DACG The Danish Anal Cancer Group

DACG VI

Beyond survival: Addressing gynecological and sexual health in women after radiotherapy for anal cancer

Version 5

Approved by the Regional Committee on Health Research Ethics (VEK) on March 28, 2025

Table of content

Protocol organization
The study is initiated by the investigators and the Danish Anal Cancer Group (DACG).

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Background

Anal cancer (AC) is a rare malignancy, with approximately 200 new cases diagnosed annually in Denmark [1]. This cancer predominantly affects women and is strongly associated with human papillomavirus (HPV) infection. The standard treatment for localized anal cancer (AC) is chemoradiotherapy (CRT). In Denmark, the standard approach involves delivering a total radiation dose of 54-60 Gy to the primary tumor and pathological lymph nodes, administered in fractions of 1.8-2 Gy per session. Elective lymph node regions are typically treated with a lower dose of 45-50 Gy[2]. This regimen has proven highly effective, achieving excellent rates of disease control and survival[3,4]. However, the long-term adverse effects of CRT remain a critical concern, one of them being gynecological and sexual health. These domains are often underreported and insufficiently addressed in routine clinical practice[5].

Radiotherapy for AC frequently affects adjacent organs at risk (OAR), including the female genital tract. This exposure can result in complications such as vaginal stenosis, dyspareunia, and broader sexual dysfunction[6]. The reported prevalence of these complications varies widely across studies. For example, some investigations report sexual dysfunction in up to 85% of female survivors (Yerramilli et al., 2019)[7], while others, such as De Francesco et al. (2016)[8], note that only 2 out of 21 women identified an impact on sexual relationships.

The wide variation in prevalence rates may be attributed to methodological heterogeneity in measuring vaginal symptoms. Many studies rely on differing assessment tools, complicating efforts to synthesize findings. Furthermore, research often focuses on sexually active individuals, potentially underestimating symptom prevalence among sexually inactive patients and leaving a significant proportion of affected women unrepresented. Additionally, physician-reported outcomes are seldom based on physical examinations, further undermining the reliability and comprehensiveness of available data. This lack of standardized assessment methods highlights a critical knowledge gap and adds to the variability in reported outcomes.

Another significant challenge is the poorly understood relationship between radiation dose and vaginal toxicity after AC treatment, which complicates the establishment of clinically relevant dose constraints for sexual OARs. While some studies have explored dose-response relationships, findings remain inconsistent. For instance, Arzola et al. (2023)[9] suggested that keeping the dose to 50% of the anterior vaginal wall <48 Gy could reduce the risks of impaired sexual function. Similarly, Son et al. (2015)[10] proposed that mean vaginal doses below 43 Gy were associated with a reduced risk of severe vaginal stenosis. Conversely, other studies, including Joseph et al. (2016)[11], have failed to demonstrate significant correlations between vaginal dose metrics and sexual dysfunction outcomes measured through standardized instruments like the EORTC-CR29.

These discrepancies underscore the urgent need for further research into the mechanisms and clinical predictors of gynecological morbidity and sexual health following CRT. Exploring dose constraints could pave the way for enhanced survivorship care in women treated for anal cancer.

Secondary preventive strategies

Despite well-documented risks, the implementation of secondary preventive strategies for mitigating long-term complications still needs to be revised. Evidence supports that vaginal dilator use and sexual counseling can reduce the risk and severity of late effects following radiation therapy[12-15]. Currently, all Danish cancer treatment centers routinely provide vaginal dilators to female patients after the end of radiation therapy with basic information on their use. The general recommendation

is to initiate dilator use approximately six to eight weeks post-radiation treatment, with a suggested frequency of three times per week.

In Denmark, patients can be referred to specialized sexual health nurses for counseling on sexual dysfunction after treatment for anal cancer. Additionally, all centers have access to late-effects clinics for further support. However, systematic documentation regarding the type and extent of counseling provided is lacking, as is a comprehensive insight into patients' satisfaction with these services. Greater patient involvement in refining guidance and care strategies is crucial to meeting unmet needs and enhancing survivors' quality of life.

Purpose

The primary objective of this study is to examine the prevalence and severity of vaginal morbidity in women following treatment for localized anal cancer and to identify predictive factors, including the potential dose-response relationship between radiation exposure and morbidity. Furthermore, the study seeks to investigate possible correlations between vaginal morbidity and patient-reported sexual dysfunction.

The secondary objective is to investigate patterns of care related to managing gynecological toxicity and sexual dysfunction, including the use of dilators and hormone therapy. The study also evaluates patient satisfaction with the guidance provided to identify areas for improvement, aiming to support the development of standardized, high-quality practices that ensure consistent and patient-centered care across Denmark's three anal cancer treatment centers.

Study design

This is a national multicenter, cross-sectional study that collects quantitative and qualitative data from gynecological examinations, questionnaires, and semi-structured interviews.

Study population

Inclusion criteria:

- Female patients aged 18 or older.
- Diagnosed with AC and treated with CRT with curative intent.
- 6–36 months post-CRT.
- Willing and able to provide informed consent.

Exclusion criteria:

- History of pelvic radiotherapy for conditions other than the current diagnosis.
- Treatment with electron beam radiotherapy.
- Non-Danish speaking

Inclusion procedures

Participants will be identified during follow-up consultations (6-36 months) at Aarhus University Hospital, Vejle Hospital, and Herlev and Gentofte Hospital. When a potential participant is identified, the treating physician responsible for the consultation will provide both oral and written information about the study. Participants will be informed that they have the right to have a companion or support person present during the initial oral information consultation. To ensure sufficient time for consideration, participants will be offered an inclusion consultation at least 24 hours after the initial

consultation. During this consultation, further questions can be addressed, and participants are welcome to bring a companion or relative.

Written informed consent will be obtained at this inclusion consultation before study participation**.** Patients will be assured of confidentiality. Patients will be informed that their participation is entirely voluntary and that they can withdraw their consent at any time without affecting their future care.

If they consent, the gynecological examination will either be performed shortly after consent or scheduled for their next follow-up visit, depending on patient preference and clinical feasibility.

Endpoints

Primary endpoint:

- Prevalence of vaginal stenosis grade 2 or higher.

Secondary endpoints:

- Gynecological findings: vaginal elasticity, adhesions, telangiectasias, ulceration, and bleeding.
- Radiation Dose to sexual organs at risk
- Patient-reported outcomes on sexual health issues
- Pattern of care; dilator use, lubrication, hormone treatment(local/systemic), received specialized sexual counseling.
- Patient satisfaction with the existing sexual rehabilitation program

Data collection

1. **Sociodemographic data**
   Sociodemographic data will be collected via a case report form (CRF) during the consultation where the gynecological examination is performed. This data includes age, smoking status, menopausal status, relationship status, WHO performance status, and comorbidities. (first part of Appendix 1)

2. **Clinical data**
   Clinical data will be extracted from medical records. They will encompass details of the anal cancer diagnosis, including tumor location (with specific information on vaginal invasion if present), tumor volume and length, histological type, and TNM classification. Information about the treatments received will be detailed, including radiation dose and fractionation schedule, as well as chemotherapy regimens. Additionally, data on any salvage surgery or recurrence will be collected, along with details of any subsequent treatments provided for the recurrence. Access to these records will be granted to the principal investigator and relevant regulatory authorities for research purposes, including monitoring, quality control, and compliance with required oversight.

3. **Gynecological examinations:**
   Comprehensive vaginal morbidity will be assessed using an electronic case report form, as detailed in Appendix 1. The morbidity assessment form is based on vaginal morbidity documentation following radiotherapy for cervical cancer, as described by Kirchheiner (2012)[16]. This methodology has also been employed in Suvaal (2023)[17].

To ensure uniform grading of vaginal morbidity across the study sites, a dedicated seminar will be held before the initiation of patient inclusion. This seminar will involve all relevant physicians responsible for assessments at the three participating centers to align understanding and grading practices, minimize inter-observer variability, and ensure consistency in evaluations throughout the study.

4. **Patient-reported outcome measures:**
   Electronic surveys will be sent following the control visit where the gynecological examination is performed. A reminder email will be sent after one week if a response is missing. If the patient cannot access the survey electronically, it will be handed in on paper form during the consultation and entered electronically afterward.

   The survey will include validated questionnaires: the European Organization for the Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) with the Anal Cancer Module (EORTC-QLQ-ANL27), EORTC Sexual Health Questionnaire (EORTC-QLQ-SH22), and Female Sexual Function Index (FSFI). See Appendix 2 for details on these questionnaires.

   In addition to the questionnaires mentioned, there will be questions regarding patterns of care, see Appendix 3

5. **Radiation Dose parameter:**
   The principal investigator will retrospectively delineate the vagina on therapy scans from the included participants in accordance with applicable delineation guidelines. Based on this, a retrospective analysis of dose-volume histograms will be performed to identify correlations between vaginal morbidity and radiation exposure.

6. **Interviews:**
   Semi-structured interviews with early participants will be conducted over the telephone using the interview guide provided in Appendix 4. The interviews will be conducted with notes taken on themes and quotes during the sessions for further analysis.

Data management

All data will be entered into a secure electronic database (REDCap) hosted at Aarhus University Hospital. Compliance with GDPR and Danish data protection regulations will be ensured.

Sample size and statistical analysis plan

Sample size

Annually, approximately 120 women in Denmark undergo treatment for anal cancer, with roughly stage distributions of 25% (Stage I), 52% (Stage II), 17% (Stage III), and 6% (Stage IV)[18]. Using survival data from the RTOG 98-11 trail[19], we calculated 1-, 2-, and 3-year survival rates assuming a linear decline from 100% survival at treatment initiation to the reported 5-year survival rates of 82% for Stage I, 74% for Stage II, 57% for Stage III, and 42% for Stage IV. From these calculations, women treated three years ago contributed approximately 99 women alive, those treated two years ago contributed 106, and those treated one year ago contributed 113, yielding a total of 318 women who have received treatment for anal cancer within a period of three years are alive and eligible for follow-up. Given the sensitive nature of topics such as gynecological toxicity and sexual dysfunction,

we conservatively estimate a participation rate of 30%. This results in an expected inclusion of 80 participants.

This sample size of approximately 80 participants will allow us to achieve 80% statistical power to detect a correlation between radiation dose and vaginal stenosis, with a significance level of 0.05 and an assumed moderate correlation coefficient of r=0.3. This power calculation ensures that the study is adequately designed to investigate the potential dose-response relationship

For the semi-structured interview sub-study, 20 participants are initially included to explore patient satisfaction with the sexual rehabilitation program. Thematic analysis will guide data collection and analysis, following an iterative approach to identify saturation. Saturation is defined as the point where no new themes, patterns, or insights emerge, ensuring data utility is maximized.

If thematic saturation is not reached after the initial sample, additional participants will be included in batches of 5 participants. This approach ensures robust, comprehensive findings aligned with the research objectives while maintaining methodological rigor [20]

Statistical analysis plan

Vaginal stenosis grade 2 or above, will be calculated as the proportion of participants meeting the criteria out of the total number of participants. A 90% confidence interval (CI) will be used to indicate the uncertainty surrounding the prevalence estimate.

Physician-reported vaginal outcomes: Variables such as adhesions, elasticity, telangiectasias, ulcerations, and bleeding will be summarized using descriptive statistics

Patient-reported outcomes (PROs): Data from the Female Sexual Function Index (FSFI), EORTC-QLQ-SH22 and EORTC-QLQ-C30 with the ANL24 supplement will be analyzed. Scores will be calculated according to the respective guidelines, transforming raw data into standardized scores. Comparisons across groups (e.g., stenosis vs. no stenosis) will be made using appropriate tests such as t-tests or Mann-Whitney U tests.

Dose-response relationship: This will be explored using logistic regression, assessing the relationship between radiation dose and vaginal stenosis grade 2 or above. A dose-response curve will also be generated using spline regression to visualize potential non-linear relationships.

Patient care satisfaction: Data from semi-structured interviews will be analyzed using thematic analysis to identify key themes and patterns related to patient satisfaction with guidance and counseling on gynecological and sexual issues post-treatment. Notes will be coded in an exploratory manner, allowing themes to emerge from the data and ensuring a comprehensive understanding of patient experiences and perspectives.

All analyses will be conducted using a predefined statistical significance level of 0.05. Results will be reported with appropriate measures of uncertainty, such as confidence intervals. Quantitative data analyses will be performed using StataSE18 software, and qualitative data will be analyzed using NVivo14 software.

Study schedule (tentative)

Protocol approved: Awaiting

Inclusion start: 01.05.2025

Inclusion end: 01.05.2026 2026

End of data collection: June 2026

Data analysis and interpretation: Fall 2026

Plans for dissemination and reporting

The findings of this study will be disseminated to ensure academic and public access to the results. Planned activities include publishing study results in peer-reviewed scientific journals and presentations at national and international conferences focusing on oncology, radiation therapy, and survivorship care. All results, whether positive, negative, or inconclusive, will be published to contribute to the broader evidence base.

Efforts will also be made to communicate the key findings in layperson-friendly formats, such as patient-oriented brochures or updates to clinical practice guidance, to benefit survivors and healthcare professionals involved in anal cancer care.

The principal investigator (Johanne Hollands Steffensen) will be first author on the papers. All investigators will be invited for a co-authorship according to the Vancouver regulations

Ethical issues, safety aspects, and complications

The study will adhere to ethical standards and obtain approval from relevant medical ethics committees. All participants will provide written and oral informed consent before inclusion in the study. No serious complications are expected from the gynecological examination. In the short term, some individuals may experience temporary discomfort during the procedure. Additionally, discussing intimate topics may be emotionally distressing for some participants. While no long-term risks are known, unforeseen burdens related to participation cannot be entirely ruled out. If you experience discomfort, you have the right to withdraw from the study at any time or choose not to answer specific questions.Emphasis will be placed on minimizing discomfort and safeguarding participant confidentiality. The anticipated benefits of the research include improved treatment outcomes and enhanced quality of life for future patients.

Funding and Financial Disclosure

The study is investigator-initiated, with the investigator independently designing and conducting the research.

Participants in this study are covered by the Danish Act on Complaints and Compensation within the Healthcare System, and any complaints can be submitted to the Danish Agency for Patient Complaints in accordance with applicable regulations.

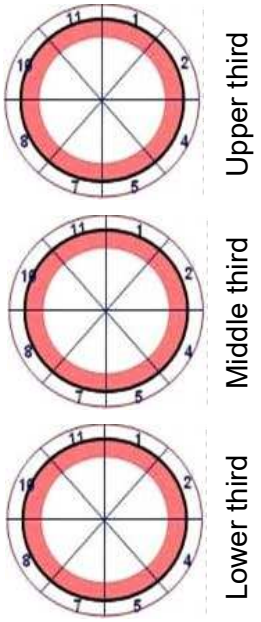
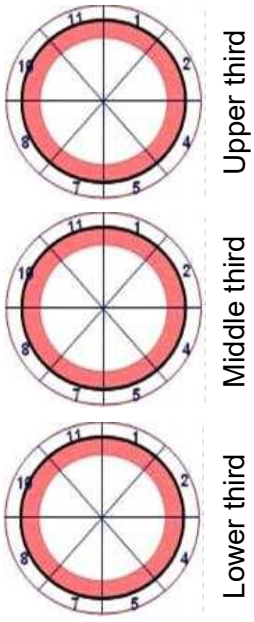
A grant from the Independent Research Fund Denmark (DKK 2.112.424) covers expenses related to the project-specific investigations. The grant funds are administered by Aarhus University. None of the researchers involved have financial interests in the project or affiliations with the funding provider. No financial compensation will be provided to study participants.

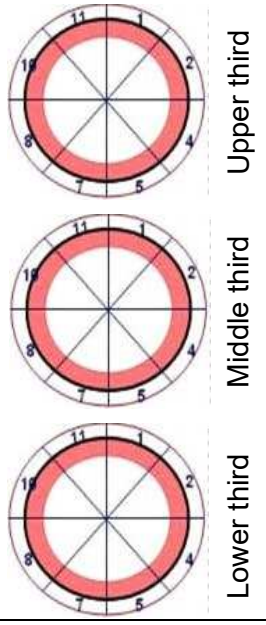
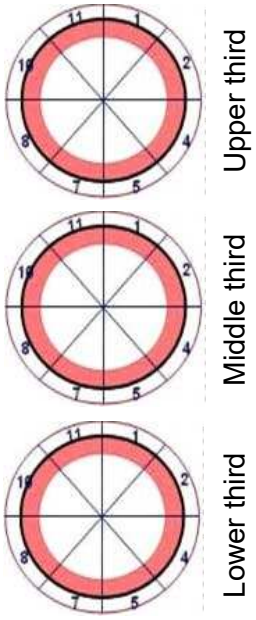
Appendix I

VAGINAL MORBIDITY AT GYNAECOLOGICAL EXAMINATION

It is advised to manually assess adhesions before inserting the speculum for gynecological examination. In addition to grading, it is mandatory to specify the exact location of toxicity on the provided 3D vaginal map, divided into upper, middle, and lower thirds.

Participant ID	
Time since last RT	
Date	
Family status	☐ no partner ☐ partner
Menopausal status	☐ premenopausal ☐ postmenopausal
Smoking status	☐ Never ☐ Previous ☐ Active
WHO performance status	☐ P0 ☐ P1 ☐ P2 ☐ P3
Specify co-morbidities	
Vaginal stricture (CTCAE v. 5)	☐ None ☐ Asymptomatic; mild vaginal shortening or narrowing ☐ Vaginal narrowing and/or shortening not interfering with physical examination ☐ Vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity, or physical examination

Vaginal Adhesions	☐ no adhesions ☐ adhesions in the upper third ☐ adhesions in the middle third ☐ adhesions in the lower third 
Vaginal Elasticity	☐ tissue soft and mobile ☐ tissue a little firm and mobile ☐ tissue quite hard with limited mobility ☐ tissue hard and immobile ☐ complete obliteration, not accessible
Vaginal Fibrosis	☐ no fibrosis ☐ fibrosis in the upper third ☐ fibrosis in the middle third ☐ fibrosis in the lower third 

Vaginal Telangiectasia	☐ no telangiectasia ☐ telangiectasia in the upper third ☐ telangiectasia in the middle third ☐ telangiectasia in the lower third 
Vaginal Telangiectasia contact bleeding	☐ no telangiectasia ☐ TA without contact bleeding ☐ TA with contact bleeding
Vaginal Fragility / Bleeding with examination	☐ none / robust ☐ development of erythema or petechiae, no surface bleeding ☐ moderate surface fragility with minimal trace bleeding ☐ overt/obvious bleeding with examination
Vaginal Ulceration	☐ none ☐ limited (<1cm^2) superficial ulceration (loss of surface epithelium) ☐ widespread (>1cm^2) or deep ulceration (loss/devitalisation of deeper tissue layers/necrosis) 

Appendix 2

Instrument	Description	Number of Items	Sub-scales	Answer Categories	References
FSFI	Measures female sexual function across six domains.	19	Desire Arousal Lubrication orgasm Satisfaction Pain	0 (no activity) to 5 (optimal function).	Rosen (2000)[21] Wiegel (2005)[22] Meston (2020)[23]
EORTC QLQ-C30	Core QoL questionnaire for cancer patients in clinical trials.	30	Functional (physical, role, emotional, cognitive, social) Symptoms (fatigue, nausea/vomiting, pain) Global health Single items (e.g., insomnia)	1 to 4 Likert scale (1 to 7 for global health status).	Aaronson(1993)[24] Osoba (1997)[25]
EORTC QLQ-ANL27	Anal cancer-specific QoL module supplementing QLQ-C30.	27	Bowel symptoms (with/without stoma) Pain/discomfort Stoma-care Vaginal symptoms Urinary frequency and urgency, swelling in legs, self-cleaning, planning activities, sex life, sexual interest, painful intercourse, and erectile problems.	1 to 4 Likert scale.	Sodergren (2023)[26]
EORTC QLQ-SH22	Sexual health assessment for cancer patients/survivors.	22	Sexual satisfaction Sexual pain Sexual activity, decreased libido, incontinence, fatigue, treatment, communication with professionals, partnership, confidence erection body image (male), body image (female), vaginal dryness	1 to 4 Likert scale.	Greimel (2021)[27]

Appendix 3

Pattern of care questionnaire:

After your radiotherapy treatment, have you, at any point, performed vaginal dilation, either by using vaginal dilators or through vaginal intercourse?	☐ No ☐ Yes
If No: Why have you not performed vaginal dilation?	----------
If Yes: How often did you perform vaginal dilation during the first 6-12 months after radiotherapy, either by using vaginal dilators or through vaginal intercourse? *If you have not reached 12 months after completing radiotherapy, how often have you performed vaginal dilation since radiotherapy, either by using vaginal dilators or through vaginal intercourse?*	☐ Not at all ☐ Less than/or one time per month ☐ 1-4 times per month ☐ 2-3 times per week or more ☐ Don't remember
How often have you performed vaginal dilation in the past 3 months, either by using vaginal dilators or through vaginal intercourse?	☐ Not at all ☐ Less than/or one time per month ☐ 1-4 times per month ☐ 2-3 times per week or more ☐ Don't remember
If Not at all: When did you stop? *And why?*	----------
Do you use any hormone therapy?	☐ No ☐ Lokal hormone treatment (e.g. Vagifem) ☐ Systemic hormone treatment
After completing radiotherapy, have you had one or more consultations with specialized sexual health nurses or another sexologist to discuss sexual issues related to your cancer treatment?	☐ No, I have not had any consultations. ☐ No, but I would have liked to. ☐ Yes, I have had one or more consultations

Appendix 4

Semi-Structured Interview Guide: Patient Satisfaction with Counseling

Introduction
Welcome

"Thank you for participating. My name is [your name], and I would like to discuss your experiences with guidance regarding gynecological and sexual issues after radiation therapy for anal cancer."

"Your input will help us improve how we support patients in the future. Participation is voluntary, and you can skip questions or end the interview anytime. Your answers will remain confidential."

"Before we begin, do you have any questions for me?"

Section 1: Background information

- Have you experienced any side effects related to gynecological issues or sexual dysfunction, such as localized pain in the vaginal area, vaginal bleeding, narrowing of the vagina, abnormal discharge, or more general effects on sexual function or desire, including impacts on body image?

Section 2: Information received

- **What and When:**

  Can you describe what information you were given about gynecological and sexual side effects?

  When during your treatment journey were you informed about these potential side effects? And by who?

- **Adequacy of information:**
  What do you think about the timing and amount of information on the topic you were given?

Section 3: Preparedness and Support

- **Preparedness:**
  Did the guidance you received make you feel adequately prepared to handle these side effects? Why or why not?

- **Barriers:**
  Were there any barriers for you to discuss gynecological or sexual issues with healthcare providers?
  If yes, what were these barriers (e.g., discomfort, lack of time, cultural factors)?

Section 4: Preferences for Communication

- **Preferred Healthcare Professional:**
  Is there a particular type of healthcare professional you feel most comfortable discussing these issues with (e.g., nurse, doctor, counselor)?

- **Suggestions for Improvement:**
  Do you have any suggestions on how guidance about these side effects could be improved for future patients?

Conclusion

- **Wrap-Up:**
  Is there anything else you would like to share about your experience or the guidance you received?
- **Thank You:**
  Thank the participant for their time and valuable insights.

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