal (primary site code 211) diagnosed between 2004 and 2015 were included. Patients were categorized as having received CRT if they received chemotherapy and external beam radiation. Patients were categorized as having received LE if they received local excision (surgery to primary site codes 20-27) but not chemotherapy or radiation. Only patients who received CRT or LE were included in the final analyses.

Study (PMID) Comparison Study Design	Study Participant Selection Criteria
Bartelink, 1997 (9164216)[4] **Radiation therapy v Chemoradiotherapy** **Randomized controlled trial**	One hundred three patients with T3-4 N0-3 or T1-2N1-3 anal cancer, with a performance status of 0 to 1 and age less than 76 years were eligible. Reasons for ineligibility were inadequate disease staging (three patients), poor physical condition (one patient), prior treatment for anal cancer (two patients), and no data for one patient. Patients were equally distributed over both treatment arms, considering prognostic factors such as age, sex, tumor size, skin involvement, tumor location, nodal stage, and largest lymph node size.
UKCCCR, 1996 (8874455)[5] **Radiation therapy v Chemoradiotherapy** **Randomized controlled trial**	Eligible patients had epidermoid carcinoma (squamous, basaloid, or cloacogenic) of the anal canal or margin, no evidence of major hepatic or renal dysfunction, and normal blood counts. After examination under anaesthesia and biopsy, the lesion was staged with the 1985 UICC classification. Metastatic work-up was according to local practice. Because local control was the main endpoint, patients with metastatic disease were not excluded. However, patients considered inappropriate for randomisation (eg, because of previous treatment, cancer at another site, or because the tumour was considered suitable for local excision only [T1 N0]) were registered but not randomised.
Northover, 2010 (20354531)[6] **Radiation therapy v Chemoradiotherapy** **Follow up to randomized controlled trial**	Eligible patients had epidermoid carcinoma (squamous, basaloid or cloacogenic) of the anal canal or margin. Patients were mainly clinically rather than radiologically staged. The tumour was staged using the 1985 UICC TNM classification (Spiessl et al,1985). Staging for distant disease was carried out according to local practice.
Flam, 1996 (8823332)[7] **RT+5FU v RT+5FU+MMC** **Randomized controlled trial**	Eligibility criteria included any epidermoid malignancy of the anal canal in which the primary tumor was measurable and presenting with any tumor or nodal stage. A Karnofsky performance status >= 60 was required. Patients were stratified before randomization by nodal status (N0 v N1), histology (keratinizing squamous v nonkeratinizing squamous), and primary tumor size (< 5 cm v >=5 cm). The randomization scheme derived by Zelen was used to achieve balance in the treatment assignments among the institutions with three stratification variables.
Goodman, 2017 (28721892)[8] **RT+MMC+Cape v RT+MMC+5FU** **Retrospective cohort**	All patients with nonmetastatic ASCC treated with definitive CRT at our institution from January 2009 through May 2014 were retrospectively reviewed. Biopsy tissue was confirmed and graded for degree of differentiation by review at MSKCC. Excluded from: metastatic disease or did not receive concurrent chemotherapy with both MMC and fluoropyrimidine-based chemotherapy (capecitabine or 5-FU).
Jones, 2018 (29859793) [9] **RT+MMC+Cape v RT+MMC+5FU** **Prospective cohort**	All 56 centers involved in the delivery of RT within the United Kingdom were approached and asked to include every patient with confirmed anal cancer treated during a 6-month period extending from February 9 to July 27, 2015.

Study (PMID) Comparison Study Design	Study Participant Selection Criteria
Peixoto, 2016 (27563458) [10] **RT+MMC+Cape v RT+MMC+5FU** **Retrospective cohort**	Curative-intent radiation with either FM or CM for newly diagnosed stage I–III anal cancer between 1998 and 2013 at the BCCA were reviewed. Initially 637 patients who received CRT for anal cancer were identified through the pharmsacy database. Sixty-four were excluded due to either prior APR or evidence or metastatic disease before embarking on CRT. Another 23 patients were excluded due to the use of cisplatin instead of mitomycin. Finally, 250 patients were excluded due to suboptimal radiation doses. The final cohort consisted of 300 patients. Eligibility criteria for CRT with either FM or CM at the BCCA include a diagnosis of stage I–III squamous cell or cloacogenic carcinoma of the anal canal and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of less than or equal to 2. Patients also need to have an adequate marrow reserve (neutrophils greater than or equal to 1.5×10 9 /L, platelets greater than 100×10 9 /L), with adequate renal (creatinine less than or equal to 1.5× ULN) and liver function (bilirubin less than or equal to 26 µmol/L; AST/Alkaline Phosphatase less than or equal to 5× ULN
Matzinger, 2009 (19643599) [11] **RT+MMC+5FU v RT+MMC+cisplatin** **Randomized controlled trial**	Eligible patients had invasive squamous cell carcinoma of the anal canal; a WHO performance status of 0 or 1; were aged up to 75 years; had a granulocyte count above 2·109cells/l; a platelet count above 100·109cells/l; and a serum creatinine level less than 120lmol/l. Tumours were staged according to the International Union Against Cancer (UICC) 1997 classification. Only patients with measurable disease (RECIST definition) were eligible: Patients with T2N0 equal to or greater than 4cm in largest dimension, T3–4N0 and N1N3, whatever the T classification, were included. Patients with other histologies or who had been previously treated, or had other primary cancers, angina pectoris, distal arteritis or those who did not agree to use adequate contraception (who were at risk of pregnancy and breastfeeding) were excluded.
Ajani, 2008 (18430910) [12] **RT+5FU+MMC v RT+5FU+cisplatin** **Randomized controlled trial**	All patients with histologically documented squamous, basaloid, or cloacogenic carcinoma of the anal canal were eligible if they were at least 18 years of age, had a Karnofsky performance score of at least 60%, had category T2 to T4 tumors (T2 = diameter of the primary cancer >2 cm but <5 cm; T3 = =5 cm; and T4 = invading adjacent organs) with any N category (pelvic or inguinal defined by clinical examination, biopsy, or imaging studies), had adequate organ function, and were willing to provide written consent. Patients were excluded if they had a T1 or M1 tumor, severe comorbid conditions (including AIDS), or major malignancy (unless successfully treated and disease-free for at least 5 years).
Gunderson, 2012 (23150707) [13] **RT+5FU+MMC vs RT+5FU+cisplatin** **Long-term update of RCT**	Patients with histologically proven squamous, basaloid, or cloacogenic carcinoma of the anal canal were eligible provided they were 18 years of age or older, had Karnofsky performance status 60, had T2-4 category cancers with any N category (pelvic or inguinal), had adequate organ function, and were willing to provide written consent. Patients were excluded if they had a T1 or M1 cancer, severe comorbid conditions (including AIDS), or major malignancy unless they had been successfully treated and were disease-free for 5 years.
Gordeyev, 2022 (Not indexed in PubMed)[33] **IMRT + capecitabine + MMC + paclitaxel Vs IMRT + capecitabine + MMC** **Randomized controlled trial**	The inclusion criteria were: histologically verified squamous cell carcinoma of the anal canal, absence of distant metastases, Karnovsky's index > 70%, age from 18 to 75 years, absence of synchronous or metachronous malignant tumors, Hb > 90 g/l, leukocytes > 3.5 × 10*9 Units/l, platelets > 120 × 10*9 Units/l, creatinine < 150 mmol/l, bilirubin < 30 mmol/l. The exclusion criteria were: tumors of the perianal skin and anal margin, metachronous and synchronous tumors, pregnancy, breast-feeding, severe concomitant diseases that exclude chemotherapy and radiation therapy, previous chemotherapy or radiation therapy, patients with contraindications to magnetic resonance imaging (MRI) of the pelvis, patients with HIV-positive status.

Study (PMID) Comparison Study Design	Study Participant Selection Criteria
James, 2013 (23578724)[14] **Cisplatin v MMC** **Randomized controlled trial**	Patients were eligible if they had histologically confirmed invasive squamous cell, basaloid or cloacogenic carcinoma of the anal canal and margin that was deemed fit for investigated treatment; a glomerular filtration rate of more than 50 mL/min; acceptable blood test results (haemoglobin >100 g/L, >1 × 10^{11} platelets per L, >3 × 10^{9} white blood cells per L); liver function tests within two times the normal range; and adequate cardiac function. Exclusion criteria were metastatic disease, other major malignancy likely to compromise life expectancy or completion of trial treatment, comorbidity including being HIV-positive and cardiac diseases, previous complete local excision, and previous radiotherapy to the pelvis.

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; HIV- human immunodeficiency virus; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; CRT- chemoradiation; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; EBRT- external beam RT; Bct- brachytherapy; N0- node negative; N>0- node positive; T1-3- any size tumor not invading adjacent organs; T4- any size tumor invading adjacent organs; NR- not reported.

Table C.3.2. Study selection criteria for Key Question 2

Study (PMID) Comparison Study Design	Study Participant Selection Criteria
Dasgupta, 2013 (23692961)[18] **IMRT v 3D CRT** **Retrospective cohort**	All patients with ASCC who were treated with definitive radiation therapy at a single institution from May 1991 to January 2010.
Elson, 2018 (30329160)[19] **IMRT v 3D CRT** **Retrospective cohort**	Records of those older than 18 years were included. SCC was identified with histology codes 8053 to 8079, and other values were excluded. The total radiation dose included the target volume plus any boost and ranged from 3600 to 5940 cGy, the number of treatment fractions ranged from 25 to 40, and the treatment time ranged from 25 to 180 days. Treatment volumes were included for the pelvis, nodes, and soft tissue only. All other sites for treatment were excluded. Patients outside these criteria were removed from the analysis. Any treatments outside the reporting facility were excluded. Only American Joint Committee on Cancer analytic stage groups I to III were included. In addition, any reports of surgery, not receiving chemotherapy, receiving any palliative therapy, or not receiving any radiation were excluded from the analysis. Only the modalities coded as 3D conformal or IMRT were included in the analysis.
Pollom, 2017 (28258896)[16] **IMRT v non-IMRT** **Retrospective cohort**	We identified patients with invasive, nonmetastatic, intact SCCA diagnosed between 2001 and 2011 and treated with both chemotherapy (capecitabine, 5-FU, MMC, or cisplatin) and radiation therapy.
Bryant, 2018 (30102186)[17] **IMRT v non-IMRT** **Retrospective cohort**	We included patients with nonmetastatic, American Joint Committee on Cancer stage I to III anal squamous cell carcinoma who received diagnoses between 2000 and 2015 and were treated with CRT.

Study (PMID) Comparison Study Design	Study Participant Selection Criteria
Mohiuddin, 2021 (34646965)[20] **Proton IMRT (IMPT) v photon IMRT** **Prospective cohort**	The study cohort included adults aged 18 years or older with squamous cell carcinoma of the anal canal or perianal skin diagnosed and treated with definitive radiation therapy between October 26, 2012, and March 20, 2018, at University of Pennsylvania (Philadelphia, Pennsylvania), Mayo Clinic in Rochester (Rochester, Minnesota), or Mayo Clinic in Arizona (Scottsdale, Arizona and Phoenix, Arizona) and affiliated network sites. Exclusion criteria included non−squamous cell histology, mixed modality treatment (specifically IMPT with >5 fractions of IMRT), age younger than 18 years, or prior pelvic radiation therapy. Patients with AJCC (eighth edition) M1 stage disease were included if their only site of metastatic disease was in the infrarenal para-aortic or common iliac lymph nodes.
Glynne-Jones, 2011 (20934265)[21] **External beam boost (EBRT) v brachytherapy (BCT) boost** **Post-hoc of randomized controlled trial**	Patients were randomized to RT alone or CMT between December 1987 and March 1994 using a 1:1 allocation ratio. Staging used the 1985 International Union Against Cancer classification.
Hannoun-Levi, 2011 (20619552)[22] **EBRT v BCT** **Prospective, non-randomized controlled trial**	From January 2000 to December 2004, 209 patients with anal carcinoma were screened for inclusion in this study. All the patients were treated in one of the following cancer centers: Antoine Lacassagne Cancer Center (Nice, France), French Red Cross Center (Toulon, France), Azurean Cancer Center (Mougins, France), and Academic Timone Hospital (Marseille, France). Eligible patients had nonmetastatic primary invasive squamous cell carcinoma according to the World Health Organization classification of tumors arising in the anal canal, treated with external beam radiotherapy, with or without brachytherapy. Patients with noninvasive squamous cell cancer, a history of pelvic radiotherapy, a history of colostomy for another cause than anal carcinoma, or missing data on tumor staging were excluded from the study. To avoid selection bias and confusing factors, all the patients included in this study were required to meet the following conditions. (1)They were to be eligible for a boost, whatever the boost technique applied. Then, patients denied a boost because of poor general status after the first radiation course (n=19), and patients with progressive tumor after the first radiation course who underwent abdominoperineal resection (n=4) were excluded. (2) They were to be eligible for BCT boost. Patients with tumor size more than 2/3 of the anal canal circumference (which is a contraindication for BCT because of the risk of long-term anal stenosis) were excluded (n=15). A total of 162 patients were definitively included in this study. The choice of the boost technique was made according to the availability of brachytherapy in each institution.
Moureau-Zabotto, 2013 (23195780)[23] **EBRT v BCT** **Retrospective cohort**	Eligible patients had nonmetastatic primary invasive squamous cell carcinoma arising in the anal canal and nodal regional lymph nodes, treated with EBRT, with or without chemotherapy, and with or without BCT. Patients with noninvasive squamous cell cancer, a history of pelvic radiation therapy, and a history of colostomy for a cause other than anal carcinoma were excluded from this study. Patients with progressive tumors after the first radiation course were also excluded, because they were considered as resistant to radiation therapy and underwent salvage surgery. The choice of boost technique was made according to the availability of BCT in each institution.

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; HIV- human immunodeficiency virus; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; CRT- chemoradiation; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; EBRT- external beam RT; Bct- brachytherapy; N0- node negative; N>0- node positive; T1-3- any size tumor not invading adjacent organs; T4- any size tumor invading adjacent organs; QoL- quality of life; NR- not reported.

Table C.3.3. Study selection criteria for Key Question 3

Study (PMID) Comparison Study Design	Study Participant Selection Criteria
Peiffert, 2012 (22529257)[24] **Standard boost v high-dose boost** **Randomized controlled trial**	Eligible patients were age 18 to 80 years and had histologically proven untreated locally advanced anal canal cancer with tumors larger than 40mm and/or involved pelvic or inguinal lymph nodes. HIV-positive patients were not excluded. Exclusion criteria were non-squamous histologies, tumors with predominant skin involvement, previous malignancy treated within 5 years, metastasis, hemoglobin lower than 11g/100mL, serum creatinine greater than 130mol/L, and any contraindication to FU.
Tournier-Rangeard, 2008 (18191265)[25] **Standard boost v high-dose boost** **Subgroup analysis of a randomized controlled trial**	Subgroup analysis of the ACCORD 03 trial: 119 patients had completed both QOL questionnaires before and 2 months after the end of treatment. The assessment of early QOL was carried out with these 119 patients.
Wegner, 2019 (31136369)[26] **45-54Gy v >54Gy** **Retrospective cohort**	Clinical stage 1 to 3 SCCA (ICD-0-3 histology code 8070) diagnosed between 2004 and 2015. As IMRT use was a recorded NCDB parameter, patients treated with IMRT were identified and compared with those receiving a non–IMRT-based radiation technique. We did exclude patients with stage IV disease, undocumented stage, nonpelvic radiation therapy, or history of surgery. In addition, we excluded patients that were not treated with systemic therapy or those patients with <2 months of follow-up to account for immortal time bias. We defined dose escalation as doses >54Gy and only included doses between 45 and 75 Gy.
Glynne-Jones, 2020 (32619648)[27] **Radiation therapy regimens** **group 1) 50.40Gy, 38-42 days (reference group)** **group 2) ≤40Gy** **group 3) >40Gy to <48.60Gy** **group 4) 50.40Gy, <38 days** **group 5) 50.40Gy, >42 days** **group 6) >52.20Gy** ***Post hoc* analysis of RCT**	ACT II was a randomised factorial phase III trial with 940 patients enrolled between 2001 and 2008, which investigated whether replacing mitomycin with cisplatin in the CRT schedule improves complete response rate, and the impact of maintenance chemotherapy (fluorouracil / cisplatin) after CRT. Methods and results have previously been reported.
Lukovic, 2023 (36455685) [28] **Dosimetric parameters on acute and late toxicities** **Prospective cohort**	Consecutive patients with histologically confirmed nonmetastatic invasive SCCA were enrolled in a prospective observational cohort study between 2008 and 2013; all patients who were treated with curative-intent IG-IMRT during the study prior were eligible. Patients were excluded if there was evidence of distant metastasis or if they had received prior pelvic radiation therapy. Patients were staged according to the American Joint Committee on Cancer/ Union for International Cancer Control 7th edition. Patients were treated according to institutional standard protocols with IG-IMRT and concurrent chemotherapy. Radiation therapy dose was based on clinicopathologic factors.

Study (PMID) Comparison Study Design	Study Participant Selection Criteria
Nilsson, 2022 (34598844) [29] **Dosimetric predictors of acute and late toxicities** **Retrospective cohort**	Patients with locally advanced non-metastatic disease (T2>=4cm - T4or N+ and M0) treated with 5FU + MMC-based concomitant chemotherapy were included.
Mehta, 2020 (32399269)[30] **≤4.72 fractions/week v >4.72 fractions/week** **Retrospective cohort**	Patients aged 18 or older diagnosed with anal cancer between 2004 and 2014 were initially identified. Patients were excluded if they had in situ primary disease without nodal metastases or distant metastases. Only patients with International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) site codes for histology of SCCA and pathologic confirmation of disease were included. Included patients received concurrent CRT, defined as a maximum 7-day period between the initiation of chemotherapy and the initiation of RT. Patients who underwent salvage surgery were included if surgery followed initiation of RT by at least 89 days (33 days for a minimal time to complete 25 fractions plus 56 days for the minimum NCCN recommended time for follow-up digital rectal exam after RT). Patients receiving non-standard RT modalities and patients receiving RT to non-pelvic sites were excluded. Patients were included if RT duration was 33–100 days, if the number of RT fractions were 25–33 fractions, and the total RT dose was 45–60 Gy. The upper bound for elapsed days of RT was based on the standard CRT arm of RTOG 98-11 which allowed for a maximum of 100 days. The lower bound of 33 days is the minimum number of possible days for delivery of 5 fractions per week with weekend breaks on a 25 fraction schedule. Bounds for fraction number and total dose were determined by NCCN guidelines, except for the upper bound of total dose. The upper bound of 60 Gy was based on the standard arm of the ACCORD 03 trial to allow for variability beyond NCCN guidelines. Finally, patients were excluded if they had a ratio of fractions to treatment days of more than 5.3 fractions per week (maximum possible RT treatment rate determined based on 25 fractions starting on a Monday including weekend breaks) to exclude accelerated fractionation regimens. Additional exclusion criteria for the OS analysis included patients with an unknown time from diagnosis to death or a time listed as '0' and patients with a prior malignancy.

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; HIV- human immunodeficiency virus; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; CRT- chemoradiation; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; EBRT- external beam RT; Bct- brachytherapy; N0- node negative; N>0- node positive; T1-3- any size tumor not invading adjacent organs; T4- any size tumor invading adjacent organs; QoL- quality of life; NR- not reported.

Table C.3.4. Study selection criteria for Key Question 4

Study (PMID) Comparison Study Design	Study Participant Selection Criteria
James, 2013 (23578724)[14] **Maintenance chemotherapy v no maintenance** **RCT**	Patients were eligible if they had histologically confirmed invasive squamous cell, basaloid or cloacogenic carcinoma of the anal canal and margin that was deemed fit for investigated treatment; a glomerular filtration rate of more than 50 mL/min; acceptable blood test results (haemoglobin >100 g/L, >1 × 10^{11} platelets per L, >3 × 10^{9} white blood cells per L); liver function tests within two times the normal range; and adequate cardiac function. Exclusion criteria were metastatic disease, other major malignancy likely to compromise life expectancy or completion of trial treatment, comorbidity including being HIV-positive and cardiac diseases, previous complete local excision, and previous radiotherapy to the pelvis.

Study (PMID) Comparison Study Design	Study Participant Selection Criteria
Peiffert, 2012 (22529257)[24] **Induction chemotherapy v no induction** **RCT**	Eligible patients were age 18 to 80 years and had histologically proven untreated locally advanced anal canal cancer with tumors larger than 40mm and/or involved pelvic or inguinal lymph nodes. HIV-positive patients were not excluded. Exclusion criteria were non-squamous histologies, tumors with predominant skin involvement, previous malignancy treated within 5 years, metastasis, hemoglobin lower than 11g/100mL, serum creatinine greater than 130mol/L, and any contraindication to FU.
Tournier-Rangeard, 2008 (18191265)[25] **Induction chemo vs none** **Subgroup analysis of RCT**	Subgroup analysis of the ACCORD 03 trial: 119 patients had completed both QOL questionnaires before and 2 months after the end of treatment. The assessment of early QOL was carried out with these 119 patients.
Glynne-Jones, 2011 (20934265)[21] **Boost vs no boost** **Post-hoc of RCT**	Secondary analyses of ACT I trial. Patients were randomized to RT alone or concurrent CRT between December 1987 and March 1994 using a 1:1 allocation ratio. Staging used the 1985 International Union Against Cancer classification.
White, 2015 (26347494)[31] **1 vs 2 cycles MMC** **Retrospective cohort**	All patients had biopsy proven, non-metastatic, squamous cell carcinoma of the anal canal and were treated with definitive, curative intent according to institutional protocols (described in detail below). Patients with adenocarcinoma or other histologies were excluded. Patients with anal margin (peri-anal skin) carcinomas without anal canal involvement were also excluded for the purposes of this study.

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; HIV- human immunodeficiency virus; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; CRT- chemoradiation; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; EBRT- external beam RT; Bct- brachytherapy; N0- node negative; N>0- node positive; T1-3- any size tumor not invading adjacent organs; T4- any size tumor invading adjacent organs; QoL- quality of life; NR- not reported.

Table C.3.5. Study selection criteria for Key Question 6

Study (PMID) Comparison Study Design	Study Participant Selection Criteria
Frazer, 2020 (32028341)[32] **Frequency of events within 1 yr vs. within 2 yrs vs. yr 3-5** **Retrospective cohort**	Once patients with nonsquamous variants of anal cancer were excluded, 140 patients treated from 2006 through 2018 met the criteria for further analysis. Medical records were analyzed to assess patient, tumor, and treatment characteristics. Staging was classified in accordance with the 7th/8th edition of the American Joint Committee on Cancer staging system. Patients were subsequently stratified into low-risk and high-risk groups according to outcomes from a RTOG 9811 analysis which showed that patients with T2-3N0 disease had statistically better outcomes for overall and diseases-free survival, locoregional failure, and distant metastasis compared with other TN categories. The high-risk group was defined as T4N0 or T1-T4N+ disease, while the low-risk group was categorized by a T1-3N0 stage range. Patients were followed post treatment every 3 months for 2 years, every 6 months in years 3 to 5 then yearly thereafter with imaging per National Comprehensive Cancer Network (NCCN) recommendations.

Abbreviations: NRSI- nonrandomized study of interventions; HIV- human immunodeficiency virus; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; N0- node negative; N>0- node positive; T1-3- any size tumor not invading adjacent organs; T4- any size tumor invading adjacent organs; QoL- quality of life; NR- not reported.

Aggregate Risk of Bias in Studies

Table C.4.1. Risk of bias in randomized controlled trials

Study (PMID) Comparison Study Design	Bias From Randomization Process	Bias From Deviation From Intended Interventions (Assignment)	Bias From Missing Outcome Data	Bias in Measurement of Outcome	Bias in Selection of Reported Result	Overall Risk of Bias (Low, Some Concerns, High)
Bartelink, 1997 (9164216) [4] **RT vs CRT** **Randomized controlled trial**	Moderate	Low	Low	Low	Low	Moderate
UKCCCR, 1996 (8874455) [5] **RT vs CRT** **Randomized controlled trial**	Low	Low	Low	Low	Low	Low
Northover, 2010 (20354531) [6] **RT vs CRT** **Randomized controlled trial**	Low	Low	Low	Moderate	High	High
Flam, 1996 (8823332) [7] **RT+5FU vs RT+5FU+MMC** **Randomized controlled trial**	Moderate	Low	Low	Low (high for toxicity outcomes due to salvage chemo-radiation)	Low	Moderate
Matzinger, 2009 (19643599) [11] **RT+MMC and: 5FU vs cisplatin** **Randomized controlled trial**	Moderate	High	High	High	Low	High

Study (PMID) Comparison Study Design	Bias From Randomization Process	Bias From Deviation From Intended Interventions (Assignment)	Bias From Missing Outcome Data	Bias in Measurement of Outcome	Bias in Selection of Reported Result	Overall Risk of Bias (Low, Some Concerns, High)
Ajani, 2008 (18430910)[12] **RT+5FU and: Cisplatin vs MMC** **Randomized controlled trial**	Low	Low	Low	Low (Moderate for toxicity outcomes)	Low	Low
Gunderson, 2012 (23150707)[13] **RT+5FU and: Cisplatin vs MMC** ***Post hoc* analyses of RCT**	Low	Low	Low	Moderate	High	High
Gordeyev, 2022 (Not indexed in PubMed)[33] **IMRT + capecitabine + MMC + paclitaxel Vs IMRT + capecitabine + MMC** **Randomized controlled trial**	Low	Low	Low	Low	Low	Low
James, 2013 (23578724)[14] **RT+5FU and: Cisplatin vs MMC** **Randomized controlled trial**	Low	Low	Low	Low	Low	Low

Study (PMID) Comparison Study Design	Bias From Randomization Process	Bias From Deviation From Intended Interventions (Assignment)	Bias From Missing Outcome Data	Bias in Measurement of Outcome	Bias in Selection of Reported Result	Overall Risk of Bias (Low, Some Concerns, High)
James, 2013 (23578724)[14] **Maintenance chemo vs none** **Randomized controlled trial**	Low	High (differential attrition: ~20% in maintenance arm)	Low	Low (Moderate for toxicity outcomes)	Low	High
Peiffert, 2012 (22529257)[24] **Standard vs high dose; and** **Induction chemotherapy vs no induction** **Randomized controlled trial**	Low	Low	High (inadequate power as reported by authors, due to attrition)	Moderate (High for toxicity outcomes)	Low	High (2 by 2 factorial design; results often not reported separately for each arm- bias from co-intervention)
Tournier-Rangeard, 2008 (18191265)[25] **Standard vs high dose; and** **Induction chemotherapy vs no induction** **Subgroup analysis of a randomized controlled trial**	Low	Low	High (outcome data in 119 patients out of 307 randomized)	High	Low	High

Abbreviations: RCT- randomized controlled trials; LE- local excision; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; CRT- chemoradiation; RoB- risk of bias

Table C.4.2. Aggregate risk of bias in nonrandomized studies of interventions

Study (PMID) Comparison Study Design	Domain Specific RoB	Overall RoB (Low, Moderate, Serious, Critical)
Chai, 2017 (29049547)[1] **Local excision vs CRT in T1N0 lesions** **Retrospective cohort**	Serious RoB from potential misclassification of treatment assignment and confounding; moderate RoB from selection bias	Serious
Deshmukh, 2018 (27755059)[2] **Local excision vs CRT or RT in T1N0 lesions** **Retrospective cohort**	Critical RoB in participant slection	Critical
Gao, 2020 (32199768)[3] **Local excision vs chemoradiotherapy in T1N0 lesions** **Retrospective cohort**	Serious RoB from potential confounding, missing outcome definition, and inadequately addressing missing data; moderate RoB in participant selection	Serious
Goodman, 2017 (28721892)[8] **RT+MMC+Cape vs RT+MMC+5FU** **Retrospective cohort**	Serious RoB from potential confounding (univariate analyses), no power calculation, and inadequately addressing missing data	Serious
Jones, 2018 (29859793)[9] **RT+MMC+Cape vs RT+MMC+5FU** **Prospective cohort**	Serious RoB from potential confounding (imbalance in number of cycles of MMC), no power calculation, and inadequately addressing missing data	Serious
Peixoto, 2016 (27563458)[10] **RT+MMC+Cape vs RT+MMC+5FU** **Retrospective cohort**	Serious RoB from potential confounding, participant selection, and inadequately addressing missing data	Serious
Dasgupta, 2013 (23692961)[18] **IMRT vs 3D CRT** **Retrospective cohort**	Critical RoB due to confounding (from variations in cointerventions in treatment regimens used; only one group used cisplatin or no chemo, so cannot adequately control for confounding by regression adjustment as covariates)	Critical
Elson, 2018 (30329160)[19] **IMRT vs 3D CRT** **Retrospective cohort**	Critical RoB due to confounding (from variations in cointerventions in treatment regimens used, chem agents not known)	Critical
Pollom, 2017 (28258896)[16] **IMRT vs non-IMRT** **Retrospective cohort**	Serious RoB from potential misclassification of treatment, participant selection, confounding (including time-varying confounding due to change in practice patterns and heterogeneity in treatment protocols), and missing data	Serious

Study (PMID) Comparison Study Design	Domain Specific RoB	Overall RoB (Low, Moderate, Serious, Critical)
Bryant, 2018 (30102186)[17] **IMRT v non-IMRT** **Retrospective cohort**	Serious RoB from potential misclassification of treatment, participant selection, confounding (including time-varying confounding due to change in practice patterns and heterogeneity in treatment protocols), and missing data	Serious
Mohiuddin, 2021 (34646965)[20] **Proton IMRT (IMPT) vs photon IMRT** **Prospective cohort**	Serious RoB from confounding (including time-varying confounding due to change in practice patterns and heterogeneity in treatment protocols), participant selection, and missing data	Serious
Glynne-Jones, 2011 (20934265)[21] **External beam boost (EBRT) vs brachytherapy (BCT) boost** **Post-hoc of randomized controlled trial**	Serious RoB from confounding (heterogeneity in treatment protocols), participant selection, and missing data	Serious
Hannoun-Levi, 2011 (20619552)[22] **EBRT vs BCT** **Prospective, non-randomized controlled trial**	Serious RoB from confounding (heterogeneity in treatment protocols), participant selection, and missing data; power calculations not reported	Serious
Moureau-Zabotto, 2013 (23195780)[23] **EBRT vs BCT** **Retrospective cohort**	Serious RoB from confounding (heterogeneity in treatment protocols), participant selection, and missing data; power calculations not reported	Serious
Wegner, 2019 (31136369)[26] **45-54Gy vs >54Gy** **Retrospective cohort**	Critical RoB due to confounding (from variations in cointerventions in treatment regimens used)	Critical
Glynne-Jones, 2020 (32619648)[27] **Radiation therapy regimens** **group 1) 50.40Gy, 38-42 days (reference group)** **group 2) ≤40Gy** **group 3) >40Gy to <48.60Gy** **group 4) 50.40Gy, <38 days** **group 5) 50.40Gy, >42 days** **group 6) >52.20Gy** ***Post hoc* analysis of RCT**	Critical RoB due to confounding (from variations in cointerventions in treatment regimens used)	Critical
Lukovic, 2023 (36455685)[28] **Dosimetric parameters on acute and late toxicities** **Prospective cohort**	Critical RoB: parameters derived using lowest p-value approach without external validation and inadequate control for confounding	Critical

Study (PMID) Comparison Study Design	Domain Specific RoB	Overall RoB (Low, Moderate, Serious, Critical)
Nilsson, 2022 (34598844)[29] **Dosimetric predictors of acute and late toxicities** **Retrospective cohort**	Critical RoB: parameters derived using lowest p-value approach without external validation and inadequate control for confounding	Critical
Mehta, 2020 (32399269)[30] **≤4.72 fractions/week vs >4.72 fractions/week** **Retrospective cohort**	Critical RoB due to confounding (from variations in cointerventions in treatment regimens used)	Critical
White, 2015 (26347494)[31] **1 cycle MMC vs 2 cycles MMC** **Retrospective cohort**	Serious RoB in participant selection (authors assume that number of cycles of MMC is due to differences in institutional protocols, but cannot confirm if 2nd dose of MMC was withheld due to patient health status or other concerns) and outcome measurement (significant difference in median followup time between groups)	Serious
Frazer, 2020 (32028341)[32] **Frequency of events within 1 yr vs. within 2 yrs vs. yr 3-5** **Retrospective cohort**	No formal hypothesis testing, no control for potential confounding, serious risk of selection bias.	Critical

Abbreviations: NRSI- nonrandomized study of interventions; LE- local excision; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; cape- capecitabine; RT- radiation therapy; CRT- chemoradiation; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; RoB- risk of bias.

Findings

Table C.5.1. Findings for Key Question 1

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Event Rate Comparison)
Chai, 2017 (29049547)[1] **Local excision vs chemoradiotherapy in T1N0 lesions** **Serious RoB** **Retrospective cohort**	Overall survival 5 years	Adjusted HR 1.06 (95% CI, 0.78 - 1.44)	85.3% (429/503)	86.8% (1,510/1,740)	0.93
	Overall survival for tumors 1cm or smaller 5 years	Adjusted HR 1.21 (95% CI, 0.63 - 2.33)	88.5% (445/503)	91.6% (1,594/1,740)	0.98
	Overall survival for tumors 1-2cm in size 5 years	Adjusted HR 1.04 (95% CI, 0.62 - 1.75)	86.6% (436/503)	86.4% (1,503/1,740)	0.78
Deshmukh, 2018 (27755059)[2]	Overall survival NR	Propensity adjusted HR 1.74 (95% CI, 0.79 - 3.83)	NR	NR	0.17

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Event Rate Comparison)
Local excision vs chemoradiotherapy, and local excision vs radiation therapy in T1N0 lesions **Critical RoB** **Retrospective cohort**	Overall survival NR	Propensity adjusted HR 2.17 (95% CI, 0.92 - 5.10)	NR	NR	0.07
Gao, 2020 (32199768)[3] **Local excision vs chemoradiotherapy in T1N0 lesions** **Serious RoB** **Retrospective cohort**	Cause-specific survival 5 years	Adjusted HR 0.48 (95% CI, 0.10-2.32)	98% (196/200)	96% (656/683)	0.36
	Cause-specific survival of tumors ≤1cm 5 years	NR	100% (200/200)	96% (656/683)	0.07
	Cause-specific survival of tumors ＞1-2cm 5 years	NR	96% (192/200)	95% (649/683)	0.49
Bartelink, 1997 (9164216)[4] **Radiation therapy vs Chemoradiotherapy** **Moderate RoB** **Randomized controlled trial**	Overall survival 5 years	NR	54%	58%	0.17
	Locoregional control 5 years	Favors CRT	50%	32%	0.02
	Progression-free survival 5 years	Trend towards CRT	NR	NR	0.05
	Colostomy-free survival 5 years	Favors CRT. (by estimated 32%)	NR	NR	0.002
	Event-free survival 5 years	Favors CRT (by estimated 18%)	NR	NR	0.03
	Severe toxicity-free survival 5 years	NSD	NR	NR	0.21
	Acute Grade 2 Diarrhea Within 6 weeks of treatment completion	NSD	31% (16/52)	29% (15/51)	NSD
	Acute Grade 3 Diarrhea Within 6 weeks of treatment completion	NSD	8% (4/52)	20% (10/51)	NSD
	Acute Grade 4 Diarrhea Within 6 weeks of treatment completion	NSD	0% (0/52)	0% (0/51)	NSD
	Acute Grade 2 Skin Reactions Within 6 weeks of treatment completion	NSD	35% (18/52)	25% (13/51)	NSD
	Acute Grade 3 Skin Reactions Within 6 weeks of treatment completion	NSD	50% (26/52)	55% (28/51)	NSD
	Acute Grade 4 Skin Reactions Within 6 weeks of treatment completion	NSD	0% (0/52)	2% (1/51)	NSD

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Event Rate Comparison)
	Late anal ulceration Greater than 6 weeks after treatment completion	NSD	4% (2/52)	18% (9/51)	NSD
	Late anal fistula Greater than 6 weeks after treatment completion	NSD	6% (3/52)	4% (2/51)	NSD
	Late anal perforation Greater than 6 weeks after treatment completion	NSD	4% (2/52)	4% (2/51)	NSD
	Late rectal stenosis requiring surgery Greater than 6 weeks after treatment completion	NR	4% (2/52)	6% (3/51)	NR
	Late skin ulceration Greater than 6 weeks after treatment completion	NR	4% (2/52)	6% (3/51)	NR
	Late severe fibrosis Greater than 6 weeks after treatment completion	NR	8% (4/52)	6% (3/51)	NR
UKCCCR, 1996 (8874455)[5] **Radiation therapy vs Chemoradiotherapy** **Low RoB** **Randomized controlled trial**	Overall survival 3 years	RR 0.86 (95% CI, 0.67 - 1.11)	58% (165/285)	65% (190/292)	0.25
	Local failure rate 3 years	RR 0.54 (95% CI, 0.42 - 0.69)	61% (174/285)	39% (114/292)	<0.001
	Deaths from anal cancer 3 years	RR 0.71 (95% CI, 0.53 - 0.95)	39% (111/285)	28% (82/292)	0.02
	Acute toxicity of the overall cohort Within 8 weeks of treatment completion	Favors RT	39% (110/285)	48% (140/292)	0.03
	Late toxicity of the overall cohort Greater than 8 weeks of treatment completion	NSD	38% (108/285)	42% (122/292)	0.39
	Acute skin toxicity Within 8 weeks of treatment completion	NSD	27% (76/285)	32% (93/292)	NSD
	Acute gastrointestinal toxicity Within 8 weeks of treatment completion	NSD	14% (39/285)	16% (46/292)	NSD
	Acute genitourinary toxicity Within 8 weeks of treatment completion	NSD	5% (13/285)	7% (20/292)	NSD
	Late skin toxicity Greater than 8 weeks of treatment completion	NSD	16% (47/285)	20% (59/292)	NSD

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Event Rate Comparison)
	Late gastrointestinal toxicity Greater than 8 weeks of treatment completion	NSD	27% (77/285)	29% (84/292)	NSD
	Late genitourinary toxicity Greater than 8 weeks of treatment completion	NSD	7% (19/285)	6% (18/292)	NSD
	Late other toxicity Greater than 8 weeks of treatment completion	NSD	5% (14/285)	8% (23/292)	NSD
Northover, 2010 (20354531)[6] **Radiation therapy vs Chemoradiotherapy** **High RoB** **Randomized controlled trial**	Overall survival 12 years	Adjusted HR 0.86 (95% CI, 0.70 - 1.04)	27.5% (78/285)	33.1% (97/292)	0.12
	Relapse-free survival 12 years	Adjusted HR 0.70 (95% CI, 0.58 - 0.84)	17.7% (50/285)	29.7% (87/292)	<0.001
	Colostomy-free survival 12 years	Adjusted HR 0.76 (95% CI, 0.63 - 0.91)	20.1% (57/285)	29.6% (87/292)	0.004
	Locoregional failure rate 12 years	Adjusted HR 0.46 (95% CI, 0.35 - 0.60)	59.1% (168/285)	33.8% (99/292)	<0.001
	Anal cancer death rate 12 years	Adjusted HR 0.67 (95% CI, 0.51 - 0.88)	48.7% (139/285)	36.2% (106/292)	0.004
	Late ulceration/radionecrosis Greater than 6 months after treatment completion	NSD	6% (18/281)	8% (23/284)	0.44
	Late anorectal toxicity Greater than 6 months after treatment completion	NSD	27% (76/281)	29% (81/284)	0.70
	Late genitourinary toxicity Greater than 6 months after treatment completion	NSD	4% (11/281)	4% (11/284)	0.98
	Late skin toxicity Greater than 6 months after treatment completion	NSD	18% (51/281)	21% (59/284)	0.43
Flam, 1996 (8823332)[7] **RT+5FU vs RT+5FU+MMC** **Moderate for RoB** **Randomized controlled trial**	Overall survival 4 years	NSD	71% (103/145)	78% (114/146)	0.31
	Disease-free survival 4 years	Favors MMC	51% (74/145)	73% (107/146)	<0.001
	Colostomy-free survival 4 years	Favors MMC	59% (86/145)	71% (104/146)	0.014
	Local failure rate 4 years	Favors MMC	34% (49/145)	16% (23/146)	<0.001
	Colostomy rate 4 years	Favors MMC	22% (32/145)	9% (13/146)	0.002
	Overall acute harms	Favors 5FU alone	5% (7/145)	14% (20/146)	0.009

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Event Rate Comparison)
	Acute hematologic toxicity	Favors 5FU alone	2% (3/145)	12% (18/146)	<0.001
	Overall late harms	NSD	<1% (1/145)	3% (5/146)	0.26
Goodman, 2017 (28721892) [8] **RT+MMC+Cape vs RT+MMC+5FU** **Critical RoB** **Retrospective cohort**	Overall survival 2 years	NR	98% (95% CI, 93 - 100) (43/44)	87% (95% CI, 79 - 96) (55/63)	0.12
	Locoregional recurrence rate 2 years	NR	8.2% (95% CI, 3 - 25) (4/44)	6.5% (95% CI, 3 - 17) (4/63)	0.78
	Incidence of distant metastases 2 years	NR	7.6% (95% CI, 3 - 23) (3/44)	14.7% (95% CI, 8 -27) (9/63)	0.26
	Colostomy creation rate 2 years	NR	9% (4/44)	5% (3/63)	0.65
	Treatment break due to toxicity	Favors capecitabine	41% (26/44)	16% (7/63)	0.006
	Acute grade 3+ neutropenia	Favors capecitabine	20% (9/44)	52% (33/63)	0.001
	Acute grade 3+ leukopenia	Favors capecitabine	32% (14/44)	54% (34/63)	0.03
	Acute grade 3+ dermatologic toxicity	NSD	2% (1/44)	13% (8/63)	0.08
	Acute grade 3+ diarrhea	NSD	2% (1/44)	0% (0/63)	0.41
Jones, 2018 (29859793) [9] **RT+MMC+Cape vs RT+MMC+5FU** **Prospective cohort**	Colostomy-free survival 1 year	NSD	77.5% (40/52)	90.7% (86/95)	0.09
	Relapse-free rates 1 year	NSD	76.2% (40/52)	79.3% (75/95)	0.80
	Overall Grade 3 or 4 toxicity rates 6 weeks after completion of CRT	NSD	45% (21/47)	55% (39/71)	0.19
	Hematologic Grade 3 or 4 toxicity rates 6 weeks after completion of CRT	Favors capecitabine	4% (2/48)	27% (18/66)	<0.001
	Non-hematologic Grade 3 or 4 toxicity rates 6 weeks after completion of CRT	NSD	43% (20/47)	42% (30/71)	0.72
	Grade 3 or 4 gastrointestinal toxicity 6 weeks after completion of CRT	NSD	17% (8/47)	13% (9/71)	0.72
	Grade 3 or 4 skin toxicity 6 weeks after completion of CRT	NSD	26% (12/47)	28% (20/71)	0.71
	Grade 3 or 4 anal pain 6 weeks after completion of CRT	NSD	19% (9/47)	9% (6/71)	0.10
	Grade 3 or 4 cardiac toxicity 6 weeks after completion of CRT	NSD	4% (2/47)	1% (1/71)	0.56

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Event Rate Comparison)
Peixoto, 2016 (27563458) [10] **RT+MMC+Cape vs RT+MMC+5FU** **Serious RoB** **Retrospective cohort**	Disease-free survival 5 years	NSD; HR 0.99 (95% CI, 0.57-1.74; ref- cape)	2-yr survival 80%	2-yr survival 79%	0.66
	Anal cancer-specific survival 5 years	NSD; HR 0.93 (95% CI, 0.46 - 1.86; ref- cape)	2-yr survival 89%	2-yr survival 88%	0.84
	Colostomy-free survival 5 years	NSD; HR 0.66 (95% CI, 0.28–1.54; ref- cape)	NR	NR	0.34
Matzinger, 2009 (19643599) [11] **RT+MMC+5FU vs RT+MMC+cisplatin** **High RoB** **Randomized controlled trial**	Progression-free survival 1 year	NSD	76.3% (95% CI, 59.3 - 86.9) (30/39)	94.2% (95% CI, 78.5 - 98.5) (35/37)	NR
	Event-free survival 1 year	NSD	74.4% (95% CI, 57.6 - 85.3) (29/39)	89.2% (95% CI, 73.7 - 95.8) (33/37)	NR
	Complete response	NSD	59% (23/39)	73% (27/37)	NR
	Acute grade 3 or 4 gastrointestinal toxicity Within 67 days of treatment initiation	NSD	26% (10/39)	27% (10/37)	NR
	Acute grade 3 or 4 skin toxicity Within 67 days of treatment initiation	NSD	44% (17/39)	41% (15/37)	NR
Ajani, 2008 (18430910)[12] **RT+5FU+MMC vs RT+5FU+cisplatin** **Low RoB** **Randomized controlled trial**	Disease-free survival 5 years	Unadjusted HR 1.20 (95% CI, 0.93 - 1.55)	60% (95% CI, 53 - 67) (194/324)	54% (95% CI, 46 - 60) (173/320)	0.17
	Overall survival 5 years	Unadjusted HR 1.28 (95% CI, 0.90 - 1.84)	75% (95% CI, 67 - 81) (243/324)	70% (95% CI, 63 - 76) (224/320)	0.10
	Colostomy creation rate 5 years	Unadjusted HR 1.68 (95% CI, 1.07 - 2.65)	10% (95% CI, 6 - 14) (32/324)	19% (95% CI, 13 - 24) (61/320)	0.02
	Time to locoregional treatment failure	Unadjusted HR 1.32 (95% CI, 0.98 - 1.78)	NR	NR	0.07
	Time to distant metastasis	Unadjusted HR 1.38 (95% CI, 0.90 - 2.10)	NR	NR	0.14
	Locoregional recurrence rate 5 years	NSD	25% (95% CI, 20 - 30) (81/324)	33% (95% CI, 27 - 40) (106/320)	NR
	Distant metastasis rate 5 years	NSD	15% (95% CI, 10 - 20) (49/324)	19% (95% CI, 14 - 24) (61/320)	NR
	Acute grade 3+ hematologic toxicity Within 8 weeks of treatment completion	NSD	61% (199/324)	42% (134/320)	NR
	Acute grade 3+ non-hematologic toxicity Within 8 weeks of treatment completion	NSD	74% (240/324)	75% (239/320)	NR

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Event Rate Comparison)
	Late grade 3+ small/large intestine toxicity Greater than 8 weeks after treatment completion	NSD	3% (10/317)	2% (6/308)	NR
	Late grade 3+ skin toxicity Greater than 8 weeks after treatment completion	NSD	3% (10/317)	2% (7/308)	NR
	Late grade 3+ bladder toxicity Greater than 8 weeks after treatment completion	NSD	1% (2/317)	<1% (1/308)	NR
	Late grade 3+ subcutaneous tissue toxicity Greater than 8 weeks after treatment completion	NSD	2% (5/317)	1% (4/308)	NR
	Late grade 3+other toxicity Greater than 8 weeks after treatment completion	NSD	4% (14/317)	5% (16/308)	NR
Gunderson, 2012 (23150707)[13] **RT+5FU+MMC vs RT+5FU+cisplatin** **High RoB** ***Post hoc* analyses of RCT**	Overall survival 5 years	Adjusted HR 1.39 (95% CI, 1.05 - 1.83)	78.3% (95% CI 73.2 - 82.5)	70.7% (95% CI 65.2 - 75.4)	0.022
	Disease-free survival 5 years	Adjusted HR 1.40 (95% CI, 1.11 - 1.78)	67.8% (95% CI 62.3 - 72.6)	57.8% (95% CI 52.1 - 63.0)	0.005
	Colostomy-free survival 5 years	Unadjusted HR 1.29 (95% CI, 0.99 - 1.67)	71.9% (95% CI, 66.5 - 76.5)	65.0% (95% CI, 59.4 - 70.0)	0.05
	Locoregional failure 5 years	Unadjusted HR 1.33 (95% CI, 0.97 - 1.83)	20.0% (95% CI, 15.6 - 24.4)	26.4% (95% CI, 21.5 - 31.3%)	0.087
	Distant metastasis rate 5 years	Unadjusted HR 1.37 (95% CI, 0.94 - 2.02)	13.1% (95% CI, 9.3 - 16.8)	18.1% (95% CI, 13.8 - 22.4)	0.12
	Colostomy failure rate 5 years	Unadjusted HR 1.48 (95% CI, 0.98 - 2.23)	11.9% (95% CI, 8.3 - 15.4)	17.3% (95% CI, 13.1 - 21.5)	0.074
	Acute grade 3+ hematologic toxicity Within 8 weeks of treatment completion	NR	61.8% (201/325)	42.0% (136/324)	<0.001
	Acute grade 3+ infectious toxicity Within 8 weeks of treatment completion	NR	18% (60/325)	11% (35/324)	NR
	Acute grade 3+ skin toxicity Within 8 weeks of treatment completion	NR	49% (159/325)	41% (133/324)	NR

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Event Rate Comparison)
	Acute grade 3+ gastrointestinal toxicity Within 8 weeks of treatment completion	NR	37% (119/325)	47% (151/324)	NR
	Acute grade 3+ pain toxicity Within 8 weeks of treatment completion	NR	24% (79/325)	18% (57/324)	NR
	Late grade 3+ skin toxicity Greater than 8 weeks after treatment completion	NR	4% (12/325)	2% (8/324)	NR
	Late grade 3+ gastrointestinal toxicity Greater than 8 weeks after treatment completion	NR	3% (10/325)	2% (8/324)	NR
	Late grade 3+ subcutaneous tissue toxicity Greater than 8 weeks after treatment completion	NR	2% (5/325)	2% (5/324)	NR
	Late grade 3+ other toxicity Greater than 8 weeks after treatment completion	NR	7% (23/325)	6% (21/324)	NR
James, 2013 (23578724)[14] **Cisplatin vs MMC** **Low RoB** **Randomized controlled trial**	Overall survival 3 years	HR 1.05 (95% CI, 0.80 - 1.38)	NR	NR	0.70
	Progression-free survival 3 years	HR 0.95 (95% CI, 0.75 - 1.19)	74% (95% CI, 69 - 77)	73% (95% CI, 69 - 77)	0.63
	Progression-free survival in patients <65 years old 3 years	HR 0.94 (95% CI, 0.65 - 1.36)	NR	NR	NSD
	Progression-free survival in patients ≥65 years old 3 years	HR 0.99 (95% CI, 0.55 - 1.76)	NR	NR	NSD
	Progression-free survival in females 3 years	HR 1.10 (95% CI, 0.72 - 1.68)	NR	NR	NSD
	Progression-free survival in males 3 years	HR 0.80 (95% CI, 0.51 - 1.27)	NR	NR	NSD
	Progression-free survival in T1+T2 patients 3 years	HR 1.13 (95% CI, 0.68 - 1.88)	83% (95% CI, 78–87)	80% (95% CI 74–84)	NSD
	Progression-free survival in T3+T4 patients 3 years	HR 0.87 (95% CI, 0.58 - 1.30)	62% (95% CI, 55–69)	65% (95% CI, 59–71)	NSD

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Event Rate Comparison)
	Progression-free survival in node negative patients 3 years	HR 0.93 (95% CI, 0.61 - 1.41)	76% (95% CI, 71–81)	76% (95% CI, 70–80)	NSD
	Progression-free survival in node positive patients 3 years	HR 1.04 (95% CI, 0.63 - 1.70)	69% (95% CI, 61–76)	67% (95% CI, 59–74)	NSD
	Colostomy-free survival 3 years	HR 1.04 (95% CI, 0.82 - 1.31)	72% (95% CI, 66 –77)	75% (95% CI, 68–80)	0.74
	Complete response 26 weeks	NSD; (difference, 0·9%, 95% CI –4·9 to 3·1)	90% (386/431)	91% (391/432)	0.64
	Anal cancer mortality 3 years	HR 1.01 (95% CI, 0.74 - 1.40)	NR	NR	0.95
	Acute grade 3+ overall toxicity Within 4 weeks of treatment completion	NSD	72% (337/468)	71% (334/472)	NSD
	Acute grade 3+ hematologic toxicity Within 4 weeks of treatment completion	Favors cisplatin (i.e. more toxicity with MMC)	16% (73/468)	26% (124/472)	<0.001
	Acute grade 3+ gastrointestinal toxicity Within 4 weeks of treatment completion	NSD	18% (85/468)	16% (75/472)	NSD
	Acute grade 3+ genitourinary toxicity Within 4 weeks of treatment completion	NSD	2% (8/468)	1% (6/472)	NSD
	Acute grade 3+ skin toxicity Within 4 weeks of treatment completion	NSD	47% (222/468)	48% (228/472)	NSD
Glynne-Jones, 2014 (24827136)[15] **Cisplatin vs MMC** **Moderate for RoB** **Randomized controlled trial**	Colostomy-free survival Median 5.1 years (range 6 days - 10.5 years)	Unadjusted HR 1.04 (95% CI, 0.82 - 1.31)	31.8% (141/444)	33.0% (145/440)	NSD
	Progression-free survival Median 5.1 years (range 6 days - 10.5 years)	Unadjusted HR 0.94 (95% CI, 0.73 - 1.19)	27.9% (124/444)	26.6% (117/440)	NSD
Gordeyev, 2022 (Not indexed in PubMed)[33] **IMRT + capecitabine + MMC + paclitaxel Vs IMRT + capecitabine + MMC**	Overall survival (up to 3 yrs)	NR	95.5%	80%	<0.001
	Disease-free survival (up to 3 yrs)	NR	87.1%	64.4%	0.001
	Colostomy-free survival (up to 3 yrs)	NR	83.2%	67.5%	0.029
	CR (at 26 weeks posttreatment)	NR	88.9%	75%	0.049
	Overall acute harms	Difference 30.5% (95% CI, 14.5% - 18.4%)	56.9%	26.4%	<0.001

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Event Rate Comparison)
Randomized controlled trial	Neutropenia (grade 3 or 4)	Difference 7% (95% CI, -4.3% - 44.4%)			NSD
	Acute dermatologic toxicity	Difference=0%	9.7%	9.7%	NSD
	Acute gastrointestinal toxicity	Paclitaxel arm vs no paclitaxel arm; grade 3-4 diarrhea: 10 (13.9%) vs 5 (6.9%) patients with difference 7% (95% CI, -3.3% to 17.6%, p=0.17); grade 3-4 proctitis: 9 (12.5%) vs 4 (5.6%) patients with difference 6.9% (95% CI, -2.9% to 17.1%, p=0.15)	13.9%	6.9%	NSD
	Acute genitourinary toxicity	1 patient per arm had grade 3 cystitis and no patients had grade 3-4 vaginitis	0%	0%	NSD

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; LE- local excision; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; CRT- chemoradiation; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; NR- not reported; NSD- no significant difference

Table C.5.2. Findings for Key Question 2

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Comparing Rates)
Dasgupta, 2013 (23692961)[18] IMRT v 3D CRT Critical Retrospective cohort	Overall survival 2 years	Propensity adjusted HR 1.14 (95% CI, 0.32 - 4.0)	93% (95% CI, 95 - 98)	90% (95% CI, 84 - 94)	0.91
	Disease-free survival 2 years	Propensity adjusted HR 0.85 (95% CI, 0.31 - 2.3)	87% (95% CI, 72 - 94)	82% (95% CI, 75 - 86)	0.20
	Distant metastasis-free survival 2 years	Propensity adjusted HR 1.23 (95% CI, 0.41 - 3.7)	86% (95% CI, 72 - 93)	88% (95% CI, 82 - 92)	0.62
	Colostomy-free survival 2 years	Propensity adjusted HR 0.58 (95% CI, 0.07 - 4.7)	97% (95% CI, 80 - 99)	91% (95% CI, 86 - 94)	0.10
Elson, 2018 (30329160)[19] IMRT v 3D CRT Critical Retrospective cohort	Overall survival 10 years	Favors IMRT Propensity adjusted HR 0.86 (95% CI, 0.74 - 0.99)	80.8%	76.7%	0.0172
Pollom, 2017 (28258896)[16]	Overall survival 2 years	HR 0.77 (95% CI, 0.59 - 1.00)	79.9% (95% CI, 75.9 - 83.3)	79.5% (95% CI, 76.3 - 82.3)	0.05

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Comparing Rates)
IMRT v non-IMRT Serious Retrospective cohort	Cause-specific survival 2 years	HR 0.75 (95% CI, 0.51 - 1.10)	89.5% (95% CI, 86.1 - 92.0)	85.7% (95% CI, 82.7 - 88.0)	0.14
Bryant, 2018 (30102186)[17] IMRT v non-IMRT Serious Retrospective cohort	Radiation treatment delay ≥10 days	HR 0.56 (95% CI, 0.32 - 1.00)	14%	20%	0.05
	Acute grade 3-4 hematologic toxicity 90 days	HR 1.06 (95% CI, 0.70 - 1.61)	47%	40%	0.79
	Overall mortality 5 years	HR 0.89 (95% CI, 0.66 - 1.21)	25.5%	45.3%	0.46
	Anal cancer mortality 5 years	HR 0.72 (95% CI, 0.45 - 1.17)	12.7%	21.4%	0.18
	Non-anal cancer mortality 5 years	HR 0.97 (95% CI, 0.62 - 1.52)	12.8%	23.9%	0.90
	Tumor-related ostomy placement 5 years	Favors IMRT HR 0.60 (95% CI, 0.37 - 0.99)	7%	12%	0.045
Mohiuddin, 2021 (34646965)[20] Proton vs photon IMRT Serious Prospective cohort	Locoregional recurrence-free survival 2 years	NR	91%	88%	0.49
	Progression-free survival 2 years	Propensity score-weighted (HR, 0.6; 95% CI, 0.4-1.1).	NR	NR	0.56
	Overall acute grade 3+ toxicity Within 2 weeks of treatment initiation	Adjusted OR 0.7 (95% CI, 0.3-1.5)	NR	NR	0.39
	Overall late grade 3+ toxicity Greater than 3 months after treatment initiation	Adjusted OR 0.8 (95% CI, 0.2-3.4)	NR	NR	0.79
Glynne-Jones, 2011 (20934265)[21] EBRT v BCT Serious *Post hoc* of RCT	Time to first locoregional relapse	HR 1.43 (99% CI, 0.89 - 2.28)	NR	NR	0.05
	Anal cancer deaths Median 13.1 years	HR 1.16 (99% CI, 0.70 - 1.93)	NR	NR	0.44
	Overall survival Median 13.1 years	HR 1.14 (99% CI, 0.81 - 1.62)	NR	NR	0.33
	Relapse-free survival Median 13.1 years	HR 1.26 (99% CI, 0.91 - 1.75)	NR	NR	0.07
	Non-anal cancer deaths Median 13.1 years	HR 1.22 (99% CI, 0.75 - 1.99)	NR	NR	0.30
Hannoun-Levi, 2011 (20619552)[22] EBRT v BCT Serious	Overall survival 5 years	NR	80%	78%	0.47
	Cumulated rate of local recurrence 5 years	HR 0.62 (95% CI 0.41 - 0.92)	33%	12%	0.002

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Comparing Rates)
Prospective, non-RCT	Colostomy-free survival 5 years	HR 0.66 (95% CI, 0.38 - 1.15)	56%	71%	0.04
Moureau-Zabotto, 2013 (23195780)[23] EBRT v BCT Serious Retrospective cohort	Overall survival 5 years	NSD	73%	76%	0.50
	Cumulated rate of local recurrence 5 years	HR 2.14 (95% CI, 0.74 - 6.19), p=0.16	32%	11%	0.02
	Cumulated rate of distant recurrence 5 years	NSD	15%	22%	0.50
	Colostomy-free survival 5 years	NSD	69%	74%	0.30
	Overall survival in N1 patients 5 years	HR 3.5 (95% CI, 0.8 - 15.8), p=0.10	77%	90%	0.07
	Cumulated rate of local recurrence in N1 patients 5 years	HR 9.7 (95% CI, 1.1 - 81.3), p=0.036	31%	4%	0.003
	Cumulated rate of distant recurrence in N1 patients 5 years	NSD	3%	13%	0.20
	Colostomy-free survival in N1 patients 5 years	HR 1.8 (95% CI, 0.6 - 4.9), p=0.30	62%	80%	0.18

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; RT- radiation therapy; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; EBRT- external beam RT; BCT- brachytherapy; NR- not reported; NSD- no significant difference.

Table C.5.3. Findings for Key Question 3

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Comparing Rates)
Peiffert, 2012 (22529257)[24] Standard boost v high-dose boost Low RCT	Colostomy-free survival 5 years	NSD	73.7% (95% CI, 65.5 - 80.5)	77.8% (95% CI, 70.1 - 84.0)	0.067
	Local control 5 years	NSD	78.2% (95% CI, 70.6 - 84.4)	83.1% (95% CI, 75.8 - 88.5)	0.28
	Specific survival 5 years	NSD	78.6% (95% CI, 70.7 - 84.9)	82.7% (95% CI, 75.4 - 88.2)	0.39
	Tumor-free survival 5 years	NSD	67.5% (95% CI, 58.7 - 75.1)	70.6% (95% CI, 62.5 - 77.6)	0.37
Tournier-Rangeard, 2008 (18191265)[25]	QLQ-C30 (Quality of Life Questionnaire)	No comparable differences but numerical values not reported.	NR	NR	NR

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Comparing Rates)
High dose boost v standard dose boost **Moderate** **RCT**	Anal Sphincter-Conservative Treatment (AS-CT) questionnaire	No comparable differences but numerical values not reported.	NR	NR	NR
Glynne-Jones, 2020 (32619648)[27] **50.4Gy in <38 days v 50.4Gy in 38-42 days** **Critical** **Post-hoc of RCT**	Overall survival 3 years	HR 0.95 (95% CI, 0.42 - 2.16)	87%	86%	0.91
	Progression-free survival 3 years	HR 1.00 (95% CI, 0.51 - 1.95)	72%	76%	0.99
Glynne-Jones, 2020 (32619648)[27] **50.4Gy in >42 days v 50.4Gy in 38-42 days** **Critical** **Post-hoc of RCT**	Overall survival 3 years	Favors 38-42 days HR 1.72 (95% CI, 1.17 - 2.54)	78%	86%	0.006
	Progression-free survival 3 years	Favors 38-42 days HR 1.57 (95% CI, 1.11 - 2.21)	62%	76%	0.01
Glynne-Jones, 2020 (32619648) [27] **≤40Gy in 38-42 days v 50.4Gy in 38-42 days** **Critical** **Post-hoc of RCT**	Overall survival 3 years	Favors 50.4Gy in 38-42 days HR 8.24 (95% CI, 3.35 - 20.27)	29%	86%	<0.001
	Progression-free survival 3 years	Favors 50.4Gy in 38-42 days HR 5.43 (95% CI, 2.24 - 13.21)	29%	76%	<0.001
Glynne-Jones, 2020 (32619648) [27] **>40 to <48.6Gy in 38-42 days v 50.4Gy in 38-42 days** **Critical** **Post-hoc of RCT**	Overall survival 3 years	Favors 50.4Gy in 38-42 days HR 3.12 (95% CI, 1.73 - 5.63)	70%	86%	<0.001
	Progression-free survival 3 years	Favors 50.4Gy in 38-42 days HR 2.12 (95% CI, 1.21 - 3.72)	63%	76%	0.009
Glynne-Jones, 2020 (32619648) [27] **≥52.2Gy in 38-42 days v 50.4Gy in 38-42 days** **Critical** **Post-hoc of RCT**	Overall survival 3 years	HR 1.57 (95% CI, 0.58 - 4.25)	73%	86%	0.37
	Progression-free survival 3 years	HR 1.60 (95% CI, 0.71 - 3.59)	59%	76%	0.26
Lukovic, 2023 (36455685)[28] **Acute Toxicities** **Critical** **Prospective cohort**	Acute grade 2+ lower pelvic bone toxicity with dose V_{45} Weekly assessment while patient undergoing treatment	Adjusted OR 1.0 (95% CI, 1.0-1.1)	NR	NR	0.04

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Comparing Rates)
Nilsson, 2022 (34598844)[29] **Acute Toxicities** **Critical** **Retrospective cohort**	Acute grade 3+ bowel cavity toxicity with dose V_{30} <90 days from the end of radiotherapy	Adjusted OR 1.02 (95% CI, 1.00-1.04)	NR	NR	0.15
	Late grade 2+ large bowel toxicity with dose V_{20} >90 days from the end of radiotherapy	Adjusted OR 1.07 (95% CI, 1.02-1.13)	NR	NR	0.01
Mehta, 2020 (32399269)[30] **≤4.72 vs >4.72 fractions/week** **Critical** **Retrospective cohort**	Overall survival 5 years	Favors >4.72 fractions/wk HR 0.70 (95% CI, 0.63 - 0.79)	NR	NR	<0.001

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; EBRT- external beam RT; Bct- brachytherapy; wk- week; NR- not reported; NSD- no significant difference.

Table C.5.4. Findings for Key Question 4

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Comparing Rates)
James, 2013 (23578724)[14] **Maintenance chemotherapy v no maintenance** **High** **RCT**	Overall survival 3 years	HR 1.07 (95% CI, 0.81 - 1.41)	NR	NR	0.65
	Progression-free survival 3 years	HR 0.95 (95% CI, 0.75 - 1.21)	74% (95% CI, 69 - 77)	73% (95% CI, 68 - 77)	0.70
	Colostomy-free survival 3 years	HR 0.87 (95% CI, 0.68 - 1.10)	NR	NR	0.24
	Anal cancer mortality 3 years	HR 1.11 (95% CI, 0.80 - 1.54)	NR	NR	0.53
Glynne-Jones, 2014 (24827136)[15] **Maintenance chemotherapy v no maintenance** **High** **RCT**	Colostomy-free survival Median 5.1 years (range 6 days - 10.5 years)	Unadjusted HR 0.87 (95% CI, 0.69 - 1.10)	30.6% (129/422)	33.8% (146/420)	NR
	Progression-free survival Median 5.1 years (range 6 days - 10.5 years)	Unadjusted HR 0.93 (95% CI, 0.72 - 1.20)	26.3% (111/422)	28.1% (118/420)	NR
Peiffert, 2012 (22529257)[24]	Colostomy-free survival 5 years	NSD	76.5% (95% CI, 68.6 - 83.0)	75.0% (95% CI, 67.0 - 81.5)	0.37

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Comparing Rates)
Induction chemotherapy v no induction **High** **RCT**	Local control 5 years	NSD	80.3% (95% CI, 72.8 - 86.1)	81.0% (95% CI, 73.5 - 86.8)	0.65
	Disease-specific survival 5 years	NSD	83.0% (95% CI, 75.8 - 88.4)	78.5% (95% CI, 70.5 - 84.7)	0.63
	Tumor-free survival 5 years	NSD	71.5% (95% CI, 63.4 - 78.5)	64.8% (95% CI, 56.6 - 72.2)	0.21
	Acute grade 3+ hematologic toxicity Within 8 weeks of completing the boost	Favors no induction	29% (44/150)	12% (19/157)	<0.001
	Acute grade 3+ gastrointestinal toxicity Within 8 weeks of completing the boost	NSD	16% (24/150)	15% (23/157)	NR
	Acute grade 3+ infectious toxicity Within 8 weeks of completing the boost	NSD	2% (3/150)	2% (3/157)	NR
	Acute grade 3+ cardiac toxicity Within 8 weeks of completing the boost	NSD	1% (2/150)	<1% (1/157)	NR
Tournier-Rangeard, 2008 (18191265)[25] **Induction chemotherapy v no induction** **High** **RCT**	QLQ-C30 (Quality of Life Questionnaire)	No comparable differences but numerical values not reported.	NR	NR	NR
	Anal Sphincter-Conservative Treatment (AS-CT) questionnaire	No comparable differences but numerical values not reported.	NR	NR	NR
Glynne-Jones, 2011 (20934265)[21] **Boost v no boost** **Serious** **Post-hoc of RCT**	Time to first locoregional relapse	HR 0.90 (99% CI, 0.48 - 1.68)	NR	NR	0.66
	Anal cancer deaths Median 13.1 years	HR 0.62 (99% CI, 0.35 - 1.12)	NR	NR	0.04
	Overall survival Median 13.1 years	HR 0.74 (99% CI, 0.48 - 1.15)	NR	NR	0.08
	Relapse-free survival Median 13.1 years	HR 0.80 (99% CI, 0.52 - 1.22)	NR	NR	0.18

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Comparing Rates)
	Non-anal cancer deaths Median 13.1 years	HR 0.88 (99% CI, 0.45 - 1.70)	NR	NR	0.62
White, 2015 (26347494)[31] 1 cycle MMC v 2 cycles MMC Moderate Retrospective cohort	Overall survival 2 years	HR 0.67 (95% CI, 0.25 - 1.83), p=0.43	84%	91%	0.16
	Progression-free survival 2 years	HR 0.85 (95% CI, 0.37 - 1.92), p=0.69	78%	85%	0.39
	Colostomy-free survival 2 years	HR 0.91 (95% CI, 0.31 - 2.67), p=0.86	87%	92%	0.51
	Cancer-specific survival 2 years	HR 0.32 (95% CI, 0.07 - 1.42), p=0.13	88%	94%	0.11
	Acute grade 3+ toxicity Within 6 months of completing radiotherapy	NR	42% (65/154)	41% (26/63)	1.0
	Acute grade 2+ hematologic toxicity Within 6 months of completing radiotherapy	Favors 1 cycle MMC	73% (113/154)	89% (56/63)	0.01
	Acute grade 2+ skin toxicity Within 6 months of completing radiotherapy	Favors 1 cycle MMC	84% (129/154)	97% (61/63)	0.006
	Acute grade 2+ gastrointestinal toxicity Within 6 months of completing radiotherapy	NR	61% (94/154)	67% (42/63)	0.54
	Acute grade 2+ genitourinary toxicity Within 6 months of completing radiotherapy	Favors 1 cycle MMC	8% (13/154)	19% (12/63)	0.04
	Radiation treatment break Within 6 months of completing radiotherapy	NR	29% (45/154)	19% (12/63)	0.13
	Late grade 3+ toxicity Greater than 6 months of completing radiotherapy	NR	7% (11/154)	5% (3/63)	0.76

Study (PMID) Comparison RoB Study Design	Outcome (+/- Stratification) Timing	Summary Finding	Intervention % Event Rate	Comparator % Event Rate	p-Value (for Comparing Rates)
	Late grade 2+ toxicity Greater than 6 months of completing radiotherapy	NR	32% (50/154)	22% (14/63)	0.14

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; EBRT- external beam RT; Bct- brachytherapy; wk- week; NR- not reported; NSD- no significant difference.

Table C.5.5. Findings for Key Question 6

Study (PMID) Comparison RoB Study Design	Summary Finding
Frazer, 2020 (32028341)[32] **Frequency of events within 1 yr vs. within 2 yrs vs. yr 3-5** **Critical** **Retrospective cohort**	There were 29 events in 140 patients (9 LR, 11 DM, and 9 LG3T), with 62% of events occurring within year 1 and 79% within 2 years. Stratified by event type, at 2 years 89% of LR, 64% of DM, and 89% LG3T were identified. At the remaining followup points, the event incidence rate was 1.3%.

Abbreviations: DM- distant metastasis; LR- locoregional recurrence; LG3T- late grade 3+ toxicity; RoB- risk of bias; yr- year.

Strength of Evidence

All outcomes were direct, and we did not detect reporting bias for any outcome-intervention pair.

Table C.6.1. Strength of evidence for Key Question 1

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
LE vs CRT, early stage	Overall survival	NRSIs: k=2 (2433); Chai, 2017 (29049547)[1]; Deshmukh, 2018 (27755059)[2]	Inconclusive. One study reported an adjusted HR for LE, 1.06 (95% CI, 0.78 - 1.44, ref- CRT, 5 yr follow-up time). Another study reported propensity score-adjusted HR for CRT, 1.74 (95% CI, 0.79 - 3.83; ref- LE; follow-up time NR) and for RT, 2.17 (95% CI, 0.92 - 5.10; ref- LE; follow-up time NR)	high; inconsistent; imprecise	insufficient
LE vs CRT, early stage	Cause-specific survival	NRSI: k=1 (883); Gao, 2020 (32199768)[3]	Inconclusive. One study reported an adjusted HR for LE, 0.48 (95% CI, 0.1- 2.3; ref- CRT; 5 yr follow-up time)	high; N/A; imprecise	insufficient
RT vs CRT	Overall survival (up to 5 yr follow-up)	RCTs: 2 trials, k=2 (695); Bartelink, 1997 (9164216)[4]; UKCCCR, 1996 (8874455)[5];	No difference. One RCT (n=110) reported 5yr overall survival rate of 54% with RT vs. 58% with CRT; p = 0.17. One RCT (n=585) reported 3yr overall survival rate of 58% with RT alone vs. 65% with CRT, (RR=0·86, 95% CI 0·67–1·11, p=0·25).	low; consistent; imprecise	moderate
RT vs CRT	Disease-specific mortality (up to 5 yr follow-up)	RCTs: 1 trial, k=1 (585); UKCCCR, 1996 (8874455)[5];	CRT favored over RT. One trial reported a rate of 28% for CRT vs. 39% for RT, RR of 0.71 for CRT (95% CI, 0.53 - 0.95, ref-RT) over median follow-up of 42 months	low; N/A; precise	moderate

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
RT vs CRT	Complete response	RCTs: 2 trials, k=2 (695); Bartelink, 1997 (9164216)[4]; UKCCCR, 1996 (8874455)[5];	CRT favored over RT. One RCT reported a complete response rate of 54% for RT vs. 80% CRT at 6 weeks post-treatment. One RCT reported a complete response rate of 30% for RT vs. 39% for CRT at 6 weeks post treatment.	moderate; inconsistent; precise	low
RT vs CRT	Local failure rate (up to 5 yr follow-up)	RCTs: 2 trials, k=2 (695); Bartelink, 1997 (9164216)[4]; UKCCCR, 1996 (8874455)[5];	CRT favored over RT. One RCT reported a 5-year rate of 50% with RT vs. 32% with CRT (p = 0.02). One RCT reported a 3-year rate of 61% with RT alone vs. 39% with CRT (RR, 0.54; 95% CI, 0.42 - 0.69; ref- RT)	moderate; consistent; precise	moderate
RT vs CRT	Colostomy-free survival (up to 5 yr follow-up)	RCTs: 1 trials, k=1 (110); Bartelink, 1997 (9164216)[4];	CRT favored over RT. Estimated improvement (favoring CRT over RT) by 32% at 5yrs (p=0.002)	moderate; N/A; precise	low
RT vs CRT	Overall acute harms	RCTs: 1 trial, k=1 (585); UKCCCR, 1996 (8874455)[5];	Significantly greater in CRT compared to RT. One RCT (n=585) reported a significant difference (p=0.03) in overall acute toxicity frequency (n=110 out of 285 patients in RT arm vs. n=140 out of 292 patients in CRT arm).	low; N/A; precise	moderate

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
RT vs CRT	Acute hematologic toxicity	RCTs: 2 trials, k=2 (695); Bartelink, 1997 (9164216)[4]; UKCCCR, 1996 (8874455)[5];	Significantly greater in CRT compared to RT. One RCT (n=110) reported one grade 4 event in CRT arm vs zero grade 4 events in RT arm. One RCT (n=585) reported greater overall hematologic toxicity in the CRT arm (n=20) versus RT arm (n=0).	moderate; consistent; imprecise	low
RT vs CRT	Acute dermatologic toxicity	RCTs: 2 trials, k=2 (695); Bartelink, 1997 (9164216)[4]; UKCCCR, 1996 (8874455)[5];	No significant difference. One RCT (n=110) reported no significant difference (p>0.05) in acute grade 3+ dermatologic toxicity event rate in CRT (n=26) vs. RT (n=29). Another RCT (n=585) reported no significant difference (p>0.05) in overall (n=76 in RT arm vs. n=93 in CRT arm) or severe dermatologic toxicity (n=39 in RT arm vs. n=50 in CRT arm).	moderate; consistent; imprecise	low
RT vs CRT	Acute gastrointestinal toxicity	RCTs: 2 trials, k=2 (695); Bartelink, 1997 (9164216)[4]; UKCCCR, 1996 (8874455)[5];	No significant difference. One RCT (n=110) reported no significant difference (p>0.05) in acute grade 3+ diarrhea in CRT (n=10) vs. RT (n=4). Another RCT (n=585) reported no significant difference (p>0.05) in overall (n=39 in RT arm vs. n=46 in CRT arm) or severe gastrointestinal toxicity (n=5 in RT arm vs. n=14 in CRT arm).	moderate; consistent; imprecise	low

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
RT vs CRT	Acute genitourinary toxicity	RCTs: 1 trial, k=1 (585); UKCCCR, 1996 (8874455)[5];	No significant difference. One RCT (n=585) reported no significant difference (p>0.05) in overall (n=13 in RT arm vs. n=20 in CRT arm) or severe toxicity event rate (n=1 in RT arm vs. n=3 in CRT arm).	moderate; N/A; imprecise	low
RT vs CRT	Overall late harms	RCTs: 1 trial, k=1 (585); UKCCCR, 1996 (8874455)[5];	No significant difference. One RCT (n=585) reported no significant difference (p=0.39) in overall late toxicity rate (n=108 out of 285 patients in RT arm vs. n=122 out of 292 patients in CRT arm).	moderate; N/A; precise	low
RT vs CRT	Late dermatologic toxicity	RCTs: 2 trials, k=2 (695); Bartelink, 1997 (9164216)[4]; UKCCCR, 1996 (8874455)[5]	No significant difference. One RCT (n=110) reported no significant difference (p>0.05) in event rate in CRT (n=3) vs. RT (n=2). Another RCT (n=585) reported no significant difference (p=0.39) with a total of 47 events in RT arm vs. 59 events in CRT arm reported after 2 months from the end of treatment.	moderate; consistent; imprecise	low
RT vs CRT	Late gastrointestinal toxicity	RCTs: 1 trials, k=1 (585); UKCCCR, 1996 (8874455)[5]	No significant difference. One RCT (n=585) reported no significant difference (p>0.05) in overall events (n=77 in RT arm vs. n=84 in CRT arm, absolute difference 1.8%; 95% CI, -5.6 to 9%, p= 0.64) reported after 2 months from the end of treatment.	moderate; N/A; precise	low

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
RT vs CRT	Late genitourinary toxicity	RCTs: 1 trial, k=1 (585); UKCCCR, 1996 (8874455)[5]	No significant difference. One RCT (n=585) reported no significant difference (p>0.05) with a total of 19 events in RT arm vs. 18 events in CRT arm reported after 2 months from the end of treatment.	moderate; N/A; precise	low
RT+5FU vs. RT+5FU+MMC	Overall survival	RCT: 1 trial, k=1 (310); Flam, 1996 (8823332)[7]	No significant difference. 71% with 5-FU vs. 78.1% with 5-FU/MMC (p = 0.31) at 4 yrs	moderate; N/A; precise	low
RT+5FU vs. RT+5FU+MMC	Complete response	RCT: 1 trial, k=1 (310); Flam, 1996 (8823332)[7]	No significant difference. 86% with 5-FU vs. 92.2% with 5-FU/MMC (p = 0.14) at 4 yrs	moderate; N/A; precise	low
RT+5FU vs. RT+5FU+MMC	Disease-free survival	RCT: 1 trial, k=1 (310); Flam, 1996 (8823332) [7]	Favors 5FU + MMC over 5FU alone. 51% 5-FU vs. 73% with 5-FU/ MMC (p<0.001) at 4 years	moderate; N/A; precise	low
RT+5FU vs. RT+5FU+MMC	Local failure rate	RCT: 1 trial, k=1 (310); Flam, 1996 (8823332) [7]	Favors 5FU + MMC over 5FU alone. 34% 5-FU vs. 16% with 5-FU/ MMC (p<0.001) at 4 years	moderate; N/A; precise	low
RT+5FU vs. RT+5FU+MMC	Colostomy-free survival	RCT: 1 trial, k=1 (310); Flam, 1996 (8823332) [7]	Favors 5FU + MMC over 5FU alone. 59% with 5-FU vs. 71% with 5-FU/MMC (p = 0.014) at 4 years	moderate; N/A; precise	low
RT+5FU vs. RT+5FU+MMC	Overall acute harms	RCT: 1 trial, k=1 (310); Flam, 1996 (8823332) [7]	Inconclusive. Greater in 5FU + MMC vs. 5FU alone. 20 events in 5FU + MMC arm vs. 7 events in 5FU arm (p<0.001).	high; N/A; imprecise	insufficient

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
RT+5FU vs. RT+5FU+MMC	Acute hematologic toxicity	RCT: 1 trial, k=1 (310); Flam, 1996 (8823332) [7]	Inconclusive. 18 events in 5FU + MMC arm vs. 3 events in 5FU arm (p<0.001).	high; N/A; imprecise	insufficient
RT+5FU vs. RT+5FU+MMC	Overall late harms	RCT: 1 trial, k=1 (310); Flam, 1996 (8823332) [7]	Inconclusive. 5 events in 5FU + MMC arm vs. 1 events in 5FU arm (p=0.26)	high; N/A; imprecise	insufficient
RT+MMC+Cape vs. RT+MMC+5FU	Overall survival	NRSI: k=1 (107); Goodman, 2017 (28721892)[8]	Inconclusive. 87% for 5-FU vs. 98% for capecitabine (P=0.12) at 2 yrs.	high; N/A; imprecise	insufficient
RT+MMC+Cape vs. RT+MMC+5FU	Distant metastasis	NRSI: k=1 (107); Goodman, 2017 (28721892)[8]	Inconclusive. 14.7% for 5-FU vs. 7.6% for capecitabine (P=0.26) at 2 yrs	high; N/A; imprecise	insufficient
RT+MMC+Cape vs. RT+MMC+5FU	Local failure rate	NRSI: k=1 (107); Goodman, 2017 (28721892)[8]	Inconclusive. 6.5% for 5-FU vs. 8.2% for capecitabine (P=0.78) at 2 yrs	high; N/A; imprecise	insufficient
RT+MMC+Cape vs. RT+MMC+5FU	Colostomy-free survival	NRSI: k=3 (507); Goodman, 2017 (28721892)[8]; Jones, 2018 (29859793)[9]; Peixoto, 2016 (27563458)[10]	Inconclusive. One study reported a colostomy rate of 5% for 5-FU vs 9% for capecitabine (p=0.65) at 2 yrs. One study reported a colostomy-free survival rate of 90.7% for 5-FU vs 77.5% for capecitabine (p=0.09) at 1 yr. One study reported an HR =0.66 for 5FU (95% CI, 0.28–1.54, ref- capecitabine).	high; consistent; imprecise	insufficient
RT+MMC+Cape vs. RT+MMC+5FU	Disease-free survival	NRSIs: k=2 (397); Jones, 2018 (29859793)[9]; Peixoto, 2016 (27563458)[10]	Inconclusive. One study reported disease-free survival rate of 76.2% for Capecitabine vs. 78.2% for 5-FU (p=0.8124) at 1 yr. One study reported an HR of 0.99 for 5-FU (95% CI, 0.57- 1.74; ref-capecitabine) at 5 yrs.	high; consistent; imprecise	insufficient

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
RT+MMC+Cape vs. RT+MMC+5FU	Complete response	NRSIs: k=1 (100); Jones, 2018 (29859793)[9]	Inconclusive. No difference at 6 months, with a rate of 88.1% for capeciatabine vs. 91.4% for 5FU (p=0.74)	high; N/A; imprecise	insufficient
RT+MMC+Cape vs. RT+MMC+5FU	Disease-specific survival	NRSIs: k=1 (300); Peixoto, 2016 (27563458)[10]	Inconclusive. No difference; with an HR of 0.93 for 5-FU (95% CI, 0.46 - 1.86; ref-capecitabine) at 5 yrs	high; N/A; imprecise	insufficient
RT+MMC+Cape vs. RT+MMC+5FU	Overall acute harms	NRSI: k=1 (118); Jones, 2018 (29859793)[9]	Inconclusive. No significant difference reported in one NRSI (n=118) between capeciatabine arm versus 5FU arm (45% versus 55%, p=0.35) .	high; N/A; precise	insufficient
RT+MMC+Cape vs. RT+MMC+5FU	Treatment break due to toxicity	NRSI: k=1 (107); Goodman, 2017 (28721892)[8]	Inconclusive. Significantly higher treatment break due to toxicity in the 5-FU group than the capecitabine group (41% vs 14%, P=0.006) was reported in one NRSI (n=107).	high; N/A; precise	insufficient
RT+MMC+Cape vs. RT+MMC+5FU	Acute hematologic toxicity	NRSIs: k=2 (221); Goodman, 2017 (28721892)[8]; Jones, 2018 (29859793)[9]	Inconclusive. Significantly greater in 5FU arm compared to capecitabine arm. One NRSI (n=107) reported Grade 3 or higher neutropenia in 33 (52%) patients in the 5-FU group and 9 (20%) in the capecitabine group during CRT or within 2 weeks of completion of therapy (P<.001). Another NRSI (n=114) reported grade 3 or higher event rate of 1 febrile neutropenia and 1 leukopenia event in the capecitabine arm versus 13 leukopenia events in the 5FU arm (p<0.001)	high; consistent; precise	insufficient

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
RT+MMC+Cape vs. RT+MMC+5FU	Acute dermatologic toxicity	NRSIs: k=2 (225); Goodman, 2017 (28721892)[8]; Jones, 2018 (29859793)[9];	Inconclusive. No significant difference. One NRSI (n=107) reported 8 events in 5FU arm vs. 1 event in capecitabine arm (p=0.08). One NRSI (n=118) reported 20 events in 5FU arm vs. 12 events in capecitabine arm (p=0.71).	high; consistent; precise	insufficient
RT+MMC+Cape vs. RT+MMC+5FU	Acute gastrointestinal toxicity	NRSIs: k=2 (225); Goodman, 2017 (28721892)[8]; Jones, 2018 (29859793)[9];	Inconclusive. No significant difference. One NRSI (n=107) reported 0 events in 5FU arm vs. 1 event in capecitabine arm (p=0.08). One NRSI (n=118) reported 9 events in 5FU arm vs. 8 events in capecitabine arm (p=0.72).	high; consistent; precise	insufficient
RT+MMC+5FU v RT+MMC+ cisplatin	Progression-free survival	RCT: 1 trial, k=1 (76); Matzinger, 2009 (19643599)[11]	Inconclusive. No significant difference; with a rate of 94.2% (95% CI,78.5–98.5%) for cisplatin vs. 76.3% (95% CI, 59.3–86.9%) for 5-FU at 1 yr	high; N/A; imprecise	insufficient
RT+MMC+5FU v RT+MMC+ cisplatin	Event-free survival	RCT: 1 trial, k=1 (76); Matzinger, 2009 (19643599)[11]	Inconclusive. No significant difference; with 89.2% (95% CI, 73.7 - 95.8) events in cisplatin arm vs. 74.4% (95% CI, 57.6 - 85.3) events in 5-FU arm at 1 yr	high; N/A; imprecise	insufficient
RT+MMC+5FU v RT+MMC+ cisplatin	Complete response	RCT: 1 trial, k=1 (76); Matzinger, 2009 (19643599)[11]	Inconclusive. No significant difference; with 73% events in cisplatin arm vs. 59% events in 5-FU arm	high; N/A; imprecise	insufficient

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
RT+MMC+5FU v RT+MMC+ cisplatin	Acute hematologic toxicity	RCT: 1 trial, k=1 (76); Matzinger, 2009 (19643599)[11]	Inconclusive. No significant difference; with 6 events in cisplatin arm vs. 4 events in 5-FU arm.	high; N/A; imprecise	insufficient
RT+MMC+5FU v RT+MMC+ cisplatin	Acute gastrointestinal toxicity	RCT: 1 trial, k=1 (76); Matzinger, 2009 (19643599)[11]	Inconclusive. No significant difference; with 9 events in cisplatin vs. 7 events for 5-FU	high; N/A; imprecise	insufficient
RT+5FU+MMC v RT+5FU+ cisplatin	Overall survival (up to 5 yr follow-up)	RCTs: 2 trials, k=2 (1622); Ajani, 2008 (18430910)[12] James, 2013 (23578724)[14]	No significant difference. One RCT reported an HR of 1.28 for MMC (95% CI, 0.90 - 1.84, p=0.17, ref- cisplatin) over a median follow-up of 2.5 years. One RCT reported an HR of 1.05 (95% CI, 0.80 - 1.38; ref- MMC) over a median follow-up of 5.1 yrs.	low; consistent; precise	moderate
RT+5FU+MMC v RT+5FU+ cisplatin	Distant metastasis (up to 5 yr follow-up)	RCT: 1 trial, k=1 (682); Ajani, 2008 (18430910)[12]	No significant difference. Frequency of 15% (95% CI, 10 - 20) events in MMC arm vs. 19% (95% CI, 14 - 24) events in cisplatin arm over a median follow-up of 2.5 yrs (p=0.14).	low; N/A; precise	moderate
RT+5FU+MMC v RT+5FU+ cisplatin	Locoregional failure (up to 5 yr follow-up)	RCT: 1 trial, k=1 (682); Ajani, 2008 (18430910)1[2]	No significant difference. One RCT reported an HR of 1.32 for MMC (95% CI, 0.98 - 1.78, p=0.07, ref- cisplatin) over a median follow-up of 2.5 yrs	low; N/A; imprecise	low

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
RT+5FU+MMC v RT+5FU+ cisplatin	Colostomy-free survival (up to 5 yr follow-up)	RCTs: 2 trials, k=2 (1622); Ajani, 2008 (18430910)[12] James, 2013 (23578724)[14]	Inconclusive. Mixed (conflicting) results. One RCT reported a statistically significant difference in colostomy rates (HR, 1.68; 95% CI, 1.07-2.65; P=0.02), with 5-year cumulative colostomy rates of 10% (95% CI, 6%-14%) in the mitomycin-based group and 19% (95% CI, 13%-24%) in the cisplatin-based group. One RCT reported no difference in absolute values and an HR of 1.04 for cisplatin (95% CI, 0.82 - 1.31; ref- MMC) over a median follow-up of 5.1 yrs.	moderate; inconsistent; imprecise	insufficient
RT+5FU+MMC v RT+5FU+ cisplatin	Disease-free survival (up to 5 yr follow-up)	RCT: 1 trial, k=1 (682); Ajani, 2008 (18430910)[12]	No significant difference. Frequency of 60% (95% CI, 53%-67%) events in MMC arm vs. 54% (95% CI, 46%-60%) events in cisplatin arm, and an HR of 1.20 for MMC (95% CI, 0.93 - 1.55, ref-cisplatin) over a median follow-up of 2.5 yrs.	low; N/A; imprecise	low
RT+5FU+MMC v RT+5FU+ cisplatin	Progression-free survival	RCT: 1 trial, k=1 (940); James, 2013 (23578724)[14]	No significant difference. One RCT reported an HR 0.95 (95% CI, 0.75 - 1.19) over a median follow-up of 5.1 yrs.	low; N/A; precise	moderate
RT+5FU+MMC v RT+5FU+ cisplatin	Complete response	RCT: 1 trial, k=1 (940); James, 2013 (23578724) [14]	No significant difference. One RCT reported a complete response frequency of 90.5% events in MMC arm vs 89.6% events in cisplatin arm.	low; N/A; precise	moderate

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
RT+5FU+MMC v RT+5FU+ cisplatin	Overall acute harms	RCTs: 2 trials, k=2 (1622); Ajani, 2008 (18430910)[12] James, 2013 (23578724)[14]	No significant difference. One RCT (n=682) reported overall grade 3+ toxicity frequency of 87% in MMC arm vs. 83% in cisplatin arm (p=0.13). One RCT (n=940) reported overall grade 3+ toxicity frequency of 71% in MMC arm vs. 72% in cisplatin arm (p>0.05).	moderate; consistent; precise	moderate
RT+5FU+MMC v RT+5FU+ cisplatin	Acute hematologic toxicity	RCTs: 2 trials, k=2 (1622); Ajani, 2008 (18430910) [12] James, 2013 (23578724) [14]	Significantly greater in MMC arm vs. cisplatin arm. One RCT (n=682) reported grade 3+ toxicity frequency of 61% in MMC arm vs. 42% in cisplatin arm (p<0.001). One RCT (n=940) reported grade 3+ toxicity frequency of 26% in MMC arm vs. 16% in cisplatin arm (p<0.001).	moderate; consistent; precise	moderate
RT+5FU+MMC v RT+5FU+ cisplatin	Acute dermatologic toxicity	RCTs: 2 trials, k=2 (1622); Ajani, 2008 (18430910) [12] James, 2013 (23578724)[14]	No significant difference. One RCT (n=682) reported grade 3+ toxicity frequency of 155 events (48%) in MMC arm vs. 132 events (41%) in cisplatin arm (difference, 7%, 95% CI, -1% to 14%, p=0.09). One RCT (n=940) reported overall grade 3+ toxicity frequency of 48% in MMC arm vs. 47% in cisplatin arm (p>0.05)	moderate; consistent; imprecise	low

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
RT+5FU+MMC v RT+5FU+ cisplatin	Acute gastrointestinal toxicity	RCTs: 2 trials, k=2 (1622); Ajani, 2008 (18430910)[12] James, 2013 (23578724) [14]	No significant difference. One RCT (n=682) reported overall grade 3 toxicity frequency of 103 events in MMC arm vs. 138 events in cisplatin arm and overall grade 4 toxicity frequency of 12 events in MMC arm vs. 8 events in cisplatin arm. One RCT (n=940) reported overall grade 3+ toxicity frequency of 16% in MMC arm vs. 18% in cisplatin arm (p>0.05)	moderate; consistent; imprecise	low
RT+5FU+MMC v RT+5FU+ cisplatin	Acute genitourinary toxicity	RCTs: 2 trials, k=2 (1622); Ajani, 2008 (18430910) [12] James, 2013 (23578724)[14]	No significant difference. One RCT (n=682) reported overall grade 3 toxicity frequency of 10 events in MMC arm vs. 1 event in cisplatin arm and overall grade 4 toxicity frequency of 11 events in MMC arm vs. 0 events in cisplatin arm. One RCT (n=940) reported overall grade 3+ toxicity frequency of 1% in MMC arm vs. 2% in cisplatin arm (p>0.05)	moderate; consistent; imprecise	low
RT+5FU+MMC v RT+5FU+ cisplatin	Overall late harms	RCTs: 1 trial, k=1 (682); Ajani, 2008 (18430910) [12]	No significant difference. One RCT (n=682) reported overall grade 3 toxicity frequency of 8% in MMC arm vs. 6% in cisplatin arm and overall grade 4 toxicity frequency of 3% in MMC arm vs. 4% in cisplatin arm.	moderate; N/A; precise	low

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
RT+5FU+MMC v RT+5FU+ cisplatin	Late dermatologic toxicity	RCTs: 1 trial, k=1 (682); Ajani, 2008 (18430910) [12]	No significant difference. One RCT (n=682) reported overall grade 3 toxicity frequency of 5 events in MMC arm vs. 3 events in cisplatin arm and overall grade 4 toxicity frequency of 5 events in MMC arm vs. 4 events in cisplatin arm.	moderate; N/A; precise	low
RT+5FU+MMC v RT+5FU+ cisplatin	Late gastrointestinal toxicity	RCTs: 1 trial, k=1 (682); Ajani, 2008 (18430910) [12]	No significant difference. One RCT (n=682) reported overall grade 3 toxicity frequency of 5 events in MMC arm vs. 5 events in cisplatin arm and overall grade 4 toxicity frequency of 5 events in MMC arm vs. 1 event in cisplatin arm.	moderate; N/A; precise	low
RT+5FU+MMC v RT+5FU+ cisplatin	Late genitourinary toxicity	RCTs: 1 trial, k=1 (682); Ajani, 2008 (18430910) [12]	No significant difference. One RCT (n=682) reported overall grade 3 toxicity frequency of 2 events in MMC arm vs. 1 event in cisplatin arm and overall grade 4 toxicity frequency of 0 events in MMC arm vs. 0 events in cisplatin arm.	moderate; N/A; precise	low
IMRT+cape+MMC+ paclitaxel v IMRT+cape+MMC	Overall survival (up to 3 yrs)	RCTs: 1 trial, k=1 (144); Gordeyev, 2022 (Not indexed in PubMed)[33]	Significantly greater in the paclitaxel arm vs no paclitaxel arm. 3 yr OS in paclitaxel arm vs no paclitaxel arm was 95.5% vs 80% (p<0.001).	low; N/A; imprecise	low
IMRT+cape+MMC+ paclitaxel v IMRT+cape+MMC	Disease-free survival (up to 3 yrs)	RCTs: 1 trial, k=1 (144); Gordeyev, 2022 (Not indexed in PubMed)[33]	Significantly greater in the paclitaxel arm vs no paclitaxel arm. 3 yr DFS in paclitaxel arm vs no paclitaxel arm was 87.1% vs 64.4% (p=0.001).	low; N/A; imprecise	low

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
IMRT+cape+MMC+ paclitaxel v IMRT+cape+MMC	Colostomy-free survival (up to 3 yrs)	RCTs: 1 trial, k=1 (144); Gordeyev, 2022 (Not indexed in PubMed)[33]	Significantly greater in the paclitaxel arm vs no paclitaxel arm. 3 yr CFS in paclitaxel arm vs no paclitaxel arm was 83.2% vs 67.5% (p=0.029).	low; N/A; imprecise	low
IMRT+cape+MMC+ paclitaxel v IMRT+cape+MMC	CR (at 26 weeks posttreatment)	RCTs: 1 trial, k=1 (144); Gordeyev, 2022 (Not indexed in PubMed)[33]	Significantly greater in the paclitaxel arm. CR in paclitaxel arm vs no paclitaxel arm was 88.9% vs 75% (p=0.049).	low; N/A; imprecise	low
IMRT+cape+MMC+ paclitaxel v IMRT+cape+MMC	Overall acute harms	RCTs: 1 trial, k=1 (144); Gordeyev, 2022 (Not indexed in PubMed)[33]	Significantly greater in the paclitaxel arm. 56.9% in paclitaxel arm vs 26.4% in no paclitaxel arm; difference 30.5% (95% CI, 14.5% - 44.4%, p < 0.001).	low; N/A; imprecise	low
IMRT+cape+MMC+ paclitaxel v IMRT+cape+MMC	Neutropenia (grade 3 or 4)	RCTs: 1 trial, k=1 (144); Gordeyev, 2022 (Not indexed in PubMed)[33]	No significant difference. 12 (16.7%) in paclitaxel arm vs 7 (9.7%) patients in no paclitaxel arm; absolute difference 7% (95% CI, - 4.3% to 18.4%, p=0.22)	low; N/A; imprecise	low
IMRT+cape+MMC+ paclitaxel v IMRT+cape+MMC	Acute dermatologic toxicity	RCTs: 1 trial, k=1 (144); Gordeyev, 2022 (Not indexed in PubMed)[33]	No significant difference. 7 patients in each arm	low; N/A; imprecise	low
IMRT+cape+MMC+ paclitaxel v IMRT+cape+MMC	Acute gastrointestinal toxicity	RCTs: 1 trial, k=1 (144); Gordeyev, 2022 (Not indexed in PubMed)[33]	No significant difference. Paclitaxel arm vs no paclitaxel arm; grade 3-4 diarrhea: 10 (13.9%) vs 5 (6.9%) patients with absolute difference 7% (95% CI, -3.3% to 17.6%, p=0.17); grade 3-4 proctitis: 9 (12.5%) vs 4 (5.6%) patients with absolute difference 6.9% (95% CI, -2.9% to 17.1%, p=0.15)	low; N/A; imprecise	low

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
IMRT+cape+MMC+ paclitaxel v IMRT+cape+MMC	Acute genitourinary toxicity	RCTs: 1 trial, k=1 (144); Gordeyev, 2022 (Not indexed in PubMed)[33]	No significant difference. 1 patient per arm had grade 3 cystitis and no patients had grade 3-4 vaginitis	low; N/A; imprecise	low

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; HIV- human immunodeficiency virus; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; CRT- chemoradiation; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; EBRT- external beam RT; Bct- brachytherapy; NR- not reported; SOE- strength of evidence; NSD- no significant difference.

Table C.6.2. Strength of evidence for Key Question 2

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
IMRT vs. non-IMRT	Overall survival	NRSI: k=2 (1944); Pollom, 2017 (28258896)[16]; Bryant, 2018 (30102186)[17]	Inconclusive. No difference. One study reported similar 2 yr rates (79.9% for IMRT and 79.5% for non-IMRT) and an adjusted HR of 0.77 for IMRT (95% CI, 0.59 - 1.00) over a median 47.4 months of follow-up time. One study reported an HR 0.89 for IMRT (95% CI, 0.66 - 1.21) over a median 5.9 yrs of follow-up time.	high; consistent; imprecise	insufficient
IMRT vs. non-IMRT	Disease-specific survival	NRSI: k=2 (1944); Pollom, 2017 (28258896)[16]; Bryant, 2018 (30102186)[17]	Inconclusive. No difference. One study reported an HR of 0.75 favoring IMRT (95% CI, 0.51 - 1.10) over a median 47.4 months of follow-up time. One study reported an HR of 0.72 favoring IMRT (95% CI, 0.45 - 1.17) over a median 5.9 yrs of follow-up time.	high; consistent; imprecise	insufficient

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
IMRT vs. non-IMRT	Colostomy-free survival	NRSI: k=1 (779); Bryant, 2018 (30102186)[17]	Inconclusive. HR of 0.60 favoring IMRT over non-IMRT(95% CI, 0.37 - 0.99)	high; N/A; imprecise	insufficient
IMRT vs. non-IMRT	Acute hematologic toxicity	NRSI: k=1 (312); Bryant, 2018 (30102186)[17]	Inconclusive. No significant difference. One NRSI (n=312) reported a frequency of 47% in the IMRT arm vs. 40% in the non-IMRT arm, with an HR of 1.06 (95% CI, 0.70-1.61).	high; N/A; imprecise	insufficient
IMRT vs. non-IMRT	Acute myelosuppression	NRSI: k=1 (1165); Pollom, 2017 (28258896)[16]	Inconclusive. No significant difference. One NRSI (n=1165) reported a frequency of 9.8 % in the IMRT arm vs. 8.5% in the non-IMRT arm within 3 months.	high; N/A; imprecise	insufficient
IMRT vs. 3D-CRT	Overall survival	NRSI: k=2 (7037); Dasgupta, 2013 (23692961)[18]; Elson, 2018 (30329160)[19]	Inconclusive. Mixed (conflicting) evidence. One study reported no difference in 2 yr rates between IMRT [90%; 95% CI: 84–94%] and 3D-CRT [93%; 95% CI: 80–98%] and a propensity-score adjusted HR of 1.14 (95% CI, 0.32 -4.0). One study reported a doubly robust HR of 0.86 favoring IMRT over 3D-CRT (95% CI, 0.74-0.99) over 12 years of follow-up.	high; inconsistent; imprecise	insufficient
IMRT vs. 3D CRT	locoregional recurrence-free survival	NRSI: k=1 (223); Dasgupta, 2013 (23692961)[18]	Inconclusive. No significant difference, HR of 0.85 for IMRT (95% CI, 0.31 - 2.3) over a median follow-up of 5 yrs	high; N/A; imprecise	insufficient

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
IMRT vs. 3D CRT	Distant metastasis-free survival	NRSI: k=1 (223); Dasgupta, 2013 (23692961)[18]	Inconclusive. No significant difference; HR of 1.23 for IMRT (95% CI, 0.41 - 3.7) over a median follow-up of 5 yrs	high; N/A; imprecise	insufficient
IMRT vs. 3D CRT	Colostomy-free survival	NRSI: k=1 (223); Dasgupta, 2013 (23692961)[18]	Inconclusive. No significant difference, HR of 0.58 for IMRT (95% CI, 0.07 - 4.7) over a median follow-up of 5 yrs	high; N/A; imprecise	insufficient
Proton IMRT vs. photon IMRT	Local control	NRSI: k=1 (208); Mohiuddin, 2021 (34646965)[20]	Inconclusive. No significant difference, 2 yr rate for proton IMRT was 91% vs. for photon IMRT was 88%; (P = 0.49)	high; N/A; imprecise	insufficient
Proton IMRT vs. photon IMRT	Progression-free survival	NRSI: k=1 (208); Mohiuddin, 2021 (34646965)[20]	Inconclusive. No significant difference; with propensity-score weighted HR of 0.6 for proton IMRT (95% CI, 0.4 - 1.1; ref- photon IMRT)	high; N/A; imprecise	insufficient
Proton IMRT vs. photon IMRT	Overall grade 3 or higher acute toxicity	NRSI: k=1 (208); Mohiuddin, 2021 (34646965)[20]	Inconclusive. No significant difference between treatment groups in overall grade 3 or greater acute toxicity (photon IMRT, 68% vs. proton IMRT, 67%; P =0.96)	high; N/A; imprecise	insufficient
Proton IMRT vs. photon IMRT	Acute hematologic toxicity	NRSI: k=1 (208); Mohiuddin, 2021 (34646965)[20]	Inconclusive. No significant difference between treatment groups in grade 3 or higher acute hematologic toxicity (photon IMRT, 47% vs. proton IMRT, 55%; P =0.29)	high; N/A; imprecise	insufficient

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
Proton IMRT vs. photon IMRT	Acute grade 3 or higher dermatologic toxicity	NRSI: k=1 (208); Mohiuddin, 2021 (34646965)[20]	Inconclusive. No significant difference between treatment groups in grade 3 or higher acute hematologic toxicity (photon IMRT, 29% vs. proton IMRT, 21%; P =0.24)	high; N/A; imprecise	insufficient
Proton IMRT vs. photon IMRT	Acute grade 3 or higher gastrointestinal toxicity	NRSI: k=1 (208); Mohiuddin, 2021 (34646965)[20]	Inconclusive. No significant difference between treatment groups in grade 3 or higher acute hematologic toxicity (photon IMRT, 20% vs. proton IMRT, 22%; P =0.70)	high; N/A; imprecise	insufficient
Proton IMRT vs. photon IMRT	Acute grade 3 or higher genitourinary toxicity	NRSI: k=1 (208); Mohiuddin, 2021 (34646965)[20]	Inconclusive. No significant difference between treatment groups in grade 3 or higher acute hematologic toxicity (photon IMRT, 1% vs. proton IMRT, 2%; P =0.50)	high; N/A; imprecise	insufficient
Proton IMRT vs. photon IMRT	Overall grade 3 or higher late toxicity	NRSI: k=1 (208); Mohiuddin, 2021 (34646965)[20]	Inconclusive. No significant difference between treatment groups in overall grade 3 or greater acute toxicity (photon IMRT, 3.5% vs. proton IMRT, 1.8%; P =0.88).	high; N/A; imprecise	insufficient
Proton IMRT vs. photon IMRT	Late grade 3 or higher dermatologic toxicity	NRSI: k=1 (208); Mohiuddin, 2021 (34646965)[20]	Inconclusive. No significant difference between treatment groups in overall grade 3 or greater acute toxicity (photon IMRT, 0% vs. proton IMRT, 0%).	high; N/A; imprecise	insufficient

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
Proton IMRT vs. photon IMRT	Late grade 3 or higher gastrointestinal toxicity	NRSI: k=1 (208); Mohiuddin, 2021 (34646965)[20]	Inconclusive. No significant difference between treatment groups in overall grade 3 or greater acute toxicity (photon IMRT, 2.1% vs. proton IMRT, 0%).	high; N/A; imprecise	insufficient
Proton IMRT vs. photon IMRT	Late grade 3 or higher genitourinary toxicity	NRSI: k=1 (208); Mohiuddin, 2021 (34646965)[20]	Inconclusive. No significant difference between treatment groups in overall grade 3 or greater acute toxicity (photon IMRT, 0% vs. proton IMRT, 1.8%).	high; N/A; imprecise	insufficient
EBRT vs. Bct	5 yr overall survival	NRSI: k=2 (391); Hannoun-Levi, 2011 (20619552)[22]; Moureau-Zabotto, 2013 (23195780)[23]	Inconclusive. No significant of a difference between EBRT and Bct. One study reported a rate of 80% for EBRT vs 78% for Bct, p=0.47. One study reported a rate of 73% for EBRT vs 76% for Bct, p=0.50.	high; consistent; precise	insufficient
EBRT vs. Bct	5 yr colostomy-free survival	NRSI: k=2 (391); Hannoun-Levi, 2011 (20619552)[22]; Moureau-Zabotto, 2013 (23195780)[23]	Inconclusive. No significant difference between EBRT and Bct. One study reported an HR of 0.66 for Bct (95% CI, 0.38 - 1.15, ref-EBRT). One study reported a rate of 69% for EBRT vs 74% for Bct, p=0.30.	high; consistent; imprecise	insufficient

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
EBRT vs. Bct	5 yr local control	NRSI: k=2 (391); Hannoun-Levi, 2011 (20619552)[22]; Moureau-Zabotto, 2013 (23195780)[23]	Inconclusive. No significant difference between EBRT and Bct. One study reported a rate of 12% for Bct vs 33% for EBRT, and an adjusted HR of 0.62 favoring Bct (95% CI, 0.41 - 0.92). One study reported an HR of 2.14 favoring Bct (95% CI, 0.74 - 6.19).	high; inconsistent; imprecise	insufficient
EBRT vs. Bct	Overall survival	NRSI: k=1 (424); Glynne-Jones, 2011 (20934265)[21]	Inconclusive. No significant difference between EBRT and Bct. HR of 1.14 for Bct (99% CI, 0.81 - 1.62) over a median follow-up of 13.1 years	high; N/A; imprecise	insufficient
EBRT vs. Bct	Disease-specific survival	NRSI: k=1 (424); Glynne-Jones, 2011 (20934265)[21]	Inconclusive. No significant difference between EBRT and Bct. HR of 1.16 for Bct (99% CI, 0.70 - 1.93) over a median follow-up of 13.1 years	high; N/A; imprecise	insufficient
EBRT vs. Bct	Locoregional control	NRSI: k=1 (424); Glynne-Jones, 2011 (20934265)[21]	Inconclusive. No significant difference between EBRT and Bct. HR of 1.43 for Bct (99% CI, 0.89 - 2.28) over a median follow-up of 13.1 years	high; N/A; imprecise	insufficient
EBRT vs. Bct	Relapse-free survival	NRSI: k=1 (424); Glynne-Jones, 2011 (20934265)[21]	Inconclusive. No significant difference between EBRT and Bct. HR of 1.26 for Bct (99% CI, 0.91 - 1.75) over a median follow-up of 13.1 years	high; N/A; imprecise	insufficient

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
EBRT vs. Bct	Late ulcers/ radionecrosis	NRSI: k=1 (424); Glynne-Jones, 2011 (20934265)[21]	Inconclusive. Significantly greater with Bct (14%) compared to EBRT (6%, p=0.003).	high; N/A; imprecise	insufficient

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; HIV- human immunodeficiency virus; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; CRT- chemoradiation; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; EBRT- external beam RT; Bct- brachytherapy; NR- not reported; SOE- strength of evidence; NSD- no significant difference.

Table C.6.3. Strength of evidence for Key Question 3

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
Standard boost (15 Gy) vs. high-dose boost (20-25 Gy)	Colostomy-free survival	RCT: 1 trial, k=1 (283); Peiffert, 2012 (22529257)[24]	Inconclusive. No difference. Standard boost, 73.7% (95% CI, 65.5 - 80.5) vs. high-dose boost, 77.8% (95% CI, 70.1 - 84.0)	high; N/A; imprecise	insufficient
Standard boost (15 Gy) vs. high-dose boost (20-25 Gy)	Overall survival	RCT: 1 trial, k=1 (283); Peiffert, 2012 (22529257)[24]	Inconclusive. No difference. Standard boost, 71% v high-dose boost, 74% (p=0.43)	high; N/A; imprecise	insufficient
Standard boost (15 Gy) vs. high-dose boost (20-25 Gy)	Disease-specific survival	RCT: 1 trial, k=1 (283); Peiffert, 2012 (22529257)[24]	Inconclusive. No difference. Standard boost, 78.6% (95% CI, 70.7 - 84.9) vs. high-dose boost, 82.7% (95% CI, 75.4 - 88.2)	high; N/A; imprecise	insufficient
Standard boost (15 Gy) vs. high-dose boost (20-25 Gy)	Local control	RCT: 1 trial, k=1 (283); Peiffert, 2012 (22529257)[24]	Inconclusive. No difference. Standard boost, 78.2% (95% CI, 70.6 - 84.4) vs. high-dose boost, 83.1% (95% CI, 75.8 - 88.5)	high; N/A; imprecise	insufficient

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
Standard boost (15 Gy) vs. high-dose boost (20-25 Gy)	Disease-free survival	RCT: 1 trial, k=1 (283); Peiffert, 2012 (22529257)[24]	Inconclusive. No difference. Standard boost, 67.5% (95% CI, 58.7 - 75.1) vs. high-dose boost, 70.6% (95% CI, 62.5 - 77.6)	high; N/A; imprecise	insufficient
Standard boost (15 Gy) vs. high-dose boost (20-25 Gy)	QLQ-C30 (Quality of Life Questionnaire)	RCT: 1 trial, k=1 (119); Tournier-Rangeard, 2008 (18191265)[25]	Inconclusive. No comparable differences but numerical values not reported.	high; N/A; imprecise	insufficient
Standard boost (15 Gy) vs. high-dose boost (20-25 Gy)	Anal Sphincter-Conservative Treatment (AS-CT) questionnaire	RCT: 1 trial, k=1 (119); Tournier-Rangeard, 2008 (18191265)[25]	Inconclusive. No comparable differences but numerical values not reported.	high; N/A; imprecise	insufficient
Dose, 45-54Gy vs. >54Gy	Overall survival (up to 5 yrs follow-up)	NRSI: k=1 (7792); Wegner, 2019 (31136369)[26]	Inconclusive. HR of 1.10 favoring 45-54 Gy (95% CI, 1.01 - 1.20)	high; N/A; precise	insufficient
Radiation therapy regimens **group 1) 50.40Gy, 38-42 days (reference group)** **group 2) ≤40Gy** **group 3) >40Gy to <48.60Gy** **group 4) 50.40Gy, <38 days** **group 5) 50.40Gy, >42 days** **group 6) >52.20Gy**	Overall survival	NRSI: k=1 (930); Glynne-Jones, 2020 (32619648)[27]	Inconclusive. No difference between groups 4 and 6 vs group 1; greater mortality in groups 5, 3, and 2 vs. group 1. HR (95% CI): (group 1) reference group; (group 2) 8.24 (3.35 to 20.27); (group 3) 3.12 (1.73 to 5.63); (group 4) 0.95 (0.42 to 2.16); (group 5) 1.72 (1.17 to 2.54); (group 6) 1.57 (0.58 to 4.25)	high; N/A; imprecise	insufficient

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
Radiation therapy regimens 1) 50.40Gy, 38-42 days (reference group) 2) ≤40Gy 3) >40Gy to <48.60Gy 4) 50.40Gy, <38 days 5) 50.40Gy, >42 days 6) >52.20Gy	Progression-free survival	NRSI: k=1 (930); Glynne-Jones, 2020 (32619648)[27]	Inconclusive. No difference between groups 4 vs 1; greater mortality in groups 5, 3 and 2 vs. group 1. HR (95% CI): (group 1) reference group; (group 2) 5.43 (2.24 to 13.21); (group 3) 2.12 (1.21 to 3.72); (group 4) 1.00 (0.51 to 1.95); (group 5) 1.57 (1.11 to 2.21); (group 6) 1.60 (0.71 to 3.59)	high; N/A; imprecise	insufficient
≤4.72 fractions/week v >4.72 fractions/week	Overall survival	NRSI: k=1 (6429); Mehta, 2020 (32399269)[30]	Inconclusive. HR of 0.70 favoring >4.72 fractions/week (95% CI, 0.63 - 0.79)	high; N/A; precise	insufficient

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; HIV- human immunodeficiency virus; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; CRT- chemoradiation; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; EBRT- external beam RT; Bct- brachytherapy; NR- not reported; SOE- strength of evidence; NSD- no significant difference.

Table C.6.4. Strength of evidence for Key Question 4

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
1 vs 2 cycles MMC	Overall survival	NRSI: k=1 (217); White, 2015 (26347494)[31]	Inconclusive. No significant difference. An HR of 0.67 for 2 cycles (95% CI, 0.25 - 1.83), p=0.43	high; N/A; imprecise	insufficient
1 vs 2 cycles MMC	Disease-specific survival	NRSI: k=1 (217); White, 2015 (26347494)[31]	Inconclusive. No significant difference. An HR of 0.85 for 2 cycles (95% CI, 0.37 - 1.92), p=0.69	high; N/A; imprecise	insufficient

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
1 vs 2 cycles MMC	Colostomy-free survival	NRSI: k=1 (217); White, 2015 (26347494)[31]	Inconclusive. No significant difference. An HR of 0.91 for 2 cycles (95% CI, 0.31 - 2.67), p=0.86	high; N/A; imprecise	insufficient
1 vs 2 cycles MMC	Progression-free survival	NRSI: k=1 (217); White, 2015 (26347494)[31]	Inconclusive. No significant difference. An HR of 0.32 for 2 cycles (95% CI, 0.07 - 1.42), p=0.13	high; N/A; imprecise	insufficient
1 vs 2 cycles MMC	Overall acute grade 3+ toxicity	NRSI: k=1 (217); White, 2015 (26347494)[31]	Inconclusive. No significant difference. Frequency of 42% with 1 cycle versus 41% with 2 cycles.	high; N/A; imprecise	insufficient
1 vs 2 cycles MMC	Overall late grade 3+ toxicity	NRSI: k=1 (217); White, 2015 (26347494)[31]	Inconclusive. No significant difference. Frequency of 7% with 1 cycle versus 5% with 2 cycles (p=0.76).	high; N/A; imprecise	insufficient
Boost v no boost	Overall survival	NRSI: k=1 (577); Glynne-Jones, 2011 (20934265)[21]	Inconclusive. No significant difference. HR of 0.74 for radiation boost (99% CI, 0.48 - 1.15)	high; N/A; imprecise	insufficient
Boost v no boost	Disease-specific survival	NRSI: k=1 (577); Glynne-Jones, 2011 (20934265)[21]	Inconclusive. No significant difference. HR of 0.62 for radiation boost (99% CI, 0.35 - 1.12)	high; N/A; imprecise	insufficient
Boost v no boost	Locoregional control	NRSI: k=1 (577); Glynne-Jones, 2011 (20934265)[21]	Inconclusive. No significant difference. HR for 0.90 favoring a radiation boost (99% CI, 0.48 - 1.68)	high; N/A; imprecise	insufficient
Boost v no boost	Relapse-free survival	NRSI: k=1 (577); Glynne-Jones, 2011 (20934265)[21]	Inconclusive. No significant difference. HR of 0.80 for radiation boost (99% CI, 0.52 - 1.22)	high; N/A; imprecise	insufficient

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
Boost v no boost	Late anorectal ulceration/ radionecrosis	NRSI: k=1 (577); Glynne-Jones, 2011 (20934265)[21]	Inconclusive. Significantly greater frequency with boost (8%) vs. no boost (0%, p=0.03)	high; N/A; precise	insufficient
Induction chemo vs. none	Colostomy-free survival	RCT: 1 trial, k=1 (283); Peiffert, 2012 (22529257)[24]	Inconclusive. No difference between induction vs. no induction therapy, the survival rates being 76.5% for induction (95% CI, 68.6 - 83.0) vs. 75.0% for no induction chemotherapy (95% CI, 67.0 - 81.5)	high; N/A; precise	insufficient
Induction chemo vs. none	Colostomy-free survival	RCT: 1 trial, k=1 (283); Peiffert, 2012 (22529257)[24]	Inconclusive. No difference between induction vs. no induction therapy, the survival rates being 76.5% for induction (95% CI, 68.6 - 83.0) vs. 75.0% for no induction chemotherapy (95% CI, 67.0 - 81.5)	high; N/A; precise	insufficient
Induction chemo vs. none	Disease-specific survival	RCT: 1 trial, k=1 (283); Peiffert, 2012 (22529257)[24]	Inconclusive. No difference between induction vs. no induction therapy, the rates being 83.0% (95% CI, 75.8 - 88.4) for induction vs. 78.5% (95% CI, 70.5 - 84.7) for no induction chemotherapy	high; N/A; imprecise	insufficient
Induction chemo vs. none	Local control	RCT: 1 trial, k=1 (283); Peiffert, 2012 (22529257)[24]	Inconclusive. No difference between induction vs. no induction therapy, the rates being 80.3% (95% CI, 72.8 - 86.1) for induction vs. 81.0% (95% CI, 73.5 - 86.8) for no induction chemotherapy	high; N/A; precise	insufficient

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
Induction chemo vs. none	Disease-free survival	RCT: 1 trial, k=1 (283); Peiffert, 2012 (22529257)[24]	Inconclusive. No difference between induction vs. no induction therapy, the rates being 71.5% (95% CI, 63.4 - 78.5) for induction vs. 64.8% (95% CI, 56.6 - 72.2) for no induction chemotherapy	high; N/A; imprecise	insufficient
Induction chemo vs. none	QLQ-C30 (Quality of Life Questionnaire)	RCT: 1 trial, k=1 (119); Tournier-Rangeard, 2008 (18191265)[25]	Inconclusive. No comparable differences but numerical values not reported.	high; N/A; imprecise	insufficient
Induction chemo vs. none	Anal Sphincter-Conservative Treatment (AS-CT) questionnaire	RCT: 1 trial, k=1 (119); Tournier-Rangeard, 2008 (18191265)[25]	Inconclusive. No comparable differences but numerical values not reported.	high; N/A; imprecise	insufficient
Induction chemo vs. none	Acute grade 3+ hematologic toxicity	RCT: 1 trial, k=1 (283); Peiffert, 2012 (22529257)[24]	Inconclusive. Significantly greater toxicity with induction chemotherapy, with a frequency of 29.3% for induction vs. 12.1% for no induction chemotherapy ($p<0.001$).	high; N/A; imprecise	insufficient
Maintenance chemo vs. none	Progression-free survival	RCT: 1 trial, k=1 (940); James, 2013 (23578724)[14]	Inconclusive. No difference between maintenance vs. no maintenance therapy, the rate being 74% for maintenance (95% CI 69–77) vs. 73% for no maintenance (95% CI 68–77)	high; N/A; precise	insufficient
Maintenance chemo vs. none	Overall survival	RCT: 1 trial, k=1 (940); James, 2013 (23578724)[14]	Inconclusive. No difference between maintenance vs. no maintenance therapy, 3-year rates were 82% MMC/Maint, 86% MMC/No-maint, 83% CisP/Maint, and 84% CisP/No-Maint	high; N/A; precise	insufficient

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
Maintenance chemo vs. none	Colostomy-free survival	RCT: 1 trial, k=1 (940); James, 2013 (23578724)[14]	Inconclusive. No difference between maintenance vs. no maintenance therapy by 3 years, the 3-year rates being 73% MMC/ maintenance , 75% Cisplatin/ maintenance , 75% MMC/ no maintenance , 72% Cisplatin/ no maintenance.	high; N/A; precise	insufficient
Maintenance chemo vs. none	Disease-specific survival	RCT: 1 trial, k=1 (940); James, 2013 (23578724)[14]	Inconclusive. No difference between maintenance vs. no maintenance therapy by 3 years, the 3-year rates being 87% MMC/ maintenance , 86% Cisplatin/ maintenance , 88% MMC/ no maintenance , 87% Cisplatin/ no maintenance.	high; N/A; precise	insufficient

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; HIV- human immunodeficiency virus; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; CRT- chemoradiation; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; EBRT- external beam RT; Bct- brachytherapy; NR- not reported; SOE- strength of evidence; NSD- no significant difference.

Table C.6.5. Strength of evidence for Key Question 6

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
MFrequency: within 1yr vs. within 2 yrs vs. year 3 to 5	Total event rate	NRSI: k=1 (138); Frazer, 2020 (32028341)[32]	Inconclusive. Frequency: within 1yr- 62% vs. within 2 yrs- 79% vs. year 3 to 5- 17%	high; N/A; imprecise	insufficient
	Late grade 3+ toxicity rate	NRSI: k=1 (138); Frazer, 2020 (32028341)[32]	Inconclusive. Frequency: within 1yr- 44% vs. within 2 yrs- 89% vs. year 3 to 5- 0%	high; N/A; imprecise	insufficient
	Local recurrence rate	NRSI: k=1 (138); Frazer, 2020 (32028341)[32]	Inconclusive. Frequency: within 1yr- 78% vs. within 2 yrs- 89% vs. year 3 to 5- 11%	high; N/A; imprecise	insufficient

Comparison	Outcome	Number of Studies (Patients) Author, Year (PMID)	Conclusion Summary of Findings From Individual Studies	Study Limitations; Consistency; Precision	SOE
	Distant metastasis rate	NRSI: k=1 (138); Frazer, 2020 (32028341)[32]	Inconclusive. Frequency: within 1yr- 64% vs. within 2 yrs- 64% vs. year 3 to 5- 36%	high; N/A; imprecise	insufficient

Abbreviations: RCT- randomized controlled trials; NRSI- nonrandomized study of interventions; HIV- human immunodeficiency virus; Chemo- chemotherapy; 5FU- 5 fluorouracil; MMC- mitomycin C; RT- radiation therapy; CRT- chemoradiation; IMRT- intensity modulated RT; IMPT- intensity modulated RT with proton beam; 3D CRT- three dimensional conformal RT; EBRT- external beam RT; Bct- brachytherapy; NR- not reported; SOE- strength of evidence; NSD- no significant difference.

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Appendix D. List of Unpublished Randomized Controlled Trials

Table D.1. List of unpublished randomized controlled trials

Clinical Trial Identifier	Study Name	Status as of October 31, 2023	Availability of Results	Population	Comparison
NCT04462042	Proton Versus Photon Therapy in Anal Squamous Cell Carcinoma - Swedish Anal Carcinoma Study	Recruiting	No	Non-metastatic anal squamous cell cancer	Conventional photon radiotherapy vs IMPT
NCT05374252	A Phase 3, Multicenter, Double-Blind Randomized Study of Mitomycin, 5-Fluorouracil and IMRT Combined With or Without Anti-PD-1 in Patients With Locally Advanced Anal Canal Squamous Carcinoma	Recruiting	No	Stage III squamous cell anal cancer	IMRT + 5FU + MMC + sintilimab (PD-1 antibody) vs IMRT + 5FU + MMC
NCT04230759	Radiochemotherapy +/- Durvalumab for Locally-advanced Anal Carcinoma. A Multicenter, Randomized, Phase II Trial of the German Anal Cancer Study Group (RADIANCE)	Active, no longer recruiting.	No	Non-metastatic anal squamous cell cancer	RT + 5FU + MMC + durvalumab vs RT + 5FU + MMC
ISRCTN88455282	PLATO - PersonaLising Anal cancer radioTherapy dOse - Incorporating Anal Cancer Trials (ACT) ACT3, ACT4 and ACT5	Active, no longer recruiting.	No	Non-metastatic anal squamous cell cancer	ACT3 appears single-arm examining whether local excision is sufficient for early-stage tumors. ACT4 - 50.4Gy in 28 fractions v 41.4Gy in 23 fractions. ACT5 - 53.2Gy in 28 fractions v 58.8Gy in 28 fractions v 61.6Gy in 28 fractions
NCT05572801	NOAC9 - A Phase II Randomised Nordic Anal Cancer Group Study on Circulating Tumor DNA Guided Follow-Up	Not yet recruiting	No	Non-metastatic anal squamous cell cancer	Standard follow-up vs follow-up including ctDNA

Clinical Trial Identifier	Study Name	Status as of October 31, 2023	Availability of Results	Population	Comparison
NCT03233711	Nivolumab After Combined Modality Therapy in Treating Patients With High Risk Stage II-IIIB Anal Cancer	Active, no longer recruiting.	No	High Risk Stage II-III nonmetastatic squamous cell anal cancer	Nivolumab + CRT versus CRT alone
NCT04166318	Lower-Dose Chemoradiation in Treating Patients With Early-Stage Anal Cancer, the DECREASE Study	Recruiting	No	Early stage nonmetastatic squamous cell anal cancer	De-intensified vs standard dose CRT (using IMRT)

Abbreviations: RCT- randomized controlled trial; 5FU- 5 fluorouracil; MMC- mitomycin C; anti-PD-1- checkpoint inhibitor immunotherapy; RT- radiation therapy; vs.- versus; IMPT- intensity modulated ration therapy with proton beam; IMRT- intensity modulated ration therapy; HT- helical tomotherapy; VMAT- Volumetric modulated arc therapy; ctDNA- cytotoxic tumor deoxyribonucleic acid.

Appendix E. PCORI Methodology Standards Checklist

Standard Category	Abbrev.	Standard	Is This Standard Applicable to This SR?	List Sections and Pages of the SR Report Where You Address This Standard	If Applicable, Describe How and Why the SR Deviated From This Standard?
Standards for Formulating Research Questions	RQ-1	Identify gaps in evidence.	Yes	Introduction; Pages 1 and 2	N/A
	RQ-2	Develop a formal study protocol.	Yes	Methods; Page 3	N/A
	RQ-3	Identify specific populations and health decision(s) affected by the research.	Yes	Table 2 and Methods; Page 3	N/A
	RQ-4	Identify and assess participant subgroups.	Yes	Methods; Page 3	N/A
	RQ-5	Select appropriate interventions and comparators.	Yes	Table 2; Pages 4 and 5	N/A
	RQ-6	Measure outcomes that people representing the population of interest notice and care about.	Yes	Table 2; Pages 4 and 5	N/A
Standards Associated with Patient-Centeredness	PC-1	Engage people representing the population of interest and other relevant stakeholders in ways that are appropriate and necessary in a given research context.	Yes	Pages vi and vii	N/A
	PC-2	Identify, select, recruit, and retain study participants representative of the spectrum of the population of interest and ensure that data are collected thoroughly and systematically from all study participants.	N/A	N/A	N/A
	PC-3	Use patient-reported outcomes when patients or people at risk of a condition are the best source of information for outcomes of interest.	Yes	Table 2	N/A
	PC-4	Support dissemination and implementation of study results.	Yes	Page 2	N/A
Standards for Data Integrity and Rigorous Analyses	IR-1	A priori, specify plans for quantitative data analysis that correspond to major aims.	Yes	Page 3	N/A
	IR-2	Assess data source adequacy.	N/A	N/A	N/A
	IR-3	Describe data linkage plans, if applicable.	N/A	N/A	N/A
	IR-4	Document validated scales and tests.	N/A	N/A	N/A
	IR-5	Provide sufficient information in reports to allow for assessments of the study's internal and external validity.	Yes	Methods section; Pages 3-7	N/A
	IR-6	Masking should be used when feasible.	Yes	Methods section; Pages 3-7	N/A

Standard Category	Abbrev.	Standard	Is This Standard Applicable to This SR?	List Sections and Pages of the SR Report Where You Address This Standard	If Applicable, Describe How and Why the SR Deviated From This Standard?
	IR-7	In the study protocol, specify a data management plan that addresses, at a minimum, the following elements: collecting data, organizing data, handling data, describing data, preserving data, and sharing data.	Yes	Methods section; Pages 3-7	N/A
Standards for Preventing and Handling Missing Data	MD-1	Describe methods to prevent and monitor missing data.	N/A	N/A	N/A
	MD-2	Use valid statistical methods to deal with missing data that properly account for statistical uncertainty due to missingness.	N/A	N/A	N/A
	MD-3	Record and report all reasons for dropout and missing data, and account for all patients in reports.	N/A	N/A	N/A
	MD-4	Examine sensitivity of inferences to missing data methods and assumptions, and incorporate into interpretation.	N/A	N/A	N/A
Standards for Heterogeneity of Treatment Effect (HTE)	HT-1	State the goals of HTE analyses, including hypotheses and the supporting evidence base.	Yes	Methods and Discussion sections; Pages 3, 6, 39, and 40	N/A
	HT-2	For all HTE analyses, provide an analysis plan, including the use of appropriate statistical methods.	N/A	N/A	N/A
	HT-3	Report all prespecified HTE analyses and, at minimum, the number of post-hoc HTE analyses, including all subgroups and outcomes analyzed.	N/A	N/A	N/A
Standards for Systematic Reviews	SR-1	Adhere to National Academy of Medicine (NAM) standards for systematic reviews of comparative effectiveness research, as appropriate.	Yes	Methods section; Page 3	N/A

Abbreviations: Abbrev. = Abbreviation; SR = systematic review; RQ = research question; PC = patient centeredness; N/A = not applicable; IR = integrity and rigor; MD = missing data; HT = heterogeneity of treatment;