Evidence-based Practice Center Systematic Review Protocol

Project Title: *Treatment of Stage I-III Squamous Cell Anal Cancer*

Publication Date: August 18, 2023

Amendment Date: September 26, 2023

(Amendments Details–see Section VI)

## I.      Background

Although anal cancer only represents1-2 percent of all gastrointestinal malignancies, incidence has risen steadily by 2-3 percent a year over the past decade.[1] Squamous cell carcinoma (SCC) is by far the most common type, accounting for over 90 percent of anal malignancies,[2-4] and risk factors include female gender, Black race, and men who have sex with men (MSM).[2,5] A well-defined relationship also exists between human papilloma virus (HPV) and squamous cell carcinoma of the anus, particularly HPV serotypes 16 and 18.[2] Given the association with HPV, much effort has been put toward prevention through screening and vaccination, but results of these initiatives are not yet clear. Treatment of SCC of the anal canal includes chemotherapy, radiation, and/or surgical intervention. Depending on the initial staging, treatment may yield a five-year survival up to 89 percent.[6]

Treatment, survival, and quality of life vary with stage of disease and tumor location. Table 1 reports SCC staging, which is based on tumor size/extent.[4,7] Anal SCCs are further classified into tumors of the anal margin, involving the perianal skin within 5 cm of the anal verge, and those of the anal canal, located between the anal verge and the dentate line.[2,4]

**Table 1. Anal cancer staging based on the version 9 edition of the American Joint Committee on Cancer staging system for anal cancer.**

| 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), N0-1 (tumor invading perirectal, inguinal, internal iliac, or obturator nodes, and/or external iliac nodes), 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), M0 |
| IV | Distant metastases (M1) |

**Abbreviations:** N0= There is no cancer in nearby lymph nodes; M0= Cancer has not spread to other parts of the body.

The National Comprehensive Cancer Network guidelines recommend chemoradiation as first line treatment for stage I-III tumors.[8] The standard radiation protocol generally follows a 30-45 Gy dose delivered over a 3.5-5 week period with a boost of an additional 5-24 Gy for most situations.[8] The chemotherapeutic agents are typically fluorouracil (5-FU), 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 Mitomycin-C (MMC), administered as a bolus on days 1 and 29.[8] These regimens present significant toxicity, which has led to increasing interest in alternative treatments to balance benefits and harms.[9-12] Indeed, standard treatment is so difficult to tolerate that up to 55 percent of patients utilize treatment breaks.[6] Ultimately, the toxicity of chemotherapy, radiation, and extended surgical resections lower adherence to prescribed protocols and potentially reduce their effectiveness.[6,13,14]

Less toxic protocols include local excision alone, 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. So, dose escalation remains a topic of investigation in patients with more advanced disease.[6] Therefore, a rigorous comparative effectiveness evaluation is needed for these emerging therapies and de-escalation strategies to identify the optimal management strategy that reduces toxicity without compromising long-term oncologic outcomes and to provide patients with the best information to support improved chances of survival and a better quality of life. A systematic review will assist clinicians, patients, and other stakeholders to make informed decisions about screening, evaluation, and treatment.

**Purpose of this review**

This systematic review will assess the effectiveness and harms of treatment for stages I-III squamous cell anal cancer. This review, funded by the Patient-Centered Outcomes Research Institute, will be used by the American Society of Clinical Oncology (ASCO) and the American Society of Radiation Oncology (ASTRO) to update clinical practice guidelines.

## II.     The Key Questions (KQs)

The KQs were posted online for public comments during the pre-award phase and comments were received between Feb 15, 2023 and March 1, 2023. Twelve individuals commented on the KQs. Regarding KQ1, commenters reported that there were no clear dilemmas and chemoradiation is the accepted standard of care. Regarding KQ2, commenters suggested adding radiation volumes and modalities. One commenter also noted the paucity of randomized controlled trials (RCTs) and probable reliance on poor quality retrospective data for synthesis. Regarding KQ3, several commenters noted the paucity of any credible data, especially for photon versus proton therapy, and some suggested merging this with KQ2. Regarding KQ4, some commenters suggested adding radiation therapy for dose de-escalation and one commenter suggested discussing treatment timing in addition to types of chemotherapy. Several commenters noted lack of completed RCTs or other credible evidence for effectiveness and harms of immunotherapy and suggested removing this question (KQ5). Multiple commenters suggested including a separate KQ regarding the frequency and type of surveillance program recommended. Multiple commenters, knowing that the current project is restricted to the treatment of anal canal, suggested also including treatment of anal margin in this systematic review. Some commenters also suggested explicitly discussing treatment considerations for HIV infected individuals as a special population of interest, especially for KQ4.

Based on public comments, we added anal margin to the scope of this systematic review, treatment volumes to KQ2, radiation therapy to KQ4, and a new KQ for effectiveness and harms of different frequencies and modalities for post-treatment surveillance strategies (KQ6). Additionally, for all KQ, we added that we will evaluate whether outcomes differ by patient characteristics such as age, sex, immunocompromised status, or other characteristics associated with health inequities (such as race/ethnicity).

**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 post-treatment 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)?

Please see Table 1 for PICOTS.

### III. Methods

#### A. Criteria for Inclusion/Exclusion of Studies in the Review

Studies will be included in the review based on the PICOTS framework and the study-specific inclusion criteria described in Table 1.

**Table 1. Population, Intervention, Comparator, Outcome, Timing, Setting/Study Design (PICOTS)**

| | Inclusion | Exclusion |
|---|---|---|
| **Population** | | |
| All KQ | Adults with stages I-III squamous cell anal cancer (anal canal and anal margin)<br><br>Patient characteristics such as age, sex, immunocompromised status, or other characteristics associated with health inequities (such as race/ethnicity) | Adults with:<br><br>• Stage IV anal cancer<br>• Lower rectal cancer that has spread to the anal canal<br>• Non-squamous 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**

| KQ1 | Alone or in combination as neoadjuvant/adjuvant or as induction/maintenance:<br><br>• Surgery, radiation therapy, or chemotherapy | • Reconstructive surgery<br>• Palliative therapy (includes chemotherapy with palliative intent)<br>• Treatment for premalignant lesions |
|---|---|---|
| KQ2 | Different modalities of radiation therapy such as, but not limited to, IMRT, proton radiation therapy, and Brachytherapy boost. | • Palliative therapy |
| KQ3 | Radiation therapy; varying:<br><br>• Doses<br>• Target (primary and nodal) volumes<br>• Fractionation schema | • Palliative therapy |
| KQ4 | • Chemotherapy and radiation therapy combinations (e.g., 5-Fluorouracil, Mitomycin-C, Cisplatin)<br>• Variations in dose of:<br>    ○ Radiation therapy<br>    ○ Chemotherapy | • Palliative therapy |
| KQ5 | Immunotherapy (e.g., pembrolizumab, nivolumab) | |

| KQ6 | Post-treatment surveillance strategies:<br><br>• Frequency<br>• Modalities (e.g., MRI, PET scans, biopsy, DRE, anoscopy, flexible sigmoidoscopy) | • Screening for primary prevention<br>• Initial staging<br>• Strategies for surveillance post non-initial treatment |
|---|---|---|
| **Comparison** | | |
| KQ1 | Alone or in combination as neoadjuvant/adjuvant or as induction/maintenance:<br><br>• Surgery, radiation therapy, or chemotherapy | • Reconstructive surgery<br>• Palliative therapy (includes chemotherapy with palliative intent)<br>• Treatment for premalignant lesions |
| KQ2 | Comparators for different modalities of radiation therapy such as, but not limited to, 3-D CRT, photon or electron radiation therapy, and external beam radiation therapy boost. | • Palliative therapy |
| KQ3 | Radiation therapy; varying:<br><br>• Doses<br>• Target (primary and nodal) volumes<br>• Fractionation schema | • Palliative therapy |
| KQ4 | • Chemotherapy and radiation therapy combinations (e.g., 5-Fluorouracil, Mitomycin-C, Cisplatin)<br>• Variations in dose<br>　○ Radiation therapy<br>　○ Chemotherapy | • Palliative therapy |

| | | |
|---|---|---|
| KQ5: | Other treatment (e.g., chemotherapy, radiation therapy, chemotherapy + radiation therapy) | |
| KQ6 | Post-treatment surveillance strategies:<br><br>• Frequency<br>• Modalities (e.g., MRI, PET scans, biopsy, DRE, anoscopy, flexible sigmoidoscopy) | • Screening for primary prevention<br>• Initial staging<br>• Strategies for surveillance post non-initial treatment |
| **Outcomes** | | |
| All KQ | • Overall survival<br><br>• Disease specific survival<br><br>• Disease-free survival (including persistence, recurrence, or relapse)<br><br>• Colostomy-free survival<br><br>• Local control<br><br>• Complete clinical response<br><br>• Salvage rate<br><br>• Sphincter preservation<br><br>• Health-related quality of life<br><br>• Treatment breaks (frequency or duration), treatment discontinuation, interruptions, or median treatment days.<br><br>• Bleeding per rectum | |

| | | |
|---|---|---|
| | • Functional outcomes (e.g., fecal or urinary incontinence, erectile dysfunction, sexual dysfunction, use of vaginal dilators)<br><br>• 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) | |
| **Timing** | | |
| All KQ | No restrictions on duration of treatments or follow-up | |
| **Setting** | | |
| All KQ | Cancer care settings | |
| **Study design** | | |
| All KQ | Randomized controlled trials, non-randomized 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), non-randomized studies with unspecified or poorly defined intervention/treatment protocol (e.g., lack of names of chemotherapy agents used), non-randomized studies with |

| | analytic techniques that don't allow drawing causal inferences. |
|---|---|

**Abbreviations**: 3-D CRT= 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; RCT=randomized controlled trial; VMAT= Volumetric modulated arc therapy.

## B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

We will search for peer-reviewed literature in the following databases: MEDLINE and Embase (via Ovid), and Cochrane Central Register of Controlled Trials (Wiley). The searches will include controlled vocabulary terms (e.g., MeSH), along with free-text words, related to anal cancer. The publication dates are limited from 2000 to the current date and restricted to English language. All searches will be updated during the public comment period. The proposed search strategy for Medline (via Ovid) is included in Appendix A and will be submitted for librarian peer review.

The reference lists of relevant existing systematic reviews and included studies will be scanned for additional eligible studies. Additional articles suggested to us from any source, including peer and public review, will be screened applying identical eligibility criteria.

To improve efficiency and accuracy in the screening process and management of the process, we will upload all search results to a web-based screening tool, PICO Portal^TM (www.picoportal.net). PICO Portal uses machine learning to sort and present first those citations most likely to be eligible. Initially, two team members will independently screen titles and abstracts of results. Then, as the machine learning system is trained, we will move to one screener when we reach a 90 percent recall rate of citations eligible for full-text screen, and then not screen citations remaining past a 95 percent recall rate of citations eligible for full-text screen. Screening will be conducted by two members independently at the full-text level using the same online system.

We will search 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 may help address the key questions in the future. We will update searches while the draft report is under public/peer review.

A Supplemental Evidence And Data for Systematic review (SEADS) portal will be available and a Federal Register Notice will be posted for this review.

### C. Data Abstraction and Data Management

Data fields to be extracted include author, year of publication, sponsorship, setting, subject inclusion and exclusion criteria, intervention and control characteristics, sample size, followup duration, participant baseline age, race/ethnicity, clinical characteristics including cancer stage and outcome timing, and results of outcomes and adverse effects. One investigator will extract data into standardized extraction forms in Microsoft Excel, and a second investigator will review and verifiy for accuracy.

### D. Assessment of Methodological Risk of Bias of Individual Studies

We will assess risk of bias of eligible studies by outcome using the Cochrane Risk of Bias Tool 2.0 for RCTs and the ROBINS-I for observational studies.[15,16]

One investigator will independently assess the risk of bias for eligible studies by outcome; a second investigator will review each risk of bias assessment. Investigators will consult to reconcile any discrepancies in the risk of bias assessments. Overall risk of bias assessments for each study-outcome will be classified as low, high, or some concerns based upon the collective risk of bias across components and confidence that the study results for a given outcome are believable given the study's limitations.

### E. Data Synthesis

Results will be organized first by key question. From there, we will organize results by intervention comparison, targeted outcome, and outcome timing. We will qualitatively summarize results in evidence tables and synthesize evidence for each unique intervention-outcome comparison with meta-analysis when possible and appropriate. We will assess the clinical and methodological heterogeneity and variation in effect size to determine appropriateness of pooling data.[16] We will

synthesize data using a Hartung, Knapp, Sidik, and Jonkman (HKSJ)[17] random effects model. We will calculate risk ratios (RR) and absolute risk differences (RD) with the corresponding 95 percent confidence intervals (CI) for binary outcomes and weighted mean differences (WMD) and/or standardized mean differences (SMD) with the corresponding 95 percent CIs for continuous outcomes if combining similar outcomes measured with different instruments. The HKSJ method is more conservative than the commonly used DerSimonian-Laird approach which may result in overly narrow confidence intervals that can lead to Type 1 error.[18] If meta-analysis is not possible, we will present results in a narrative "Summary of Findings" table.

We will identify heterogeneity (inconsistency) through visual inspection of the forest plots to assess the amount of overlap of CIs, and the $I^2$ statistic, which quantifies inconsistency across studies to assess the impact of heterogeneity on the meta-analysis.[19,20] When we find heterogeneity, we will attempt to determine possible reasons for it by examining individual study and subgroup characteristics.

### F. Grading the Evidence Quality for Major Comparisons and Outcomes

ASTRO and ASCO intend to use this evidence report to develop their guidelines on this topic. Because these organizations use Grading of Recommendations Assessment, Development and Evaluation (GRADE)[21] for rating evidence certainty, we will use the GRADE approach to assess the overall quality of evidence. We will present the overall certainty or strength of the evidence for each outcome according to a modified GRADE approach. This approach assesses five criteria which measure either internal validity (risk of bias, inconsistency, imprecision, publication bias) or external validity (directness of results).[21] RCTs start out as high certainty and may be rated down for any one of the five criteria. Non-randomized trials start out as low-certainty evidence and are assessed on additional criteria (evidence of a large magnitude of effect, a dose-effect relationship, and for the effect of residual opposing confounding). For each comparison, one review author will rate the certainty of evidence for each outcome as high, moderate, low, or very low using GRADEpro GDT (www.gradepro.org). These ratings will then be reviewed by a second

investigator. We will resolve any discrepancies by consensus, or, if needed, by discussion with a third reviewer.

For each comparison, we will present a summary of the evidence for the main outcomes in a "Summary of Findings" table as well as a full Evidence Profile, which provides key information about the best estimate of the magnitude of the effect in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome.[22] For outcomes measured on a scale, we will consider the minimal clinically important difference, which represents the threshold of clinically significant change, to be a directly validated value for a particular measure, obtained from peer-reviewed literature. If we are unable to find directly validated minimal clinically important difference for a particular measure, we will rely on the conventional value, which is one half the standard deviation of the baseline score.[23] If meta-analysis is not possible, we will present results in a narrative "Summary of Findings" table or Evidence Profile.

### G. Assessing Applicability

Applicability of studies is generally determined according to the PICOTS framework. Study characteristics that may affect applicability include, but are not limited to, the population from which the study participants are enrolled, diagnostic assessment processes, narrow eligibility criteria, and patient and intervention characteristics different than those described by population studies.[24] In particular, we will consider disease stage and the presence or absence of subgroups of interest when determining study groupings and potential sensitivity analyses to inform for whom the review findings may apply.

### IV. References

1. Tang J, Zhu L, Huang Y, et al. Development and validation of prognostic survival nomograms for patients with anal canal cancer: a SEER-based study. International Journal of General Medicine. 2021:10065-81.

2.  Pessia B, Romano L, Giuliani A, et al. Squamous cell anal cancer: Management and therapeutic options. Annals of Medicine and Surgery. 2020;55:36-46.

3.  Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA: a cancer journal for clinicians. 2016;66(4):271-89.

4.  Stewart DB, Gaertner WB, Glasgow SC, et al. The American Society of Colon and Rectal Surgeons clinical practice guidelines for anal squamous cell cancers (revised 2018). Diseases of the Colon &amp; Rectum. 2018;61(7):755-74.

5.  Bojko MM, Kucejko RJ, Poggio JL. Racial Disparities and the Effect of County Level Income on the Incidence and Survival of Young Men with Anal Cancer. Health Equity. 2018 Aug 1;2(1):193-198. doi: 10.1089/heq.2018.0018. PMID: 30283867; PMCID: PMC6110184.

6.  Osborne MC, Maykel J, Johnson EK, et al. Anal squamous cell carcinoma: an evolution in disease and management. World Journal of Gastroenterology: WJG. 2014;20(36):13052.

7.  Janczewski, L. M., Faski, J., Nelson, H., Gollub, M. J., Eng, C., Brierley, J. D., Palefsky, J. M., Goldberg, R. M., Washington, M. K., Asare, E. A., Goodman, K. A., & American Joint Committee on Cancer Expert Panel on Cancers of the Lower Gastrointestinal, Anus Disease Site (2023). Survival outcomes used to generate version 9 American Joint Committee on Cancer staging system for anal cancer. CA: a cancer journal for clinicians, 10.3322/caac.21780. Advance online publication. https://doi.org/10.3322/caac.21780

8.  Network NCC. NCCN Guidelines - Anal Carcinoma version 1.2023. 2023. https://www.nccn.org/guidelines/guidelines-detail?category=1&amp;id=1414.

9.  Bartelink H, Roelofsen F, Eschwege F, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. Journal of clinical oncology. 1997;15(5):2040-9.

10. James RD, Glynne-Jones R, Meadows HM, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2× 2 factorial trial. The lancet oncology. 2013;14(6):516-24.

11. Hałka J, Spaleniak S, Kade G, et al. The Nephrotoxicity of Drugs Used in Causal Oncological Therapies. Current Oncology. 2022;29(12):9681-94.

12. Kunadu A, Stalls JS, Labuschagne H, et al. Mitomycin induced pulmonary veno-occlusive disease. Respiratory Medicine Case Reports. 2021;34:101437.

13. Pretta A, Trevisi E, Bregni G, Deleporte A, Hendlisz A, Sclafani F. Treatment compliance in early-stage anal cancer. Ann Oncol. 2020 Oct;31(10):1282-1284.

14. Jones CM, Adams R, Downing A, Glynne-Jones R, Harrison M, Hawkins M, Sebag-Montefiore D, Gilbert DC, Muirhead R. Toxicity, Tolerability, and Compliance of Concurrent Capecitabine or 5-Fluorouracil in Radical Management of Anal Cancer With Single-dose Mitomycin-C and Intensity Modulated Radiation Therapy: Evaluation of a National Cohort. Int J Radiat Oncol Biol Phys. 2018 Aug 1;101(5):1202-1211.

15. Sterne JAC SJ, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi: 10.1136/bmj.l4898. PMID: 31462531.

16. Sterne JA HM, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919. doi: 10.1136/bmj.i4919.

17. Fu R GG, Grant M, Shamliyan T, Sedrakyan A, Wilt TJ, Griffith L, Oremus M, Raina P, Ismaila A, Santaguida P, Lau J, Trikalinos TA. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. *Journal of Clinical Epidemiology*. 2011;64(11):1187-97. doi: 10.1016/j.jclinepi.2010.08.010. PMID: 21477993.

18. IntHout J IJ, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC medical research methodology*. 2014;14(1):25. doi: 10.1186/1471-2288-14-25. PMID: 24548571.

19. Higgins JP TS, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557. PMID: 12958120.

20. Deeks J HJ, Altman D. Chapter 9.5.2: Identifying and measuring heterogeneity. In: Higgins JPT GS, editor. Cochrane Handbook for Systematic Reviews of Interventions: Version 510. The Cochrane Collaboration; 2011.

21. Guyatt GH OA, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? . *BMJ*. 2008;336(7651):995-8. doi: 10.1136/bmj.39490.551019.BE. PMID: 18456631.

22. Guyatt G OA, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, Atkins D, Kunz R, Montori V, Jaeschke R, Rind D, Dahm P, Akl EA, Meerpohl J, Vist G, Berliner E, Norris S, Falck-Ytter Y, Schünemann HJ. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *Journal of Clinical Epidemiology*. 2013;66(2):151-7. doi: 10.1016/j.jclinepi.2012.01.006. PMID: 22542023.

23. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care. 2003 May;41(5):582-92.

24. Atkins D, Chang S, Gartlehner G, et al. Assessing the Applicability of Studies When Comparing Medical Interventions. 2010 Dec 30. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK53480/

## V. Definition of Terms

Abbreviations:

| | |
|---|---|
| AHRQ | Agency for Healthcare Research and Quality |
| CI | Confidence interval |
| 3D-CRT | Three-dimensional conformal radiation therapy |
| DRE | Digital rectal exam |
| EPC | Evidence-based Practice Center |
| 5-FU | 5-Fluorouracil |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HKSJ | Hartung, Knapp, Sidik, and Jonkman |
| IMRT | Intensity-modulated radiation therapy |
| KQ | Key Question |
| MMC | Mitomycin C |
| MRI | Magnetic Resonance Imaging |
| PET | Positron Emission Tomography |
| PICOTS | Population, Intervention, Comparator, Outcomes, Timing, and Study design/setting |
| RCT | Randomized controlled trial |
| RD | Risk difference |

| | | |
|---|---|---|
| RR | Risk ratio | |
| SCCa | Squamous cell carcinoma | |
| SMD | Standardized mean differences | |
| SR | Systematic Review | |
| TOO | Task Order Officer | |
| US | United States | |
| VMAT | Volumetric modulated arc therapy | |
| WMD | Weighted mean differences | |

## VI.    Summary of Protocol Amendments

We have proposed amendments to the protocol as summarized in the table below.
Changes will not be incorporated into the protocol.

| Date | Section | Original Protocol | Revised Protocol | Rationale |
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|---|---|---|---|---|
| 9.26.2023 | Section III, subsection F | ASTRO and ASCO intend to use this evidence report to develop their guidelines on this topic. Because these organizations use Grading of Recommendations Assessment, Development and Evaluation (GRADE)[21] for rating evidence certainty, we will use the GRADE approach to assess the overall quality of evidence. We will present the overall certainty or strength of the evidence for each outcome according to a modified GRADE approach. This approach assesses five criteria which measure either internal validity (risk of bias, inconsistency, imprecision, publication bias) or external validity (directness of results).[21,22] RCTs start out as high certainty and may be rated down for any one of the five criteria. Non-randomized trials start out as low-certainty evidence and are assessed on additional criteria (evidence of a large magnitude of effect, a dose-effect relationship, and for the effect of residual opposing confounding). For each comparison, one review author will rate the certainty of evidence for each outcome as high, moderate, low, or very low using GRADEpro GDT (www.gradepro.org).<br><br>Reference 21: Guyatt GH OA, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? . BMJ. 2008;336(7651):995-8. doi: 10.1136/bmj.39490.551019.BE. PMID: 18456631.<br><br>22. Guyatt G OA, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, Atkins D, Kunz R, Montori V, Jaeschke R, Rind D, Dahm P, Akl EA, Meerpohl J, Vist G, Berliner E, Norris S, Falck-Ytter Y, Schünemann HJ. GRADE guidelines: 11. Making an overall rating of confidence in effect | The strength of evidence assessment will clearly document uncertainty, outline the reasons for insufficient evidence where appropriate, and communicate our confidence in the findings. The outcomes that will be considered for summary of findings statements are stated in the PICOTS table (Table 1). If necessary, we will consult with the TEP regarding prioritizing outcomes to subject to strength of evidence to focus attention on outcomes most clinically relevant and important to patients and clinicians.<br><br>The grading process will be conducted as outlined in the AHRQ methods guide.[21] The overall strength of evidence for outcomes within each comparison will be evaluated based on five required domains: (1) study limitations (risk of bias); (2) directness (single, direct link between intervention and outcome); (3) consistency (similarity of effect direction and size); (4) precision (degree of certainty around an estimate); and (5) reporting bias. For each comparison, one investigator will rate the strength quality of evidence for each outcome as high, moderate, low, or insufficient. These ratings will then be reviewed by a second investigator and confirmed by team consensus.<br><br>Reference 21: Berkman ND, Lohr KN, Ansari M, et al. AHRQ Methods for Effective Health Care Grading the Strength of a Body of Evidence When Assessing Health Care | This change reflects a programmatic decision to follow AHRQ guidance regarding strength of evidence. It also provides more clarity regarding which outcomes will move forward to strength of evidence assessment. |

| | | estimates for a single outcome and for all outcomes. Journal of Clinical Epidemiology. 2013;66(2):151-7. doi: 10.1016/j.jclinepi.2012.01.006. PMID: 22542023. | Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Agency for Healthcare Research and Quality (US); 2008. | |
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## VII.    Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) posted the Key Questions on the AHRQ Effective Health Care Website for public comment. The EPC refined and drafted the key questions after review of the public comments, and input from Key Informants. This input is intended to ensure that the key questions are specific and relevant.

## VIII.    Key Informants

Key Informants are the end-users of research; they can include patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into the decisional dilemmas and help keep the focus on Key Questions that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for the systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

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 are invited to serve as Key Informants and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## IX.    Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information

to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest.  Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## X.    Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

## XI.    EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

## XII.    Role of the Funder

This project was funded under Contract No. 75Q80120D00008 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

## XIII. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

**Appendix A: Search Strategy**

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 chemoradiation 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) adj2 (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 adj2 (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/8-128897255

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