

# Topic Brief: Anal Carcinoma Treatment

#### Date: 7/13/2022 Nomination Number: 1004

**Purpose:** This document summarizes the information addressing a nomination submitted on June 3, 2022, through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

**Issue:** Anal carcinoma is a relatively rare but increasingly prevalent cancer. The nominators for this topic seek the creation of a systematic review to establish clear guidance for the treatment of this condition.

Link to nomination

#### Recommendation

- X Systematic review
- $\hfill\square$  Technical brief
- $\Box$  Evidence map
- $\square$  Rapid review
- □ Rapid response
- □ Expanded topic brief

While the evidence we found is limited and varied, the topic was nominated by two guideline groups, American Society of Clinical Oncology (ASCO) and American Society for Radiation Oncology (ASTRO), so a new systematic review would have high impact.

#### Background

Anal cancer is a disease in which malignant cells form in the tissues of the anus and at the end of the large intestine, below the rectum. Based on data from 2017 to 2019, roughly 0.2 percent of people will be diagnosed with anal cancer at some point in their lifetime, and the five-year survival rate is approximately 70 percent. While the condition is relatively uncommon, age-adjusted death rates have been rising an average of 3.5 percent each year over the last decade.<sup>1</sup> An analysis conducted in 2019 found that the average lifetime cost of anal cancer was estimated to be approximately \$50,000 for patients, and the disease-related lifetime economic burden for Medicare patients in the United States was approximately \$112 million.<sup>2</sup>

Major risk factors for anal carcinoma include human papillomavirus (HPV)-16 and HPV-18, two strains of HPV with genes that can cause healthy cell to act abnormally. Conditions with lowered immunity also increase the risk of anal carcinoma. This would include things like acquired immune deficiency syndrome (AIDS), which is advanced HIV infection without current

suppressive treatments); taking medications that cause immunosuppression for organ transplants; and smoking.<sup>3</sup> The treatment of anal cancer is dependent upon the stage of an individual's carcinoma, their overall health, and their personal preferences.<sup>4</sup> Treatment may include chemotherapy, radiation, and/or surgery.

#### Scope

- 1. What is the comparative effectiveness of different modalities of initial treatment for stages 1-3 squamous cell anal cancer?
- 2. What is the comparative effectiveness of different radiation therapy doses and fractionation schemes for initial treatment of stage 1-3 squamous cell anal cancer?
- 3. What is the comparative effectiveness of different radiation therapy types for initial treatment of stages 1-3 squamous cell anal cancer?
- 4. What is the comparative effectiveness of different chemotherapy types or combinations of chemotherapy types and dose de-escalation for initial treatment of stages 1-3 squamous cell anal cancer?
- 5. What is the effectiveness of immunotherapy for initial treatment of stages 1-3 squamous cell anal cancer?
  - a. How do outcomes vary based on the conditions surrounding immunotherapy (e.g., other treatments given, patient characteristics, tumor characteristics)?

Questions	1. Comparative effectiveness of initial treatment modalities	<ol> <li>Comparative effectiveness of radiation therapy doses and fractionation schemes of initial treatment</li> </ol>
Population	Adults with stages 1-3 squamous cell anal cancer Subgroup: stage, age, tumor characteristics, etc.	Adults with stages 1-3 squamous cell anal cancer
Interventions	<ul> <li>a. Chemoradiation</li> <li>b. Induction or maintenance chemotherapy</li> <li>c. Surgery</li> </ul>	Radiation therapy: a. Doses b. Fractionation schemes
Comparators	<ul><li>a. Radiation Therapy</li><li>b. Chemoradiation</li><li>c. Other treatment</li></ul>	Other: a. Doses b. Fractionation schemes
Outcomes	Overall survival Disease-free survival Colostomy-free survival Local control Pathologic complete response Salvage rate Sphincter preservation Acute and late toxicity Health-related quality of life Harms of treatment	Overall survival Disease-free survival Local control Pathologic complete response Salvage rate Sphincter preservation Acute and late toxicity Health-related quality of life Harms of treatment

Table 1. Questions and PICOs (population, intervention, comparator, outcome)

**Table 2.** Questions and PICOs (population, intervention, comparator, outcome)

Questions	3. Comparative effectiveness of radiation therapy types for initial treatment	4.	Comparative effectiveness of different chemotherapy types or combinations of chemotherapy types and dose de- escalation for initial treatment
			escalation for initial treatment

Population	Adults with stages 1-3 squamous cell anal cancer	Adults with stages 1-3 squamous cell anal cancer
Interventions	IMRT Proton radiation therapy Brachytherapy	<ol> <li>Chemotherapy types/combinations (e.g., fluorouracil, mitomycin, cisplatin)</li> <li>Dose de-escalation</li> </ol>
Comparators	3-D CRT Photon radiation therapy Electron therapy boost	<ol> <li>Chemotherapy types/combinations (e.g., fluorouracil, mitomycin, cisplatin)</li> <li>Other dose de-escalation</li> </ol>
Outcomes	Overall survival Disease-free survival Colostomy-free survival Local control Pathologic complete response Salvage rate Sphincter preservation Acute and late toxicity Health-related quality of life Harms of treatment	Overall survival Disease-free survival Local control Pathologic complete response Salvage rate Sphincter preservation Acute and late toxicity Health-related quality of life Harms of treatment

**Abbreviations:** IMRT=intensity-modulated radiation therapy; 3-D CRT= three-dimensional conformal radiation therapy.

	ons and Ficos (population, intervention, comparator, outcome)	
Questions	5. Effectiveness of immunotherapy for initial treatment of stages 1-3 anal carcinoma	
	a. How do outcomes vary based on the conditions surrounding immunotherapy	
Population	Adults with stages 1-3 squamous cell anal cancer	
	Subgroup: other treatments, patient characteristics, tumor characteristics, stage	
Interventions	Immunotherapy (e.g., pembrolizumab, nivolumab)	
Comparators	Other treatment (e.g., chemotherapy, radiation, chemotherapy + radiation)	
Outcomes	Overall survival	
	Disease-free survival	
	Colostomy-free survival	
	Local control	
	Pathologic complete response	
	Salvage rate	
	Sphincter preservation	
	Acute and late toxicity	
	Health-related quality of life	
	Harms of treatment	

#### **Table 3.** Questions and PICOs (population, intervention, comparator, outcome)

#### **Assessment Methods**

See Appendix A.

#### **Summary of Literature Findings**

We did not find any systematic reviews that would address the full scope of the nomination and found limited and varied evidence for each of the five Key Questions (KQs) from a review of the entire search yield.

For KQ 1, we found two retrospective studies, one comparing chemoradiation to radiation therapy alone,<sup>5</sup> and one comparing surgery followed by postoperative radiation therapy or chemoradiation to surgery alone.<sup>6</sup>

For KQ 2, we found one retrospective study assessing lower versus higher doses of radiation therapy,<sup>7</sup> and one non-randomized controlled study assessing low-dose versus high-dose brachytherapy doses.<sup>8</sup>

For KQ 3, we found two retrospective<sup>9, 10</sup> and one non-randomized control study<sup>8</sup> comparing IMRT to 3-D RT; a non-randomized controlled study comparing brachytherapy to electron boost therapy<sup>11</sup>; and an ongoing randomized control trial comparing proton and photon radiotherapy.<sup>12</sup>

For KQ 4, we found one randomized controlled trial comparing avelumab + cetuximab;<sup>13</sup> two retrospective studies comparing one and two doses of mitomycin<sup>14</sup>, and capecitabine to 5-FU,<sup>15</sup> respectively; and two ongoing randomized controlled trials comparing de-intensified chemoradiation to standard dose chemoradiation,<sup>16</sup> and carboplatin + paclitaxel + retifanlimab to carboplatin+paclitaxel+placebo,<sup>17</sup> respectively.

For KQ 5, we found two studies of durvalumab: one ongoing randomized control trial of radio chemotherapy with versus without durvalumab,<sup>18</sup> and a randomized controlled trial comparing standard care + durvalumab to standard care.<sup>19</sup> We found two studies assessing the adjunctive use of nivolumab: one ongoing randomized control trial comparing carboplatin +paclitaxel + nivolumab to carboplatin + paclitaxel,<sup>20</sup> and an ongoing non-randomized controlled study comparing nivolumab to mitomycin.<sup>21</sup> We also found an ongoing randomized controlled trial comparing traditional chemoradiotherapy with PD-1 antibody Sintilimab to traditional treatment without Sintilimab.<sup>22</sup>

Question	Systematic reviews (7/2019-7/2022)	Primary studies (7/2017-7/2022)
Question 1: Comparative effectiveness of initial treatment modalities	Total: 0	Total: 2 • RCT: 0 • Retrospective Cohort: 2 <sup>5, 6</sup> Clinicaltrials.gov:0
Question 2: Comparative effectiveness of radiation therapy doses and fractionation schemes of initial treatment	Total: 0	Total: 2 • RCT: 0 • Non-randomized controlled: 1 <sup>8</sup> • Retrospective: 1 <sup>7</sup> Clinicaltrials.gov:0
Question 3: Comparative effectiveness of IMRT versus 3-D CRT for initial treatment	Total: 0	Total: 5 • RCT • Retrospective: 2 <sup>9, 10</sup> • Non-randomized controlled: 2 <sup>11, 23</sup> Clinicaltrials.gov: 1 <sup>12</sup>
Question 4: Comparative effectiveness of different chemotherapy types or combinations of chemotherapy types and dose de-escalation for initial treatment	Total: 0	Total: 5 • RCT: 1 <sup>13</sup> • Retrospective: 2 <sup>14, 15</sup> Clinicaltrials.gov: 2 <sup>16, 17</sup>
Question 5: Effectiveness of immunotherapy for	Total: 0	Total: 5 • RCT: 1 <sup>19</sup>

**Table 2.** Literature identified for each Key Question

Question	Systematic reviews (7/2019-7/2022)	Primary studies (7/2017-7/2022)
initial treatment of stages 1-3 anal carcinoma		Clinicaltrials.gov: 4 <sup>18, 20-22</sup>

Abbreviations: AHRQ=Association for Healthcare Research and Quality; IMRT=intensity-modulated radiation therapy; RCT=randomized controlled trial; 3-D CRT= three-dimensional conformal radiation therapy.

See Appendix B for detailed assessments of all EPC selection criteria.

#### **Summary of Selection Criteria Assessment**

While anal cancer is a relatively rare condition, it disproportionately affects a vulnerable population, persons living with HIV, and guidance on treatment is lacking. While the evidence is limited and varied, a new systematic review would have high impact as two guideline organizations would support the development of new guidelines.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

#### **Related Resources**

We identified additional information in the course of our assessment that might be useful. We found a systematic review and meta-analysis that may be of interest as it covers a portion of KQ 1, examining radiotherapy alone versus chemoradiotherapy for stage I anal cancer. The authors found that patients treated with chemoradiotherapy had and increased 5-year overall survival compared to radiotherapy alone, but no difference in 5-year disease-free survival.<sup>24</sup>

#### References

1. Cancer Stat Facts: Anal Cancer. NIH National Cancer Institute. doi: <u>https://seer.cancer.gov/statfacts/html/anus.html#:~:text=Rate%20of%20New%20Cases%20and</u> <u>%20Deaths%20per%20100%2C000%3A,age-</u>

adjusted%20and%20based%20on%202015%E2%80%932019%20cases%20and%20deaths.

2. Deshmukh AA, Zhao H, Franzini L, et al. Total Lifetime and Cancer-related Costs for Elderly Patients Diagnosed With Anal Cancer in the United States. Am J Clin Oncol. 2018

Feb;41(2):121-7. doi: 10.1097/coc.00000000000238. PMID: 26523440.

3. About Anal Cancer. American Cancer Society. doi: <u>https://www.cancer.org/cancer/anal-cancer/about.html</u>.

4. Anal Cancer. Mayo Clinic. doi: <u>https://www.mayoclinic.org/diseases-conditions/anal-cancer/diagnosis-treatment/drc-20354146</u>.

5. Buckstein M, Arens Y, Wisnivesky J, et al. A Population-Based Cohort Analysis of Chemoradiation Versus Radiation Alone for Definitive Treatment of Stage I Anal Cancer in Older Patients. Diseases of the Colon & Rectum. 2018 Jul;61(7):787-94. doi: https://dx.doi.org/10.1097/DCR.00000000001103. PMID: 29771796.

6. Leon O, Hagberg O, Johnsson A. Primary surgery with or without postoperative radiotherapy in early stage squamous cell carcinoma in the anal canal and anal margin. Acta Oncologica. 2018 Sep;57(9):1209-15. doi: <u>https://dx.doi.org/10.1080/0284186X.2018.1442931</u>. PMID: 29490558.
7. Johnsson A, Leon O, Gunnlaugsson A, et al. Determinants for local tumour control probability

after radiotherapy of anal cancer. Radiotherapy & Oncology. 2018 08;128(2):380-6. doi: https://dx.doi.org/10.1016/j.radonc.2018.06.007. PMID: 29934107.

8. Varela Cagetti L, Zemmour C, Salem N, et al. High-dose-rate vs. low-dose-rate interstitial brachytherapy boost for anal cancers. Brachytherapy. 2019 Nov - Dec;18(6):814-22. doi: <u>https://dx.doi.org/10.1016/j.brachy.2019.08.005</u>. PMID: 31515067.

9. Agarwal MS, Hitchcock KE, Morris CG, et al. Outcomes after intensity-modulated compared with 3-dimensional conformal radiotherapy with chemotherapy for squamous cell carcinoma of the anal canal. Current Oncology. 2019 08;26(4):e515-e21. doi:

https://dx.doi.org/10.3747/co.26.4311. PMID: 31548820.

10. Elson JK, Kharofa JR. Imrt improves survival and reduces treatment time in squamous cell carcinoma of the anal canal: a national cancer database study. International journal of radiation oncology biology physics. 2017;99(2):E146. doi: <u>https://doi.org/10.1016/j.ijrobp.2017.06.950</u>.

11. Kent C, Bessell EM, Scholefield JH, et al. Chemoradiotherapy with Brachytherapy or Electron Therapy Boost for Locally Advanced Squamous Cell Carcinoma of the Anus—Reducing the Colostomy Rate. Journal of Gastrointestinal Cancer. 2017;48(1):1. doi: https://doi.org/10.1007/s12029-016-9850-4.

12. Proton Versus Photon Therapy in Anal Squamous Cell Carcinoma (SWANCA). Clinical Trials.gov. doi: <u>https://clinicaltrials.gov/ct2/show/NCT04462042</u>.

13. Lonardi S, Prete AA, Morano F, et al. Randomized phase II trial of avelumab alone or in combination with cetuximab for patients with previously treated, locally advanced, or metastatic squamous cell anal carcinoma: the CARACAS study. Journal for immunotherapy of cancer. 2021;9(11). doi: <u>https://doi.org/10.1136/jitc-2021-002996</u>.

14. Al Habsi Z, Abraham AG, Al Balushi M, et al. Are two too many when it comes to the treatment of anal canal cancer with concurrent radiation and mitomycin C? Journal of clinical oncology. 2022;40(4 SUPPL). doi: <u>https://doi.org/10.1200/JCO.2022.40.4-suppl.003</u>.

15. Goodman KA, Julie D, Cercek A, et al. Capecitabine With Mitomycin Reduces Acute Hematologic Toxicity and Treatment Delays in Patients Undergoing Definitive Chemoradiation Using Intensity Modulated Radiation Therapy for Anal Cancer. International Journal of Radiation Oncology, Biology, Physics. 2017 08 01;98(5):1087-95. doi: https://dx.doi.org/10.1016/j.ijrobp.2017.03.022. PMID: 28721892.

16. Lower-dose chemoradiation in treating patients with early-stage anal cancer, the DECREASE study. Clinical Trials.gov. doi:

 $\label{eq:https://clinicaltrials.gov/ct2/show/NCT04166318?term=squamous&recrs=abdf&cond=%28%28a\\nal+OR+anus%29+AND+%28cancer+OR+carcinoma+OR+neoplasm%29%29&age=1&sfpd_s\\=07%2F26%2F2019&sfpd_e=07%2F26%2F2022&draw=2&rank=11.$ 

17. Carboplatin-paclitaxel With Retifanlimab or Placebo in Participants With Locally Advanced or Metastatic Squamous Cell Anal Carcinoma (POD1UM-303/InterAACT 2). Clinical Trials.gov. doi: https://www.clinicaltrials.gov/ct2/show/NCT04472429.

18. Radiochemotherapy +/- Durvalumab for Locally-advanced Anal Carcinoma. A Multicenter, Randomized, Phase II Trial of the German Anal Cancer Study Group (RADIANCE). Clinical Trials.gov. doi:

19. Martin D, Balermpas P, Gollrad J, et al. RADIANCE - Radiochemotherapy with or without Durvalumab in the treatment of anal squamous cell carcinoma: A randomized multicenter phase II trial. Clinical and Translational Radiation Oncology. 2020 Jul;23:43-9. doi: https://dx.doi.org/10.1016/j.ctro.2020.04.010. PMID: 32420463.

20. EA2176: Phase 3 Clinical Trial of Carboplatin and Paclitaxel +/- Nivolumab in Metastatic Anal Cancer Patients. Clinical Trials.gov. doi:

 $\label{eq:https://clinicaltrials.gov/ct2/show/NCT04444921?term=squamous&recrs=abdf&cond=%28%28a nal+OR+anus%29+AND+%28cancer+OR+carcinoma+OR+neoplasm%29%29&age=1&sfpd_s=07%2F26%2F2019&sfpd_e=07%2F26%2F2022&draw=2&rank=19.$ 

21. Therapy Adapted for High Risk and Low Risk HIV-Associated Anal Cancer. Clinical Trials.gov. doi:

 $\label{eq:https://clinicaltrials.gov/ct2/show/NCT04929028?term=squamous&recrs=abdf&cond=%28%28a nal+OR+anus%29+AND+%28cancer+OR+carcinoma+OR+neoplasm%29%29&age=1&sfpd_s=07%2F26%2F2019&sfpd_e=07%2F26%2F2022&draw=2&rank=20.$ 

22. Chemoradiotherapy Combined With or Without PD-1 Blockade in Anal Canal Squamous Carcinoma Patients. ClinicalTrials.gov. doi:

 $\label{eq:https://clinicaltrials.gov/ct2/show/NCT05374252?term=squamous&recrs=abdf&cond=%28%28a nal+OR+anus%29+AND+%28cancer+OR+carcinoma+OR+neoplasm%29%29&age=1&sfpd_s=07%2F26%2F2019&sfpd_e=07%2F26%2F2022&draw=2&rank=4.$ 

23. Dell'Acqua V, Kobiela J, Kraja F, et al. Genital marginal failures after intensity-modulated radiation therapy (IMRT) in squamous cell anal cancer: no higher risk with IMRT when compared to 3DCRT. Medical Oncology. 2018 Mar 28;35(5):59. doi: https://dx.doi.org/10.1007/s12022.018\_1118\_2\_DMUD; 20504584

https://dx.doi.org/10.1007/s12032-018-1118-3. PMID: 29594584.

24. Talwar G, Daniel R, McKechnie T, et al. Radiotherapy alone versus chemoradiotherapy for stage I anal squamous cell carcinoma: a systematic review and meta-analysis. International journal of colorectal disease. 2021 2021. doi: <u>https://doi.org/10.1007/s00384-021-03846-5</u>.

#### Author

Emily Gean Lisa Winterbottom Charli Armstrong

**Conflict of Interest:** None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

#### Acknowledgements

Christine Chang

This report was developed by the Scientific Resource Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA 290-2017-00003C). The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact EPC@ahrq.hhs.gov.

## **Appendix A: Methods**

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

#### **Appropriateness and Importance**

We assessed the nomination for appropriateness and importance.

#### Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years July 25, 2019 -July 25, 2022 on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
  - AHRQ Evidence Reports <u>https://www.ahrq.gov/research/findings/evidence-based-reports/index.html</u>
  - EHC Program <u>https://effectivehealthcare.ahrq.gov/</u>
  - US Preventive Services Task Force <u>https://www.uspreventiveservicestaskforce.org/</u>
  - AHRQ Technology Assessment Program <u>https://www.ahrq.gov/research/findings/ta/index.html</u>
- US Department of Veterans Affairs Products publications
  - o Evidence Synthesis Program https://www.hsrd.research.va.gov/publications/esp/
  - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program <u>https://www.healthquality.va.gov/</u>
- Cochrane Systematic Reviews <u>https://www.cochranelibrary.com/</u>
- PROSPERO Database (international prospective register of systematic reviews and protocols) <u>http://www.crd.york.ac.uk/prospero/</u>
- PubMed <u>https://www.ncbi.nlm.nih.gov/pubmed/</u>
- Joanna Briggs Institute <u>http://joannabriggs.org/</u>
- Epistemonikos https://www.epistemonikos.org/

#### Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

#### Feasibility of New Evidence Review

We conducted a limited literature search in PubMed and PsycInfo for the last five years July 25, 2017- July 25, 2022. We reviewed all studies identified titles and abstracts for inclusion. We classified identified studies by question and study design to estimate the size and scope of a potential evidence review.

Search strategy **Ovid MEDLINE ALL 1946 to July 25, 2022** Date searched: July 26, 2022 1 Anal Gland Neoplasms/ or Anus Neoplasms/ (6981) 2 (((anal\$2 or anus) adj3 (cancer or carcinoma\$1 or neoplas\$1)) or ASCC or SCAC or SSCA).ti.ab.kf. (5551)

3 or/1-2 (9187)

4 (local\* or locoregional\$2 or ((stage or stages) adj2 (early or "1" or "2" or "3" or one or two or three or "I" or "II" or "III"))).ti,ab,kf. or squamous.hw,ti,ab,kf. (2023999)

5 and/3-4 (4186)

6 exp radiotherapy/ (202988)

7 (brachytherap\* or fraction\* or "Intensity-modulated" or IMRT or irradiat\* or neoadjuvant or neutron or proton or radia\* or radio\* or "three-dimensional" or 3DCRT or 3D-CRT or x-ray).ti,ab.kf. (2929574)

8 or/6-7 (2960594)

9 and  $\sqrt{5,8}$  (1706)

10 limit 9 to english language (1450)

11 limit 10 to yr="2019 -Current" (319)

12 11 and ((meta-analysis or "systematic review").pt. or ((metaanal\* or meta-anal\* or (evidence or scoping or systematic or umbrella)) adj3 (review or synthesis)).ti.) (13)

13 limit 10 to yr="2017 -Current" (480)

14 13 not ((Animals/ not Humans/) or (case or review).ti. or (case or comment or editorial or letter or news or review).pt.) (352)

15 14 and (("controlled clinical trial" or "randomized controlled trial").pt. or (control\$2 or placebo or random\* or trial).ti.) (19)

16 14 and (exp cohort studies/ or exp epidemiologic studies/ or (before-after or cohort or comparative or evaluation or follow-up or longitudinal or nonrandom\* or "non-randomized" or phase or program\* or prospective or prospective or pre-post or retrospective).ti.) (193)

17Chemoradiotherapy/ or Chemoradiotherapy, Adjuvant/ or Chemotherapy, Adjuvant/ or Hyperthermic Intraperitoneal Chemotherapy/ or Consolidation Chemotherapy/ or Drug Therapy/ or Induction Chemotherapy/ or Maintenance Chemotherapy/ or dt.fs. (2580489)

18 (chemotherap\* or chemo-therap\* or chemoradi\* or chemo-radi\* or radiochemo\* or radiochemo\*).ti,ab,kf. (496683)

19 (carboplatin or cisplatin or fluorouracil or mitomycin).ti,ab,kf. (127020)

20 or/17-18 (2832995)

21 and/5,20 (1699)

22 limit 21 to english language (1483)

23 limit 22 to yr="2019 -Current" (358)

24 23 and ((meta-analysis or "systematic review").pt. or ((metaanal\* or meta-anal\* or (evidence or scoping or systematic or umbrella)) adj3 (review or synthesis)).ti.) (15)

25 limit 22 to yr="2017 -Current" (543)

26 25 not ((Animals/ not Humans/) or (case or review).ti. or (case or comment or editorial or letter or news or review).pt.) (396)

27 26 and (("controlled clinical trial" or "randomized controlled trial").pt. or (control\$2 or placebo or random\* or trial).ti.) (25)

28 26 and (exp cohort studies/ or exp epidemiologic studies/ or (before-after or cohort or comparative or evaluation or follow-up or longitudinal or nonrandom\* or "non-randomized" or phase or program\* or prospective or prospective or pre-post or retrospective).ti.) (213)

29 exp Immunotherapy/ or exp Antineoplastic Agents, Immunological/ or Immune Checkpoint Inhibitors/ (377981)

30 (immunotherap\* or immuno-therap\* or adjuvant or checkpoint-inhibit\$4 or ICI\$1 or "anti-PD-1").ti,ab,kf. (300550)

31 Nivolumab/ or (carboplatin or cetuximab or Erbitux or nivolumab or Opdivo or paclitaxel or pembrolizumab or Keytruda or Retifanlimab).ti,ab,kf. (64134)

32 or/29-31 (645498)

33 and/5,32 (328)

34 limit 33 to english language (283)

35 limit 34 to yr="2019 -Current" (78)

36 35 and ((meta-analysis or "systematic review").pt. or ((metaanal\* or meta-anal\* or (evidence or scoping or systematic or umbrella)) adj3 (review or synthesis)).ti.) (1)

37 limit 34 to yr="2017 -Current" (121)

38 37 not ((Animals/ not Humans/) or (case or review).ti. or (case or comment or editorial or letter or news or review).pt.) (70)

39 38 and (("controlled clinical trial" or "randomized controlled trial").pt. or (control\$2 or placebo or random\* or trial).ti.) (8)

40 38 and (exp cohort studies/ or exp epidemiologic studies/ or (before-after or cohort or comparative or evaluation or follow-up or longitudinal or nonrandom\* or "non-randomized" or phase or program\* or prospective or prospective or pre-post or retrospective).ti.) (39)

### **Ovid EBM Reviews - Cochrane Central Register of Controlled Trials June 2022**

Date searched: July 26, 2022

1 Anal Gland Neoplasms/ or Anus Neoplasms/ (136)

```
2 (((anal$2 or anus) adj3 (cancer or carcinoma$1 or neoplas$1)) or ASCC or SCAC or
```

SSCA).ti,ab. (427)

3or/1-2 (479)

4 (local\* or locoregional\$2 or ((stage or stages) adj2 (early or "1" or "2" or "3" or one or two or three or "I" or "II" or "III"))).ti,ab. or squamous.hw,ti,ab. (138568)

5and/3-4 (234)

6 exp radiotherapy/ (6675)

7 (brachytherap\* or fraction\* or "Intensity-modulated" or IMRT or irradiat\* or neoadjuvant or neutron or proton or radia\* or radio\* or "three-dimensional" or 3DCRT or 3D-CRT or x-ray).ti,ab. (158516)

8 or/6-7 (159095)

9 and/5,8 (139)

10 limit 9 to yr="2017 -Current" (55)

11 Chemoradiotherapy/ or Chemoradiotherapy, Adjuvant/ or Chemotherapy, Adjuvant/ or Hyperthermic Intraperitoneal Chemotherapy/ or Consolidation Chemotherapy/ or Drug Therapy/ or Induction Chemotherapy/ or Maintenance Chemotherapy/ (6159)

12 (chemotherap\* or chemo-therap\* or chemoradi\* or chemo-radi\* or radiochemo\* or radiochemo\*).ti,ab. (77849)

13 (carboplatin or cisplatin or fluorouracil or mitomycin).ti,ab. (27230)

14 or/11-12 (80332)

15 and/5,14 (139)

16 limit 15 to yr="2017 -Current" (64)

17 exp Immunotherapy/ or exp Antineoplastic Agents, Immunological/ or Immune Checkpoint Inhibitors/ (15081)

18 (immunotherap\* or immuno-therap\* or adjuvant or checkpoint-inhibit\$4 or ICI\$1 or "anti-PD-1").ti,ab. (43544)

19 Nivolumab/ or (carboplatin or cetuximab or Erbitux or nivolumab or Opdivo or paclitaxel or pembrolizumab or Keytruda or Retifanlimab).ti,ab. (20165)

20 or/17-19 (69773)

21 and/5,20 (54)

22 limit 21 to yr="2017 -Current" (32)

#### **EPISTEMONIKOS**

Date searched: July 26, 2020

(title:(title:((((anal AND (cancer\* OR carcinoma\* OR neoplas\*))) OR ASCC OR SCAC OR SSCA) AND (local OR localized OR locoregional OR (stage AND (early OR 1 OR 2 OR 3 OR one OR two OR three OR I OR II OR III)))))) OR abstract:(title:((((anal AND (cancer\* OR carcinoma\* OR neoplas\*))) OR ASCC OR SCAC OR SSCA) AND (local OR localized OR locoregional OR (stage AND (early OR 1 OR 2 OR 3 OR one OR two OR three OR I OR II OR III)))))) (5)

#### PROSPERO

Date searched: July 26, 2022

(((((anal OR anus) AND (cancer\* OR carcinoma\* OR neoplas\*)) or ASCC or SCAC or SSCA) AND (local OR localized OR locoregional OR (stage AND (early OR 1 OR 2 OR 3 OR one OR two OR three OR I OR II OR III)))) AND (brachytherap\* OR fraction\* OR Intensity-modulated OR IMRT OR irradiat\* OR neoadjuvant OR neutron OR proton OR radia\* OR radio\* OR threedimensional OR 3DCRT OR 3D-CRT OR x-ray OR chemotherap\* OR chemo-therap\* OR chemoradi\* OR chemo-radi\* OR radiochemo\* OR radio-chemo\* OR immunotherap\* OR immuno-therap\* OR adjuvant OR checkpoint-inhibition OR ICI OR anti-PD-1 OR anti-PD1 OR antiPD1)) AND (Systematic Review OR Meta-Analysis OR IPD OR PMA OR Network metaanalysis OR Review of reviews):RT

#### Clinical Trials.gov

#### Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change, if a partner organization would use this evidence review to influence practice, and if the topic supports a priority area of AHRQ or the Department of Health and Human Services.

## Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the United States?	Yes.
1b. Is the nomination a request for an evidence report?	Yes.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	While the incidence of anal cancer is not particularly high, it disproportionately affects persons living with HIV, which represent a vulnerable population. <sup>3</sup>
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes. While the incidence of anal cancer is not particularly high, it disproportionately affects persons living with HIV, a vulnerable population. <sup>3</sup> An analysis conducted in 2019 found that the average lifetime cost of anal cancer was estimated to be approximately \$50,000 for patients, and the disease-related lifetime economic burden for Medicare patients in the United States was approximately \$112 million. <sup>2</sup>
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes.
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes. An analysis conducted in 2019 found that the average lifetime cost of anal cancer was estimated to be approximately \$50,000 for patients, and the disease-related lifetime economic burden for Medicare patients in the United States was approximately \$112 million. <sup>2</sup>
3. Desirability of a New Evidence Review/Absence of Duplication	
<ul> <li>3. A recent high-quality systematic review or other evidence review is not available on this topic</li> <li>4. Impact of a New Evidence Review</li> </ul>	Yes. We did not find any systematic reviews covering the scope of the nomination.
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes. Guidelines for treatment of anal cancer are lacking.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)? 5. Primary Research	Yes. A lack of guidelines may lead to practice variation.
<ul> <li>5. Effectively utilizes existing research and knowledge by considering:</li> <li>Adequacy (type and volume) of research for conducting a systematic review</li> <li>Newly available evidence (particularly for updates or new technologies)</li> </ul>	Out of a review of the entire literature yield, we found the following relevant studies: KQ1: 2 studies KQ2: 2 studies KQ3: 5 studies KQ4: 5 studies KQ5: 5 studies

	We estimate that the size of a new systematic review would be limited.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change and supports a priority of AHRQ or Department of Health and Human Services	Yes. Anal cancer is more prevalent among a vulnerable population, persons living with HIV.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes. Two guideline groups, ASCO and ASTRO would work to develop guidelines using a new systematic review.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; ASCO= American Society of Clinical Oncology; ASTRO=American Society for Radiation Oncology; HIV=human immunodeficiency virus; KQ=key question.

## **Appendix C. Topic Nomination**

A topic nomination was submitted on the EHC website:

Submitted on Friday, June 3, 2022 - 11:22

#### Submit a Topic for a New Evidence Review

# 1. What is the decision or change (e.g. clinical topic, practice guideline, system design, delivery of care) you are facing or struggling with where a summary of the evidence would be helpful?

Anal cancer is a relatively rare cancer, with a higher prevalence among patients with human immunodeficiency virus (HIV). While there are only approximately 9,440 new cases per year, the incidence of this cancer has been increasing for many years. The ASCO Gastrointestinal Guidelines Advisory Group identified a need for guidance for this patient population. This disease site is of particular interest to both ASCO and ASTRO. Although chemoradiation is the definitive treatment for anal cancer, it is a complex disease with inherent challenges especially related to radiation planning and toxicity.

#### 2. Why are you struggling with this issue?

Clinicians need data to guide treatment with respect to indications for chemotherapy, radiation or chemoradiation. Areas of uncertainty include radiation dose and fractionation, dose de-escalation, and data to guide use of IMRT rather than 3-D CRT as well as type of chemotherapy, and potential role of immunotherapy.

# 3. What do you want to see changed? How will you know that your issue is improving or has been addressed?

We would like to see less uncertainty amongst clinicians regarding how to treat this disease site, and ultimately less variation in practice.

#### 4. When do you need the evidence report?

Sat, 06/03/2023

#### 5. What will you do with the evidence report?

The evidence report will be the basis for a clinical practice guideline.

#### **Optional Information About You**

#### What is your role or perspective?

Professional Society Staff

# If you are you making a suggestion on behalf of an organization, please state the name of the organization

American Society of Clinical Oncology and American Society of Radiation Oncology

#### May we contact you if we have questions about your nomination?

Yes

**Full Name** Erin Kennedy (ASCO) and Lisa Bradfield (ASTRO)

Title Guidelines Specialist

#### **Email Address**

erin.kennedy@asco.org

**is\_production** Yes

**Form Type** Topic Nomination

The results of this submission may be viewed at:

https://effectivehealthcare.ahrq.gov/admin/structure/webform/manage/topic\_nomination\_form/su bmission/593