

CENTER FOR CLINICAL GUIDELINES | CANCER

Management guidelines of late adverse effects after chemoradiation for anal cancer

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Background

This clinical practice guideline is developed in collaboration between the Danish Multidisciplinary Cancer Groups (DMCG.dk) and the Danish Clinical Registries (RKKP). The development is part of an intensified guideline effort launched in relation to the National Cancer Plan IV. The aim is to support high quality cancer care across the Danish healthcare system. The guideline content is approved by the disease specific Multidisciplinary Cancer Group, whereas the format is approved by the Center for Clinical Practice Guidelines | Cancer. Further information about clinical practice guidelines concerning cancer treatment in Denmark can be found here: www.dmcg.dk/kliniske-retningslinjer

The target users of this guideline are health care professionals working in the Danish healthcare system. The guideline consists of systematically prepared statements that can be used as a decision-making support tool by healthcare professionals and patients, when deciding on appropriate and correct care in a specific clinical situation.

Clinical practice guidelines concerning Danish cancer care is characterized as professional advice. The guidelines are not legally binding and professional judgment in the specific clinical context will always determine what the appropriate and correct medical care is. Adherence to the guideline recommendations is no guarantee for a successful outcome and sometimes care corresponding to a lower level of evidence will be preferred due to the individual patient's situation.

The clinical practice guideline contains central recommendations (chapter 1) and a description of the scientific evidence (chapters 3+4). Recommendations marked A are the strongest, whereas recommendations marked D are the weakest. For further information on strength of evidence see the"Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations", https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Information on the target population (chapter 2) and the method of development (chapter 5) is also included in the guideline. Please see the table of contents for page reference.
Information on the national integrated cancer pathways – descriptions of the patient journey through the healthcare system – can be accessed at the Danish Health Authority website: https://www.sst.dk/en/disease-and-treatment/cancer/cancer-pathways.

Development of this clinical practice guideline has been funded by The Danish Health Authority (National Cancer Plan IV) and the Danish Clinical Registries (RKKP).

Revisions to previous version (changelog)

Revisions to version 1.0

Guideline chapter	Description of revisions or additions
Recommendations	Addition of two new recommendations regarding lymphedema (recommendation 13 and 14).
Literature and evidence review	Addition of evidence level to all references.
Literature search	An updated seasch was performed.
Literature review	Upon revision an additional 15 articles were included and a section on lymphedema was added.

1. Anbefalinger - DA (Quick Guide)

Diagnosticering og monitorering af senfølger

1. **Der bør etableres tilbud om systematisk evaluering af livskvalitet og behandlingsrelaterede symptomer efter behandling for anal cancer for at identificere patienter der har behov for yderligere støtte, udredning eller behandling for senfølger (Evidensniveau 3b) (C).**

Psykosociale aspekter

2. **Opfølgning af patienter behandlet for anal cancer bør omfatte tilbud om evaluering af sundhedsrelateret livskvalitet (Evidensniveau 2b) (B).**

Senfølger i mave- og tarmkanalen

3. **Patienter behandlet for anal cancer bør rutinemæssigt tilbydes screening for gastrointestinale senfølger da det forekommer hos op til 65% (Evidensniveau 2a) (B).**

4. **Patienter med vedvarende gastrointestinale symptomer (> 3-6 måneder efter behandling) er rektal inspektion og -eksploration med vurdering af anal tonus, udelukkelse af anal stenose og undersøgelse med stift rektoskop eller fleksibel**

sigmoidoskopi med udelukkelse af recidiv de nødvendige minimumsundersøgelser (Evidensniveau 5) (D)

5. **Ved persisterende symptomer (> 3-6 måneder efter behandling) bør patienten tilbydes henvisning til specialiseret enhed (Evidensniveau 5) (D)**

Senfølger i urinvejene

6. **Patienter behandlet for anal cancer bør rutinemæssigt tilbydes screening for urogenitale senfølger, da det forekommer hos optil 45% (Evidensniveau 3a) (B).**

7. **Ved persisterende symptomer (> 3-6 måneder efter behandling) bør der tilbydes henvisning til specialiseret enhed (Evidensniveau 5) (D)**

Seksuel dysfunktion

8. **Patienter behandlet for anal cancer bør rutinemæssigt tilbydes screening for seksuel dysfunktion da det forekommer hos optil 90% af mænd og optil 100% af kvinder (Evidensniveau 3a) (B).**

9. **Ved persisterende symptomer bør der tilbydes henvisning til specialiseret enhed (Evidensniveau 5) (D)**

Smerte

10. **Patienter behandlet for anal cancer med vedvarende smerter bør gennemgå udredning mhp bestemmelse af udløsende årsag (er).**

11. **Insufficiensfrakturer detekteres bedst ved MR scanning af bækkenet (Evidensniveau 3b) (B)**

12. **Ved persisterende smerter bør der tilbydes henvisning til specialiseret enhed (Evidensniveau 5) (D)**

Lymfødem

13. **Patienter behandlet for anal cancer bør rutinemæssigt tilbydes screening for sekundært lymfødem da det er hyppigt forekommende og tidlig diagnose påvirker prognosen (Evidensniveau 5) (D)**

14. **Ved oplevelse eller objektive fund af hævelse eller tyngdefornemmelse i bækken/ genitalia og/eller underekstremiteter hos patienter behandlet for anal cancer bør der tilbydes henvisning til specialiseret enhed (Evidensniveau 5) (D)**

Recommendations - ENG (Quick Guide)

Diagnosing and monitoring of late adverse effects

1. **To identify patients who require further specialist evaluation or support after treatment and to offer optimal tailored treatments, it is recommended to monitor Quality of Life and late adverse effects accurately and systematically following treatment (Evidence level 3b) (Grade C).**

Psychosocial Distress

2. **Anal cancer survivors should be offered long-term follow-up of including evaluation of HRQOL (Evidence level 2b) (Grade B).**

Late gastrointestinal adverse effects

3. **Anal cancer survivors should be offered routinely screening for late gastrointestinal adverse effects as they are found in up to 65% (Evidence Level 2a) (Grade B).**

4. **In patients with persisting GI symptoms (> 3-6 months after treatment), rectal examination with assessment of anal tone, exclusion of anal stenosis and a rigid proctoscopy or flexible sigmoidoscopy with exclusion of recurrence is the minimum investigation needed (Evidence level 5) (Grade D)**

5. **Patients with persisting symptoms (> 3-6 months after treatment) should be offered referral for treatment in specialized units (Evidence level 5) (Grade D).**

Late Urological adverse effects

6. **Anal cancer survivors should be offered routinely screening for late urological toxicity as it is found in up to 45% (Evidence level 3a) (Grade B).**

7. **Patients with persisting symptoms (> 3-6 months after treatment) should be offered referral for treatment in specialized units (Evidence level 5) (Grade D).**

Sexual Dysfunction

8. **Anal cancer survivors should be offered routinely screening for late sexual dysfunction as it affects up to 90% of men and up to 100% of women (Level of Evidence 3a) (Grade B).**

9. **Patients with persisting symptoms should be offered referral for treatment in specialized units (Evidence level 5) (Grade D).**

Pain

10. **Anal cancer survivors with persisting pain should undergo diagnostic work up to determine cause (Evidence level 5) (Grade D).**

11. **MRI should be the preferred imaging modality for detecting pelvic insufficiency factures (Evidence level 3b) (Grade B)**

12. **Patients with persisting symptoms should be offered referral for specialized treatment (Evidence level 5) (Grade D).**

Lymphedema

13. **Anal cancer survivors should be offered routinely screening for secondary lymphoedema as it is common and early diagnosis affects treatment outcome positively (Evidence level 5) (Grade D)**

14. **Anal cancer survivors with self-reported or objectively assessed swelling or heaviness in the lower body should be referred for treatment at specialized units/ certified lymphedema therapist (Evidence level 5) (Grade D)**

2. Introduction

Although squamous cell carcinomas of the anal canal (anal cancer) are relatively rare, the incidence has been increasing over the last 2 decades along with the age at time of diagnose decreasing (1, 2). Increases in the prevalence of exposures, such as cigarette smoking, anal intercourse, HPV infection, and the number of lifetime sexual partners, may account for the increasing incidence of anal cancer in men and women (2).

The first-line treatment of anal cancer is concomitant chemoradiotherapy (CRT). The purpose of the treatment is cure/ tumor control, preservation of sphincter function, and the best possible quality of life. Surgery and CRT are, however never compared directly in a randomized study, but CRT has, in addition to sphincter preservation, shown better local control and survival in several studies (3). Currently, surgery plays a minor role up front in managing anal cancer. Patients with severe anal pain or fecal incontinence can be offered a temporary, relieving stoma. In the case of cancer recurrence, salvage surgery may be offered. CRT for anal cancer involves a variable amount of radiation delivered to the rectum, the anal canal and the sphincter apparatus, large and small intestines as well as surrounding inguinal lymph nodes. Scattered radiation to a minor extend may also affect the skin, small bowel, female internal genitals, male genitals and the bony structures in the pelvis.

The significant improvements in treatment for anal cancer have led to a growing population of anal cancer survivors. However, surviving anal cancer often comes with the price of late adverse effects to the treatment. Research has revealed substantial unmet needs due to long-term symptoms, and functioning impairments after treatment that can negatively impact on health-related quality of life (4, 5).

This guideline has examined the (lack of) scientific evidence for management of late adverse effects after CRT for anal cancer and extrapolated knowledge from other pelvic malignancies treated with pelvic CRT with the aim to guide clinical management of late adverse effects.

Symptoms have been divided into overall categories including: Psychosocial-, bowel-, urinary-, sexual- (man and women) and pain symptoms or –complaints and examined these individually.

Objective

The overall objective is to guide clinical management of late adverse effects following CRT for anal cancer.

Target population

This guideline applies to all survivors of anal cancer after treatment with CRT. Patients who have undergone salvage surgery for anal cancer are not targeted in this guideline. The principles may also be applicable for patients with other pelvic organ cancers treated with CRT presenting with Pelvic Radiation Disease (6).

Target User

This guideline is developed to support clinical decision-making and quality improvement. Thus, the target

users are healthcare professionals working with treatment and follow-up for anal cancer and their affiliated clinical units taking care of late adverse effects following cancer therapy.

3. Scientific evidence

Diagnosing and monitoring of late adverse effects

1. To identify patients who require further specialist evaluation or support after treatment and to offer optimal tailored treatments, it is recommended to monitor Quality of Life and late adverse effects accurately and systematically following treatment (Evidence level 3b) (Grade C).

Literature review and evidence description

Grading of symptoms

According to the literature, the most frequently used toxicity assessment tools were the national cancer institute Common Terminology Criteria for Adverse Events (CTCAE) classification, the Radiation Therapy Oncology Group (RTOG/ EORTC) radiation morbidity scoring scheme (7) and the Late Effect on Normal Tissues- Subjective, Objective, Management and Analytic (LENT-SOMA) (8).

Toxicity in CTCAE is graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4), with specific parameters according to the anal canal (12 specific symptoms defined including anal fistula, anal hemorrhage, anal mucositis, anal necrosis, anal pain, anal ulcer, abdominal distension, abdominal pain, diarrhea, flatulence, fecal incontinence and proctitis). Death (Grade 5) is used in some of the criteria to denote a fatality. The timing of adverse events is not defined in CTCAE. This scale has been adapted for patients to self-report (NCI-PRO-CTCAE) (9).

The LENT-SOMA Score is obtained after completing a series of questions in a structured interview, which grade subjective and objective symptoms and score for the requirement for medical intervention. Scores can then be summed and divided by the total number of questions to give an overall score of between 0 (no symptoms) and 5 (fatal toxicity).

The RTOG/EORTC morbidity criteria grade severity by symptoms into four grades. Grade 1 is ‘slight’, Grade 2 is ‘intermittent’, and Grade 3 is ‘bleeding requiring surgery’. Grade 4 includes necrosis, perforation, and fistula. The late morbidity scoring scheme grades toxicity that occurs >90 days after the commencement of treatment. None of these systems have been validated specifically for anal cancer patients.

Patient Reported Outcomes (PROs)

Asking patients to report their own symptoms via patient reported outcomes (PROs) has proven extremely acceptable to patients in the oncology clinic setting. Reviews suggest improvement of symptom/ function monitoring, communication and clinical decision-making as a result (10). Further, use of investigator lead toxicity grading significantly underestimate morbidity compared to patient administrated reporting with PROs (11). A prospective study of 100 anal cancer patients used both CTCAE and PROs to evaluate acute toxicity and found that PROs were markedly higher with only slight to fair agreement to CTCAE (C30/CR29) (12).

A study examining the use of a modified self-administered Inflammatory Bowel Disease questionnaire and the Vaizey Incontinence questionnaire for late toxicity after pelvic radiation in 142 patients (8 anal cancer) found highly significant correlation between the degree of gastrointestinal dysfunction recorded in patients who had completed pelvic radiotherapy at least 3 months previously in comparison to scores recorded when the staff administered the LENT-SOMA questionnaire (13).

Using an internet-based platform, another study found that for lower GI cancer survivors (119 anal cancer patients), it was feasible to obtain PROs from an Internet-based survivorship tool. Survivors reported a wide spectrum of late and long-term effects, and these could be used to inform counseling at the time of diagnosis and to help anticipate and respond to disease-related and treatment-related sequelae during follow-up (14).

Most studies have used the EORTC QLQ-C30 questionnaire (cancer-specific QoL) and the colorectal cancer module QLQ-CR38(/29) (site-specific QoL) that consists of 38 (29) items covering symptoms and side-effects related to different treatment modalities, body image, sexuality and future perspective. The RTOG/EORTC is currently finalizing international validation for anal cancer with the aim of setting common standards for morbidity reporting for both clinical and scientific use (https://qol.eortc.org/questionnaire/qlq-anl27/) (15). The EORTC QLQANL27 can be used by clinicians to measure the impact of anal cancer and its treatment on their patients both within the acute and long-term follow-up context (16). A recent study evaluated this tool and found good psychometric properties and availability in 16 languages including Danish.

Quality of Life is a multi-dimensional construct shaped by physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to important features of their environment (10). Physical symptoms experienced as a result of disease and treatment impacts on Quality of Life judgements (17). But the patient´s response in terms of coping strategies, goals and expectations from treatment significantly affects their perception of Quality of Life. Therefore, assumptions regarding Quality of Life cannot be made from an inspection of toxicity grades; only the patient can provide an accurate estimate of Quality of Life (18).

Psychosocial Distress

2. Anal cancer survivors should be offered long-term follow-up of including evaluation of HRQOL (Evidence level 2b) (Grade B).

Literature review and evidence description

The cost for the patient of long-term survivorship after anal cancer are the long-term sequelae of the disease and late adverse effects that may have a significant impact on health-related quality of life (HRQOL). HRQOL is complex and characterized as subjective and multi-dimensional. HRQOL assessment does not solely reflect symptom burden, but includes factors not directly related to disease-related or treatment-related effects.

Cancer survivors in general are at elevated risk of psychosocial distress and mental health concerns; a nationwide matched cohort study from Sweden found that psychosocial distress can persist for as long as 10 years post-diagnosis (19) (evidence level 3a). Further, distress - often related to fear of recurrence - is

common in cancer survivors and can negatively affect Quality of Life (19) (evidence level 3a). Quality of Life judgements are affected by the survivor´s physical health. Likewise, the survivor´s coping strategies, goals and expectation from treatment can significantly affects their perception of Quality of Life (17).

Generally, the literature on HRQOL in anal cancer survivors is of poor quality, limited by single center studies with low sample sizes and cross-sectional designs (10). Resent reviews point out that no anal cancer specific Quality of Life instrument exist. However, this is now remedied as the EORTC QLQ-ANL27 (15) has completed phase III and is available for use in clinical trials. A larger phase IV international validation study to confirm its psychometric properties is now underway.

Reduced overall or global Quality of Life scores were reported in cross sectional studies with long-term follow-up (4, 20, 21) (evidence level 3b). However, others found global QOL outcomes acceptable as they were similar to normative data (22-24) (evidence level 3b). Longitudinal studies found a significant decrease in Quality of Life immediately following treatment, but substantial improvements were reported at 1-year follow up (25-27) (evidence level 3a).

Among anal cancer survivors with decreased long-term Quality of Life the cause seems to be multifactorial (28). Consistently, the studies point to bowel dysfunction such as fecal incontinence, fecal urgency and fecal frequency as detrimental to Quality of Life (20-22, 24, 29, 30) (evidence level 2c). Sexual dysfunction and urinary incontinence were also associated to lower overall Quality of Life (20, 30, 31) (evidence level 2c).

The survivors report impairment of physical function as well as role - and social function following treatment, but the latter two scales improved significantly at one-year follow-up (25, 26) (evidence level 3a). Disease related symptoms were frequently reported in cross sectional studies in form of fatigue, diarrhea, appetite loss, buttock pain, flatulence, and fecal incontinence/diarrhea (20, 21, 24) (evidence level 3b). Social, physical, role and emotional functioning as well as future perspective have been found to be negatively associated with gastrointestinal late adverse effects, most specifically sphincter insufficiency leading to anal incontinence (4, 24). In fact, gastrointestinal late adverse effects have been found to be an independent risk factor for lower emotional and social functioning (24) (evidence level 3b).

Using the EORTC C-30 *and* the EORTC QLQ-ANL27 in 52 anal cancer patients Sauter et al. evaluated long term QoL (71 (7-176) months) by telephone interviews and compared EORTC C-30 outcomes to a German reference population. In comparison to the German reference population, anal cancer patients had a statistically significant reduction in role, emotional, and social functioning, but higher cognitive functioning, as well as overall global health. Among patients, males showed a better emotional functioning and patients younger than 70 years seemed to obtain a better physical- and role functioning, as well as a better global QoL. In the functioning scales, patients showed significantly high scores in bowel function without stoma, and in female sexual functioning compared to the german reference population. Most common symptoms were micturition frequency, leg edema, toilet proximity, cleanliness, and planning activities. The symptoms pain and leg edema seemed to occur more often in patients with advanced T-stages (29) (evidence level 3b).

Symptoms from the pelvic organs such as diarrhea, pain, fecal incontinence, and sexual problems are often perceived as private and embarrassing and may affect self-confidence and have impact on daily life. The nature and severity of symptoms seem to negatively affect a person's ability to function and enjoy life and

might result in avoidance or isolation (20). The private and tabooed nature of pelvic symptoms may restrain survivors from mentioning this when unasked. The recognition of the symptoms and dysfunction may contribute to relief and help survivors to cope with impaired function and pelvic symptoms. An increased awareness and acceptance of the extent of the problem will stimulate and facilitate multidisciplinary collaboration often necessary.

Actions strategies

- The only existing disease specific tool, the EORTC QLQ-ANL27, should be translated, validated and implemented in everyday practice (Grade D).

Late gastrointestinal adverse effects

3. **Anal cancer survivors should be offered routinely screening for late gastrointestinal adverse effects as they are found in up to 65% (Evidence Level 2a) (Grade B).**

4. **In patients with persisting GI symptoms (> 3-6 months after treatment), rectal examination with assessment of anal tone, exclusion of anal stenosis and a rigid proctoscopy or flexible sigmoidoscopy with exclusion of recurrence is the minimum investigation needed (Evidence level 5) (Grade D)**

5. **Patients with persisting symptoms (> 3-6 months after treatment) should be offered referral for treatment in specialized units (Evidence level 5) (Grade D).**

Literature review and evidence description

The overall incidence of any gastrointestinal (GI) late adverse effect after CRT for anal cancer has been reported to be anywhere from 7–64.5% (5). Late adverse effects tend to occur in tissues with a low turnover of cells, such as subcutaneous tissue, fatty tissue, muscle, and within tissues that contain rapidly proliferating cells, such as the wall of the intestine. As an anal cancer is arising from squamous cells in the anal canal and in the anal margins, this area is the primary target of radiation therapy, and damage to the integrated and delicate function of anal continence is predictable.

Anal cancer survivors have been shown to have lower anal resting-, squeeze- and yield- pressures, as well as reduced resistance to flow when compared to healthy volunteers, whereas rectal volume is found unaltered in comparison (32). Similarly, a study recording cortical evoked potentials during anal and rectal stimuli in anal cancer patients after CRT, found impaired peripheral and cortical processing that the authors suspected to cause dys-integration of consciously perceived ano-rectal sensory stimuli possible contributing to various degrees of incontinence (33).

Reviewing the literature, the most common symptoms of late GI adverse effects in anal *and* rectal cancer (treated with surgery with or without CRT) patients are fecal urgency (14-78%), fecal incontinence (7-60%), tenesmus (13-36%), diarrhea (45-60%), excessive flatulence (38-55%), pain (13-27%), bloating (13-32%), and rectal bleeding (23-25%) (4, 5, 13, 20, 34-37).

GI adverse effects can effectively be monitored with PROs (38) either in the format of a fecal incontinence specific questionnaire (Inflammatory Bowel Disease questionnaire and the Vaizey Incontinence questionnaire) (13), modified use of the Low Anterior Resection Syndrome score (12, 39), or as a part of the EORTC QLQ-ANL27 (15).

Diarrhea

The incidence of diarrhea ranges from 0-26.7% of anal cancer survivors (5) and the incidence of severe diarrhea (Grade 3 CTCAE or stool frequency >8/day in LENT-SOMA) ranges from 0.4-4.9 % (5) (Evidence level 3b). Although psychological factors may contribute to episodes of loose stool after pelvic radiotherapy, specific physiological problems can commonly be defined, including small-bowel bacterial overgrowth, bile-acid malabsorption, carbohydrate malabsorption, changes in transit, development of small and/or large bowel strictures, neoplasia, or new-onset primary inflammatory bowel disease (Evidence level 4).

Treatment

Treatment of diarrhea should follow gastrointestinal work-up for the cause of the diarrhea. Studies suggest that in 8–15% of patients with diarrhea following pelvic radiation, the diarrhea is caused by small bowel bacterial overgrowth, though reliable diagnosis is difficult. Optimum treatment strategies are not defined, however, antibiotic treatment targeting gram-negative bacilli used for up to 2 weeks may abolish symptoms (6, 40) (Evidence level 2b).

A chronic reduction in bile-acid absorption is common after pelvic radiation and it may cause diarrhea (6, 41). The condition is diagnosed by the selenium homocholic acid taurine (SeHCAT) test and responds to bile acid sequestrants. Data suggest that patients with radiation induced bile-acid malabsorption benefit from regular use of bile-acid sequestrants (colestyramine; 4 g twice a day) (6) (Evidence level 2a) or other bile-acid sequestrants. Dietary advice to reduce fat intake often adds to the effect of bile-acid sequestrants. New-onset lactose malabsorption persists after radiotherapy in about 5% of patients and frequently causes diarrhea that requires qualified dietary advice[6] (Evidence level 5).

Other causes of diarrhea include: large-bowel strictures (3–15% of patients with diarrhea after pelvic radiotherapy); small-bowel strictures (9%); disease relapse (4–10%); new neoplasia in the gastrointestinal tract (8%); new-onset inflammatory bowel disease (i.e., Crohn's disease, or ulcerative, lymphocytic, or collagenous colitis—4%); or radiation proctitis (33%)) (6).

If no cause for diarrhea is found dietary counselling, psyllium or Linn seeds or antidiarrheal drugs may be of help (Evidence level 5). A questionnaire-based study on 254 patients treated for pelvic cancers found that two thirds had made changes in dietary habits (notable changes were reduction of sugary foods (48%) and alcohol (41%)). Receipt of support from the health care team was significantly associated with dietary change, however, only 43% had received this kind of support and more than two thirds stated that they would like to receive additional dietary support (42) (evidence level 3b).

Fecal incontinence

The reported rate of fecal incontinence following radiotherapy ranges from 0 to 45% (5, 20) and most likely overlapping the incidence of diarrhea. One study of 84 anal cancer patients specified incontinence and reported Incontinence for solid stools, liquid stools and gas to occur at least monthly in 31%, 54% and 79% of patients, respectively. Overall, 40% of patients reported great distress from incontinence for solid or liquid stools at least monthly. Fecal urgency occurring at least monthly was experienced by 87% of patients and caused great distress in 43% (37). There are no studies examining treatment algorithms for fecal incontinence specifically in anal cancer survivors, however, algorithms for treatment of pelvic radiation disease have been investigated (40).

Treatment

Several treatments exist that may alleviate symptoms. Treatment can be directed towards: stool consistency (dietary counselling, psyllium or Linn seeds, antidiarrheal drugs), towards improving anal sphincter function, (pelvic floor muscle training, biofeedback, plugs), towards better rectal emptying (toileting training, enemas transanal irrigation), or towards neural co-ordination (sacral nerve modulation). A colostomy to divert the fecal flow has a role in the few patients (between 5 and 12%) who have substantial loss of rectal volume and who have not responded to other interventions (43).

Few studies have been published about interventions for the management of patients with fecal incontinence after pelvic radiotherapy. In one retrospective study of 15 patients, the use of phenylephrine gel benefited three quarters of all patients with fecal incontinence who had not responded to other treatments, with a substantial benefit in 25% of patients who were treated (44) (Evidence level 4). In another retrospective study of 13 patients with fecal incontinence after pelvic radiotherapy refractory to other treatment (4 anal cancer patients) seven patients (54%) had successful percutaneous nerve evaluation, with the number of incontinence episodes in the 3-week bowel diary reduced from median of 24 (range 4–56) to 4 (range3–6) (45) (Evidence level 4).

Radiation proctitis

Radiation proctitis includes a handful of symptoms including bleeding, pain, fecal urgency, and incontinence. Also radiation proctitis has a natural overlap with fecal incontinence. The incidence of radiation proctitis in anal cancer survivors ranges from 0 to 40% (5). Diagnose is based on clinical history, endoscopic and histologic findings. No studies have examined management of proctitis specifically for anal cancer survivors. Since the radiation accumulated in the rectum and the anal canal differ substantial between types of pelvic organ cancers, radiation proctitis is a condition with various symptoms or combinations of symptoms. The studies are heterogeneous in their intend, and the effect of treatment most likely differ between radiation proctitis after pelvic radiation towards other pelvic organ cancers

Treatment

The evidence for treatment of hemorrhagic radiation proctitis was summarized in a 2016 Cochrane review; Sucralfate enemas are more effective than corticosteroid or mesalazine enemas (46) (Evidence level 2b). Oral metronidazole seems beneficial in patients with both diarrhea and rectal bleeding but with no cytotoxic

neuropathy (47) (Evidence level 2b). Three endoscopic treatment options exist (argon plasma coagulation, laser therapy, or applied formalin (4%)), however, none of these options have been examined in a randomized setting (Evidence level 4) (47).

Two studies reported the use of formalin in treating chronic radiation-induced hemorrhagic proctitis. One study (15 patients, including two anal cancer patients) showed that 87% patients had complete cessation of bleeding (48). One prospective study (33 patients including 11 anal cancer) also stated that formalin was effective treatment for chronic radiation-induced hemorrhagic proctitis, but not suitable for anal cancer survivors due to the increased morbidities of anal stricture and FI (49) (Evidence level 3b).

In a small RCT daily self-administered colonic irrigation plus oral ciprofloxacin and metronidazole was superior to formalin application in terms of bleeding, urgency and diarrhea (50).

A randomized, double-blinded, sham-controlled phase 3 trial studied the clinical benefits of hyperbaric oxygen in patients with chronic bowel dysfunction after radiotherapy for pelvic malignancies (84 cases, including eight anal cancer) included patients with at least grade 2 gastrointestinal symptoms in any category of the LENT SOMA scoring system and found no evidence that patients with radiation-induced chronic gastrointestinal symptoms, including those patients with rectal bleeding, benefit from hyperbaric oxygen therapy[47]. However, specifically for radiation proctitis proven refractory to other interventions, a multicenter, randomized, controlled, double-blind trial with crossover and long-term follow-up evaluated the effect of hyperbaric oxygen therapy for these patients (n=120, no anal cancer patients) found a significantly increased chance of improvement or cure following hyperbaric oxygen treatment (RR 1.72; 95% CI 1.0 to 2.9, P value = 0.04) (51) (Evidence level 2b). A recent combined retrospective and prospective trail of 52 pelvic cancer patients found a statistically significant relationship between the severity of late averse effect (toxicity) on presentation and the subsequent absolute reduction in LENT-SOMA scores (P = 0.003) which may explain the different findings as confounding by indication (52).

Action strategies

- Endoanal ultrasonography may define sphincter defects prior to treatment of the anal cancer (eg, after childbirth or previous anal surgery). Anorectal physiology testing is often not needed but may direct management in selected cases (Evidence level 5) (Grade D)
- Treatment of diarrhea should follow gastrointestinal work-up for the cause of the diarrhea (Evidence level 5) (Grade D)
- If small bowel bacterial overgrowth is found or suspected, antibiotic treatment targeting gram-negative bacilli is recommended (Evidence level 2b) (Grade D)
- Patients with bile-acid malabsorption may benefit from regular use of bile-acid sequestrants (colestyramine; 4 g twice a day) or other bile-acod sequestrants (Evidence level 2b) (Grade D).
- If no cause for diarrhea is found dietary counselling, psyllium or Linn seeds or antidiarrheal drugs may be of help and should be prioritized (Evidence level 5) (Grade D)
- Fecal incontinence following CRT for anal cancer should follow treatment algorithm for fecal incontinence (Evidence level 5) (Grade D)

- In the case of refractory fecal incontinence, the use of phenylephrine and sacral nerve stimulation may have a place (Evidence level 4) (Grade D)
- A colostomy should be considered in severe cases with failure of other treatment modalities (Evidence level 5) (Grade D)
- Most cases of radiation proctitis do not require treatment. If treatment is needed, we recommend the use of Sucralfate enemas (Evidence level 2a) (Grade D)
- Topical application of Formalin (4%) and Argon Plasma coagulation may control episodes of bleeding in hemorrhagic radiation proctitis, but risk associated with these procedures is considerable (Evidence level 3b) (Grade D)
- Colonic irrigation plus ciprofloxacin and metronidazole may be a suitable option for managing hemorrhagic or non-hemorrhagic radiation proctitis in anal cancer patients (Evidence level 2b) (Grade D).
- Hyperbaric oxygen therapy may have a role in the treatment of refractory radiation proctitis (Evidence level 2b) (Grade D)

Management of late gastrointestinal adverse effects in anal cancer survivors (logistics)

A few studies have investigated model for care of patients after pelvic radiation (53, 54). One study (218 patients, - 15% GI cancer survivors) was a three-armed randomized controlled trial comparing usual care (a detailed self-help booklet) with a gastroenterologist-led algorithm-based treatment and a nurse led algorithm-based treatment of late gastrointestinal adverse effects. Though no clinically relevant improvement was found in the booklet group, clinically relevant improvements (changes in Inflammatory Bowel Disease Questionnaire–Bowel (IBDQ-B)) were found in both the gastroenterologist-led and the nurse-led treatment groups. The was no difference between these groups (53). The trial was not powered to detect the effect of intervention for gastrointestinal symptoms on Quality of Life, but there did not seem to be obvious change in any group. This finding might be because although intervention improved patients' gastrointestinal symptoms, many had other unresolved symptoms affecting their urinary, sexual, or lymphatic systems.

At the three Danish centers treating anal cancer, a prospective data base on acute and late adverse effects has been set up, still including patients. Patients will be followed 3 years after therapy. Patients revealing need for further GI evaluation and treatment can be referred to specialized investigation and algorithm-based treatment at the regional clinical units dedicated to late GI toxicity.

Action strategies

- We do recommend the establishment of dedicated late adverse effect clinics. We encourage that dedicated clinics are multi-disciplinary, embracing symptoms arising from the entire pelvic region and covering all pelvic organ cancers (Evidence level 5) (Grade D).
- Organized in a multidisciplinary setting, and with the right algorithms, data supports that these can be nurse-led (Evidence level 2b) (Grade B).

Late Urological adverse effects

6. **Anal cancer survivors should be offered routinely screening for late urological toxicity as it is found in up to 45% (Evidence level 3a) (Grade B).**

7. **Patients with persisting symptoms (> 3-6 months after treatment) should be offered referral for treatment in specialized units (Evidence level 5) (Grade D).**

Literature review and evidence description

Urological complications following pelvic radiotherapy include lower urinary tract symptoms (LUTS), radiation cystitis, stricture disease, fistula formation and the development of secondary urological cancers. Urological late adverse effects are reported in 3-45% of anal cancer survivors after CRT (20, 35-37, 55, 56). One cross-sectional study examining 84 anal cancer survivors found that 45% of patients experienced urinary incontinence at least once monthly and 48% experienced urinary urgency at least once monthly. 79% of these patients reported that urinary incontinence caused moderate or great distress, the same was true for 55% of patients experiencing urinary urgency. Morbidities due to dysuria, daytime urinary frequency and nocturia were, however, minor (37) (Evidence level 3b).

Lower urinary tract symptoms (LUTS)

The bladder is particularly sensitive to certain cytotoxic drugs and radiation, leading to cystitis, fibrosis and occasionally diminished bladder volume. This can cause symptoms of urinary frequency, dysuria, hematuria and sphincter dysfunction (57). LUTS may be divided into irritative (storage), obstructive (voiding) and postmicturition symptoms. Symptoms such as urinary incontinence, frequency, urgency and nocturia are often the most bothersome of LUTS (58). The symptoms of LUTS can develop months to years after the treatment for pelvic cancers, hence, regular assessment of LUTS in cancer survivors is necessary (58).

General assessment of LUTS includes self-reported incontinence, questionnaires and a three-day voiding dairy with registration of fluid intake, voiding episodes, voided volume and a pad test. Moreover, dipstick urinalysis for leucocytes and nitrites to rule out infection and hematuria. Additional assessment bladder ultrasound for identifying residual and structural issues may be useful (58). In men, it is important to keep in mind that the prevalence of LUTS increases with age and new LUTS can be indicative of prostate hyperplasia or cancer and physical examination should include a prostate exam (58). In women gynecological examination is recommended to evaluate for pelvic organ prolapse and vaginal atrophy.

Treatment

The evidence-base for conservative management of LUTS after treatment for pelvic cancers is small and characterized by variations in patient characteristics. Furthermore, although guidelines exist for treating both men and women with LUTS, these are not specific to cancer patients and are based on benign disease causality (58). Hence, the recommendations are based on indirect evidence.

Conservative management of LUTS is the first line treatment and includes lifestyle interventions such as moderating fluid intake, avoidance of known bladder irritants such as caffeine and alcohol and smoking cessation.. Use of e.g. pads and collecting devices is an option for patients with less symptoms (58, 59) (evidence level 5). Pelvic floor muscle training (PFMT) with or without biofeedback seems beneficial and can be initiated prior to treatment commencement: Two studies have assessed the effects of PFMT and multidisciplinary rehabilitation after pelvic radiotherapy, and both demonstrated significant improvements (60, 61) (evidence level 2b). In postmenopausal women vaginal estrogen treatment has shown improvement overactive bladder symptoms and is recommended as initial treatment (62) (Evidence level 1a).

Oral medication is centered around the use of Alpha-blockers and antimuscarinics/mirabegron (beta-3 agonist). Sequencing of medication should be tailored depending on what is the most bothersome symptom of LUTS identified on assessment. Alpha-blockers can be used to treat LUTS such as compromised bladder emptying. Antimuscarinics/mirabegron can be used to treat urgency and incontinence (overactive bladder) as they relax smooth muscles (58) (Evidence level 2a). It is recommended in the European Association of Urology (EAU) guidelines to initiate with antimuscarinics if the main bothersome symptom of LUTS is urgency urine incontinence (63) (Evidence level 1b).

As third-line treatment for irritative urinary symptoms intravesical installations are an option. Onabotulinum toxin A can be considered for the patient with the ability to empty the bladder and with uninhibited bladder contractions (64) (Evidence level 4). For patients with irritative urinary symptoms in the absence of uninhibited contractions percutaneous tibial nerve stimulation (PTNS) or sacral nerve stimulation (SNS) can be considered (Evidence level 4).

Simple cystectomy is reserved for the treatment of intractable functional problems when all other management options have failed.

Radiation cystitis

Radiation cystitis develops in 5%-10% of patients treated with pelvic radiotherapy, radiation cystitis includes hematuria, frequency, urgency, and pelvic pain (65).

Treatment

A variety of treatment options are described for radiation-induced hemorrhagic cystitis. These management strategies can be sub-classified into systemic medical therapies, HBO, intravesical, ablative, and definitive surgical techniques (66).

Systemic medical therapies for hemorrhagic cystitis are appealing as they are non-invasive and hospital admission is avoided. WF10 is an intravenous formulation (Tetrachlorodecaoxygen) that reduces inflammation so that a host-derived healing can commence. In one randomized controlled trial, patients treated with WF10 had a significantly decreased rate of recurrent hematuria after 12 months (67) (Evidence level 2b). Sodium pentosan (100 mg) administration three times daily, may reduce or cease symptoms (68) (Evidence level 3 b). Tranexamic acid has been used to treat urological hemorrhagic emergencies however evidence of efficacy in the hemorrhagic radiation cystitis is lacking (59, 65).

In a pilot study, 30 symptomatic prostate cancer patients treated with CRT received bladder instillation therapy with Hyaluronic Acid and Chondroitin Sulfate weekly for the first month and then at weeks 6, 8, and 12 (one year total) which significantly reduced overall symptoms and bother (69) (Evidence level 3b).

Hyperbaric oxygen is used to treat severe hematuria refractory to conventional management with response rates ranging from 27% to 96% (65) (Evidence level 4). With hyperbaric oxygen, patients spend 90 minutes 5-7 days per week in a hyperbaric chamber inspiring 100% oxygen between 2-2.4 atmospheres (ATMs). A total of 40 HBO treatments extending over an 8-week period are typically administered. Randomized controlled trials with long-term follow-up are lacking and needed as treatments are expensive and time-consuming. However, a recent combined retrospective and prospective trail of 52 pelvic cancer patients found a statistically significant improvement with a mean LENT-SOMA score reduction of 3.7 (2.4 to 5.0; $P < 0.001$) when treating radiation cystitis and claimed the intervention is a cost effective alternative to conventional treatments as the worst affected had the greatest potential for improvement (52) (evidence level 3b).

Intravesical instillations of Hyaluronic acid to is used to upgrade the glycosaminoglycan (GAG) protective layer to reduce exposure of underlying epithelial cells to host urine. It has been safely administered with success for the treatment of chemical and radiation cystitis, resulting in improvements in urinary symptoms and bladder pain (58, 65) (Evidence level 3a).

Ablation and coagulation of ruptured submucosal vasculature with laser therapy, argon beam therapy or simple fulguration with a coagulation electrode is advantageous as these modalities can immediately control hemorrhage and are associated with complete response in 75-97.5% of cases. Disadvantages with these modalities are requirement of general or spinal anesthesia. Small series seems promising (59, 65, 70) (Evidence level 3b).

Urinary diversion with or without cystectomy can be performed if all other less invasive treatment modalities have failed (65).

Stricture disease

Can occur in the ureters or in the urethra. If unrecognized, partial or total permanent loss of kidney function may ensue. Surgery (urethroplasty, dilation, urinary diversion or reconstruction) remains the only definitive long-term option for managing these strictures (59) (Evidence level 5).

Fistula formation

Management of a fistula in the urinary tract or bladder is drainage. Good urinary drainage will keep a low pressure within the system and avoid urinary leakage through the fistula. In some cases fistula surgery is an option (59) (Evidence level 5).

Actions strategies

- First line treatment for LUTS after pelvic radiotherapy is conservative management including lifestyle interventions such as moderating fluid intake, avoidance of known bladder irritants such as caffeine and alcohol and smoking cessation (Evidence level 5) (Grade D)

- Pelvic Floor Muscle Training with or without biofeedback may alleviate symptoms (Evidence level 2b) (Grade D)
- Sequencing of oral medication should be tailored depending on what is the most bothersome symptom of LUTS identified on assessment and includes alpha-blockers and antimuscarinics.
- In postmenopausal women vaginal estrogen treatment has shown improvement in overactive bladder symptoms and is recommended as initial treatment (Evidence level1a)) (Grade D)
- Radiation cystitis may be treated systemically with WF10 or Sodium Pentosan, or intravesical installations of Hyaluronic acid (Evidence level 3a) (Grade D).
- Hyperbaric oxygen may be used to treat severe hematuria/ radiation cystitis refractory to conventional management (Evidence level 4) (Grade D).
- Radiation cystitis can be treated with ablation of ruptured submucosal vasculature with laser-, coagulation- or argon beam therapy (Evidence level 5) (Grade D).
- Simple cystectomy is reserved for refractory conditions.

Sexual Dysfunction

8. Anal cancer survivors should be offered routinely screening for late sexual dysfunction as it affects up to 90% of men and up to 100% of women (Level of Evidence 3a) (Grade B).

9. Patients with persisting symptoms should be offered referral for treatment in specialized units (Evidence level 5) (Grade D).

Literature review and evidence description

Prevalence rates of sexual difficulties associated with anal cancer and its treatment are sparsely investigated and much less in male survivors compared to females. Existing literature is mainly retrospective, consisting of small sample sizes (71, 72).

Among female anal cancer survivors treated with RCT vaginal stenosis has been reported in up to 79% (73), vaginal dryness in up to 85% and dyspareunia in up to 100% (4) (Evidence level 2a). Maximum symptom prevalence for female-related sexual dysfunction was experienced between 2 and 5 years from diagnosis (14) (Evidence level 3b)

In male anal cancer survivors up to 90% have complaints of erectile dysfunction (difficulties getting and maintaining an erection) but also orgasmic dysfunction and pain (4) (Evidence level 2a). However, the sexual dysfunction of male anal cancer survivors has received very little attention.

In one study, female cancer patients indicated that sexual matters were never discussed with their healthcare providers. 81% stated that it was extremely important to discuss (72). For sexually active women, sexual dysfunction, most notably Sexual/Relationship Satisfaction was most consistently associated with specific measures of psychological well-being (31) (Evidence level 3b). Sexual well-being is acknowledged as a core aspect of quality of life for people affected by cancer, particularly those receiving treatment for pelvic

malignancies. Body image, anxiety, and cancer-specific posttraumatic distress have been associated with subscales of sexual functioning, while a global QOL measure was largely unrelated (31).

Screening

No specific tool for screening the sexual function of anal cancer patients is available. However, disease-specific quality of life modules, which contain sexual morbidity item(s), such as RTOG/EORTC, enables routine screening for treatment-induced sexual difficulties/concerns at the very least. The RTOG/EORTC is currently finalizing international validation for anal cancer survivors (https://qol.eortc.org/questionnaire/qlq-anl27/) and include seven items on sexual function and one screening question (15). This has the potential to standardize reporting of sexual dysfunction both in the clinical setting and in research.

Treatment

No specific data exists on the treatment of sexual dysfunction in anal cancer survivors. Recommendations have extrapolated from existing literature of primarily pelvic malignancies.

Psychosexual aspects

While sexual dysfunction may result from physiological treatment effects, desire, orgasmic pleasure, and sexual satisfaction are also strongly related to psychological function (e.g., sexual performance anxiety). A systematic review identified 27 studies that compiled together showed moderate support for the effectiveness and feasibility of psychological interventions targeting sexual complaints following cancer in both men and women (evidence level 2a). However, a strong placebo response was observed (74). Approaches could be psychosexual therapy (sensate focus), psychological therapy (mindfulness, cognitive behavioral therapy), couple therapy (discrepant desire), alone or in combination with pharmacological or device (e.g. vibrators, constriction rings) interventions and target affected individuals or couples (74).

Sexual pain in women

Sexual pain difficulties in women are predominantly associated with radiation-induced vaginal dryness, vaginal stenosis and dyspareunia. The most effective management for superficial dyspareunia in women with treatment-induced menopause is the prompt offer of hormone replacement therapy (HRT) and, where appropriate, vaginal estrogens (75) (Evidence level 2b). If contraindicated, then non-hormonal vaginal moisturizers can be used. Furthermore, most women will also need to use an intimate lubricant (water, oil or silicone based) to decrease friction associated with penetrative sexual intercourse or vulval contact (Evidence level 5).

For women with introital- or vaginal fibrosis and/or deep dyspareunia after radiotherapy, vaginal dilation is recommended (75, 76) (Evidence level 2b). The stenosis occurs as a result of the formation of adhesions, together with the circumferential fibrosis of upper vaginal tissue. This leads to contraction of the vaginal vault and a shortened vagina. A systematic Cochrane review by Denton et al in 2015 found evidence is sufficient to endorse the widespread recommendation for the use of vaginal dilators (76). However, in order to disrupt the cycle that can arise from repeated experience of sexual pain, couples may be asked to refrain from penetrative sexual activity while vaginal health strategies are introduced, with subsequent gradual introduction of sexual

expression using graduated exposure to vaginal dilation and penetration within a framework of sensate focus (74) (Evidence level 5).

A Swedish study followed a cohort of 260 women irradiated for pelvic cancers (44 with anal cancer) before and after treatment interventions in a nurse-led clinic using PROMs. The overall goal with the interventions was to provide treatment and support for radiotherapy-induced late effects and chronic states in order to improve quality of life. Sexual interventions consisted of both psychoeducational efforts and efforts to provide a broader perspective of sexuality and sexual experiences; information was provided about common radiotherapy-induced vaginal changes and menopausal symptoms, the consequences of the lack of estrogen that may affect the patient, and infertility. Counseling concerning vaginal dilator therapy, topical estrogen, guidance, and suggestions regarding lack of desire and barriers to intimacy and partner communication were also given. They found significantly more women reported increased rather than decreased satisfaction with overall sexual health post-intervention. They also reported significantly reduced superficial genital pain, reduced deep genital pain, increased QoL, and reduced levels of depression/ anxiety post-intervention. Further, a significant association between reduced urgency to defecate and improved satisfaction with overall sexual health and between reduced urgency to defecate with fecal leakage and reduced anxious mode was found (30) (evidence level 2b).

Arousal

For men the penile erection is important objective feedback that reinforces subjective sexual feelings of arousal, whereas for many women there is limited awareness of the objective vaginal changes that accompany subjective sexual arousal. Most evidence behind the management of treatment-induced erectile difficulties after pelvic radiotherapy stems from studies of prostate cancer survivors (75, 77). The efficacy of oral PDE5-Is has been established in RTCs of external beam radiotherapy for prostate cancer, with significant improvement in assisted erectile function compared with placebo (78) (evidence level 1b). Options for second line therapies for erectile dysfunction not responsive to PDE5-Is include vacuum erectile devices, intra-cavernosal injections, and transurethral alprostadil however, evidence of treatment after radiation induced erectile difficulties is lacking (72) (Evidence level 5).

Action strategies

- Sexual functioning in anal cancer patients after pelvic radiation requires focused assessment by providers, beyond broad Quality of Life assessments (Evidence level 4) (Grade C).
- Hormone replacement therapy (HRT) ± vaginal estrogens should be offered to women with treatment-induced menopause and superficial dyspareunia (Evidence level 2c) (Grade D).
- Introital- or vaginal fibrosis and/or deep dyspareunia can be treated with vaginal dilation (Evidence level 2b) (Grade D).
- Erectile dysfunction can be treated with oral PDE5-Is (Evidence level 1b) (Grade D).
- Evidence suggest moderate effectiveness of psychological interventions targeting sexual complaints following cancer in both men and women (Evidence level 2a) (Grade D).

Pain

10. **Anal cancer survivors with persisting pain should undergo diagnostic work up to determine cause (Evidence level 5) (Grade D).**

11. **MRI should be the preferred imaging modality for detecting pelvic insufficiency factures (Evidence level 3b) (Grade B)**

12. **Patients with persisting symptoms should be offered referral for specialized treatment (Evidence level 5) (Grade D).**

Literature review and evidence description

Prolonged pelvic pain is defined as a pain that has lasted more than 6 months. It can have its origin in all the organs of the pelvis and arise after undergoing cancer treatment. Prolonged pain can lead via various mechanisms in the nervous system to altered function and various symptoms / discomfort in skin, bladder, muscles, intestines and gynecological organ (79).

Treatment must be based on diagnostic work up to determine the mechanism of the pain. Often there are several different mechanisms at the same time. The analysis is done in close consultation with the patient and is followed by a treatment plan. Analgesics often have a limited effect, and especially opioids entail a risk of increased intestinal problems such as constipation and difficulty emptying, which in the long run can cause increased pain (Evidence level 5).

Evidence-based pain rehabilitation programs, available through referral in most regions, focus on learning to manage and live with pain as a long-term condition.

Pelvic Insufficiency fractures

Pelvic insufficiency fracture (PIF) is a well-known late adverse effect after pelvic CRT that can be misinterpreted clinically as local recurrence causing pain and decreased mobility (80, 81) (Evidence level 3a). PIFs are described in up to 50% of anal cancer patients after CRT (82-85) (Evidence level 2b), but best documented after radiation for gynecological cancers (86) (Evidence level 2a).

Studies on PIFs after CRT are mainly retrospective and characterized by heterogeneity in definition, timing, imaging methods, RT techniques and follow up. Imaging method is important as MR is estimated to have a sensitivity of 99-100 % and a specificity of 85 % for stress fractures in general and found better than CT (sensitivity 69%) in pelvic/femoral area (87, 88) (Evidence level 3b).

In anal cancer survivors, studies on PIFs are often smaller case series, and there are no systematic reviews or meta-analyses. Generally, it has been found that fracture sites are predominantly in weight bearing areas, that there is a relation to higher radiation doses, and an increased incidence with increasing age and postmenopausal status. Time to detection was 11 months after CRT (3-66 months) (82, 89-95) (Evidence level 2b). A recent prospective study using MRI (n=27) found 51.9% of patients having PIFs after radiotherapy for anal cancer and the majority had pain in the pelvic area (85).

Two recent large studies (systematic review and meta-analyses) on PIF after RT for gynecological cancers (n= 3929 and n=6488) found incidences of PIF of 9.4% and 14%, detected a median of 8-39 and 7.1-19 months after RT (86, 96). Most frequently found risk factors across studies were advanced age, postmenopausal status, low BMI and osteoporosis, older RT treatment techniques and higher RT doses (86). Most frequent localization was sacral body/near sacroiliacal joint (60-73.6%) followed by pubic bones (12-13%). The ratio of symptomatic patients differs but is generally around 50-60% (86). These data seem comparable to data from anal cancer, but as radiation dose, techniques and chemotherapy are different, data are not directly applicable.

Treatment

Studies on treatment and preventive measures for PIFs are lacking. In the 2020 systematic review on gynecological patients, information on treatment of PIFs was available for 456 patients. Conservative treatment was applied for 84.6% (analgesics, bed rest, observation), hospitalization or surgery for 9,4%, and bone directed therapies were used in 6% (bisphosphonates, calcium, vitamin D and hormone replacement therapy) (86) (Evidence level 2a).

A Cochrane review on pharmacological interventions for prevention of PIF associated with pelvic RT has been conducted (97). Two RCTs, both in men undergoing pelvic RT and hormone replacement therapy for prostate cancer, were included. The review concluded that there is insufficient evidence that zoledronic acid and other medicines are sufficient to prevent radiation induced bone complications (Evidence level1a).

The ESMO 2020 guidelines on Bone Health in cancer do not specifically address CRT induced PIFs. However, it is stated: "All patients receiving treatments that are known to adversely affect bone health should be advised to consume a calcium enriched diet (or supplement). exercise moderately and take 1000-2000 IU vitamin D3 every day".

Action strategies

- Conservative treatment of PIF could be considered. (Grade D).

Radiation dermatitis

Chronic radiation dermatitis is a late side effect of skin irradiation which is mostly caused by the imbalance of proinflammatory and profibrotic cytokines. The incidence of chronic radiation dermatitis in anal cancer survivors is unknown.

Clinical manifestation includes changes in skin appearance, wounds, ulcerations, necrosis, fibrosis, and secondary cancers. The most severe complication of irradiation is extensive radiation-induced fibrosis (RIF). RIF can manifest in many ways, such as skin induration and retraction, lymphedema or restriction of joint motion. Diagnosis of chronic radiation dermatitis is usually made by clinical examination (98).

If the clinical presentation is unclear or suspicious, a biopsy and histopathological examination are obligatory (98).

Available literature data on the management of chronic radiation dermatitis are unsatisfactory. Most of the interventions are based only on clinical practice and extrapolation of management used in similar conditions.

Action strategies

- If the clinical presentation is unclear or suspicious, a biopsy and histopathological examination are obligatory (Evidence level 3b) (Grade D)
- If necessary, refer patient for treatment in specialized units (Evidence level 5) (Grade D).

Lymphedema

13. Anal cancer survivors should be offered routinely screening for secondary lymphoedema as it is common and early diagnosis affects treatment outcome positively (Evidence level 5) (Grade D)

14. Anal cancer survivors with self-reported or objectively assessed swelling or heaviness in the lower body should be referred for treatment at specialized units/ certified lymphedema therapist (Evidence level 5) (Grade D)

Literature review and evidence description

Lower body lymphedema is a common complication following pelvic radiation. Lymphedema is a pathological process wherein the lymphatic system is overloaded, and lymph fluid accumulates in the interstitial space, causing local or systemic swelling. In anal cancer patients specifically, lower body lymphedema has been reported to occur in 12-16% of survivors (37, 99). Obesity (BMI >30 kg/m2), localized infection, increased number of nodes removed, and higher initial extent of disease increase the risk of lymphedema (100). Joo et al. found the median time to the development of lymphedema in anal cancer survivors was 31.4 months post treatment (range, 6.5–114.9 months). Early detection/diagnosis is key for optimal lymphedema management because stages 0 and 1 may be reversible, whereas stages 2 and 3 are less responsive to treatment. Stages 0 and 1 include more subtle symptoms such as feeling of heaviness or bloating (stage 0) or increasing girth, heaviness or stiffness due to fluid accumulation (stage1) (100). If left untreated, complication may arise such as impaired function, chronic infections, and feeling of heaviness and stiffness that can negatively affect the quality of life (101).

Screening

At follow up visits anal cancer survivors should be screened for swelling (frequency, severity, interference with daily activities), pain/discomfort/heaviness, range of motion and mobility (ie, bending, stretching, flexibility) of lower limbs and strength of lower limbs (100). The EORTC QLQ-ANL27 does have items of pain (though specified around the anus and while sitting) as well as an item of swelling of the lower limbs.

As such, reported symptoms or objectively assessed swelling/ decreased mobility of lower body requires specialist assessment and if lymphedema is present, lymphatic therapy (100, 101) (Evidence level 5).

No specific data exists on the treatment of secondary lymphedema in anal cancer survivors. Recommendations have been extrapolated from existing literature of pelvic malignancies.

Treatment

Patient education

Survivors should be educated regarding signs and symptoms of lymphedema and its complications and the importance of rapid reporting to the treatment team. Self-care management is becoming increasingly important including infection prevention measures, risk reduction strategies and maintenance of skin integrity in the affected area (100).

Complex Decongestive Therapy (CDT)

CDT is applied in the lymphedema treatment as the current treatment standard in most places. Treatment is divided into two phases; the intensive phase and the maintenance phase. The intensive phase contains manual lymphatic drainage (MLD), skin care, compression bandages, and exercises. MLD is performed by applying intermittent and gentle pressure with four basic hand holds that stimulate lymphatic capillaries by increasing lymph vessel contraction and providing temporary lymphatic drainage from the affected body area... The purpose of the intensive phase is to reduce extremity volume. The maintenance phase contains MLD, skin care, compression garment appliance, and exercises. The purpose of this phase is to provide and optimizing the reduced body area volume. Self-care of the patient (daily skin care with moisturizer, self-bandaging, and self-drainage), awareness of signs of infections, avoiding excessive heat or cold, persistence of wearing compression garments, and daily exercise are the important parameters for the successful long-term lymphedema management (100, 101).

Intermittent Pneumatic Compression (IPC)

IPC applies pressure, imitating a muscle pump within the inflation and deflation processes. IPC also reduces capillary filtration and lymph production, so it can control lymphedema. It can be used during maintenance or to reduce symptoms. It is also necessary to adjust the pressure and duration of the IPC according to the patient's tissue condition. Applying too much pressure may cause harm because of the collapse of lymph collectors along with triggered lymphangiospasm (101).

Surgical options

Generally, surgical approaches are not considered first line treatment due to either inefficacy or potential complications. The surgical management of lymphedema is classified as either physiologic (reconstructive) or reductive (excisional or ablative).However, a recent meta analysis of the efficacy of lymphatic reconstructive microsurgery (37 studies included, 2 RCTs) found that patients who underwent microsurgery had a significantly better chance of achieving an excellent result than patients who received conservative treatment (odds ratio 7.07). The two most common reconstructive procedures were lymphovenous bypass (LVB, also known as lymphovenous shunt) and vascularized lymph node transplantation (VLNT). The study reported that the affected limb circumference was reduced by approximately 45% after the microsurgery, that 63% of the patients no longer needed physiotherapy, and that 96% were free from painful skin infections. Lymphography

showed that lymphatic transport capacity was enhanced. 12% of the patients reported that edema reappeared in the long-term, 26% required reoperation for unsatisfactory results, and 32% experienced lymphatic leakage (102).

In advanced-stage lymphedema, the soft tissues, which are edematous and fibrotic, are surgically removed with either direct excision or by liposuction. Excisional procedures excise the redundant subcutaneous and/or cutaneous tissue, but lymph flow is not restored. Liposuction represents a less invasive method and has been widely utilized as a reductive method to remove the hypertrophied fat of the affected extremity especially in breast cancer survivors with significant arm reduction and a reduction in cellulitis episodes (103). However, liposuction does not provide an improvement of the lymphatic system, and therefore, patients need to wear compression garments lifelong to prevent recurrence or worsening of symptoms (104).

Pharmacological treatment

Pharmacological treatment is in general ineffective. Antibiotics are used for lymphangitis, cellulitis, and erysipelas, which have symptoms such as widespread erythema, pain, and high fever. Fungal infections develop on the foot and genital area, which are often found together with lower extremity lymphedema. This condition is treated with antimycotic drugs, such as fluconazole and terbinafine (101).

Action strategies:

- Local skin infections are common and can be managed with antibiotics or anti-fungals (Grade D).

Summary literature review and evidence description

The recommendations and action strategies are based upon systematic search for literature providing 57 articles for full-text review. Of these 34 are included in the finalized guideline. Further searches on relevant refence literature from related fields provided an additional 59 articles also included in the guideline. Upon revision in 2022 additional 15 articles were included and a section on lymphedema was added.

The given levels of evidence and grades of recommendations are according to the Oxford Centre for Evidence-based Medicine (www.cebm.net/?o=1025).

Patient values and preferences

Our recommendations have not been evaluated by the target population. The chosen complaint/ symptom categories have been identified based on the available literature and the experience of the participating expert panel. Other late adverse effects of cancer treatment less specific for anal cancer survivors are not covered here. Based on the experience of the expert panel our recommendations are to routinely offer patients screening for these conditions, as a substantial proportion of patients prefer not to participate in such screenings.

Rationale

The literature clearly tells us, that a large proportion of anal cancer survivors suffer from late adverse effects and that these potentially effect Quality of Life. As anal cancer is relatively rare, managing physicians may not have much experience dealing with late adverse effects of CRT. Therefor our recommendations are centered around offering the relevant screening and referral to specialized units. When going through the scientific evidence we present actions strategies for management based on indirect evidence.

Comments and considerations

There is a striking lack of direct evidence behind these recommendation and further research in the area is encouraged.

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5. Methods

Literature search

A systematic search of the electronic databases Pubmed Central, CINAHL and Embase was conducted using Medical Subject Headings (MeSH) with the word anal cancer with relevant subheadings* and by specifying limits species (human), languages (English). The search included studies from date of inception up to June 2020 (August 2020 for CINAHL). Further, a search in the Cochrane library was conducted. *The word concepts used for the search were anal cancer as population and radiotherapy as the medical intervention. Late toxicity and/ or survivorship was added as comparative intervention. We defined five organ specific complaint/ symptom categories (bowel, urinary, psychosocial, pain and sexual) and conducted individual searches in all of these categories. All the synonyms and associated sub-terms were combined using the operator "OR" and, afterward, were combined altogether with the other concepts by the operator "AND." One reviewer (SH) independently screened the titles and the abstracts for each reference. The articles (57) retained for full-text review were screened by the two reviewers to assess quality and evidence level. Of these 34 are included in the finalized guideline. Further searches on relevant refence literature from related fields provided an additional 59 articles also included in the guideline.

As very little data is available specifically for anal cancer, knowledge was extrapolated from other patient categories exposed to pelvic radiation due to malignancy. Reference list in relevant literature were studied and relevant studies included.

Evidence assessment and articulation of the recommendations

At least two team members were assigned to each of the five symptom categories. These members individually extracted data and graded the quality of evidence and the strength of recommendation into a shared internet based platform. This data was again merged and discussed in plenum in case of discrepancies before the final articulation of recommendation was made. As very little evidence exist to support recommendations specifically for anal cancer patients, we chose to grade the level of evidence for relevant literature concerning pelvic radiation disease in general, but to grade all recommendations that are not based specifically on anal cancer studies as Grade D, no direct research evidence/ expert opinion.

Stakeholder involvement

The group behind these guideline consisted of oncologist (ESH, KLGS,CJSK), surgical gastroenterologists (PC, BTO, PMF, SH) and a sexologist (AHM). Two external urologists (MGK, CHG) were consulted. Upon revision, a section on secondary lymphedema was added. This was revised by Physiotherapist and representative of Danish Society of Oncologic and palliative Physiotherapy, Gunn Ammitzbøll. No patients were involved in the development of these guidelines.

External review and guideline approval

The guideline has not been externally reviewed. As the expert panel did not include urological expertise, the section on late urological adverse effects was reviewed to two external urological consultants (MGK, CHG). The guideline is approved by the DACG.

Recommendations which generate increased costs

The recommendations are not expected to add significant additional costs.

Need for further research

Very little literature exists specifically regarding anal cancer survivors. Most studies are limited by sample size (single center) and design (cross-sectional, small retrospective cohort studies). There is a striking need for standardize assessment tool and collaboration between centers in order to generate high quality evidence within this field.

Authors

- Susanne Haas, MD PhD, Danish Cancer Society National Research Center for survivorship and late adverse effects following pelvic organ cancer, Department of Surgery, Aarhus University Hospital, Denmark.
- Anette Højer Mikkelsen, Clinical Sexology, Specialist in Sexological Counselling (authorized in Nordic Association of Clinical Sexology), nurse RN., MSc. Sexological Center, Aalborg University Hospital.
- Camilla Kronborg, Clinical Oncology, MD, PhD, Danish Centre for Particle Therapy
- Birthe Thing Oggesen, MD, General Surgeon, Herlev Hospital, Denmark
- Pia Faaborg Møller, MD PhD, Colorectal Surgeon, Department of Surgery, Vejle Hospital, Denmark
- Eva Serup-Hansen, MD PhD, Consultant oncologist, Herlev Hospital, Denmark
- Peter Christensen, MD, DMSci, Phd, Professor, Consultant Colorectal Surgeon, Danish Cancer Society National Research Center for survivorship and late adverse effects following pelvic organ cancer, Department of Surgery, Aarhus University Hospital.

None of the authors have any conflicts of interests.

6. Monitoring

Standards and indicators

No national quality assurance database has been established treatment and related data of anal cancer.

Plan for audit and feedback

The content of the guideline will be updated and re-evaluated every second year by the group of authors.

7. Appendix

Appendix 1 – Search strategy

Titel (på retningslinje)	*Management guidelines of late adverse effects after chemoradiation for anal cancer*
DMCG	*DACG*
Kontakt med metodespecialist	*Nej*
Senest udfyldt	*08.06.2020*

Afgrænsning af emne	
Baggrund	Senfølger efter strålebehandling af anal cancer mhp etablering af behandlingsguideline herfor
Inklusions- og eksklusionskriterier	*Publikationsdato (periode): 2000 til dags dato* *Sprog: engelsk, dansk, svensk, norsk* *Publikationstype: Primærlitteratur, herunder RCT'er og kohortestudier har interesse*

Engelsk *Alle tænkelige søgeord bør indsættes.*	*Anal cancer* *Squamous cell carcinoma of the anus* *Anal squamous cell carcinoma* *Anal tumor* *Anal* *Cancer* *Pelvic cancer*	*Radiaiton* *Radiotherapy* *Chemoradiotherapy* *5-FU-based CRT* *Mitomycin C*	*Late effects* *Survivorship* *Late toxicity* late radiation tissue injury late adverse effects toxicity	*Anorectal dysfunction* *Bowel dysfunction* *Urinary dysfunction* *Pelvic pain* *Pain* *Accelerated bone loss* *Sexual dysfuntion*

Pelvic organ cancer			*Pelvic radiaiton disease* *Psycosoical* *Quality of life* *Lymfedema* *Treatment models* *rehabilitaion* *Care* *rehabilitation*

Søgning efter guidelines

Databaser (Guidelines)	Dato for søgning	Ansvarlig for søgningen
G-I-N International http://www.g-i-n.net/library/international-guidelines-library	(02.06.2020)	Susanne Haas
NICE (UK) https://www.nice.org.uk/guidance/published?type=apg,csg,cg,mpg,ph,sg,sc	(02.06.2020)	Susanne Haas
Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/our-guidelines.html	(02.06.2020)	Susanne Haas

Søgning efter systematiske reviews

Databaser (systematiske reviews)	Dato for søgning	Ansvarlig for søgningen
Pubmed	10-12/06.2020	Susanne Haas

Søgning efter primærlitteratur (fx randomiserede kontrollerede forsøg)

Databaser (primær litteratur)	Dato for søgning (dd/mm/åååå)	Ansvarlig for søgningen (navn(e))
Medline / pubmed	10-12/06 2020	Susanne Haas
THE COCHRANE LIBRARY	14-07-2020	Susanne Haas
CINAHL	19-08-2020	Conni Skrubbeltrang
Pubmed	10-12/06 2020	Susanne Haas

1: (((((((anal cancer) OR squamous cell carcinoma of the anus) OR anal tumor) OR anal) OR Cancer) OR carcinoma) OR Tumor) OR pelvic cancer) OR pelvic tumor) Sort by: Author

2: Search ((((radiotherapy) OR radiation) OR chemoradiation) OR Chemoradiotherapy) OR CRT Sort by: Author

3: Search ((late effects) OR survivorship Sort by: Author

4: Search (((((((bowel dysfuction) OR urinary dysfunction) OR pelvic pain) OR pain) OR seual dysfunction) OR accelerated bone loss) OR psychosocial) OR quality of life) OR lymphedema Sort by: Author

Search four was conducted with the fives complaint/ symptom categories: Final search for late GI adverse effects:

((((("anal cancer") OR "anal tumor") OR "pelvic cancer") OR "pelvic tumor")))) AND ((((radiotherapy) OR radiation) OR chemoradiation) OR Chemoradiotherapy) OR CRT))))) AND ((((((("late effects") OR survivorship) OR "Late toxicity") OR "late radiation tissue injury") OR "late adverse effects"))))) AND (((((("bowel dysfunction") or fecal incontinence) OR urge) OR urgency) OR rectal bleeding)))))

1) Final search for late urinary adverse effects:

((((("anal cancer") OR "anal tumor") OR "pelvic cancer") OR "pelvic tumor")))) AND ((((radiotherapy) OR radiation) OR chemoradiation) OR Chemoradiotherapy) OR CRT))))) AND ((((((("late effects") OR survivorship) OR "Late toxicity") OR "late radiation tissue injury") OR "late adverse effects"))))) AND ((((((("urinary dysfunction") or "urinary incontinence") OR "hemorrhagic cystitis") OR "radiation induced cystitis") OR bladder toxicity) OR bladder dysfunction))))))

2) Final search for sexual dysfunction:

((((("anal cancer") OR "anal tumor") OR "pelvic cancer") OR "pelvic tumor")))) AND ((((radiotherapy) OR radiation) OR chemoradiation) OR Chemoradiotherapy) OR CRT))))) AND ((((((("late effects") OR survivorship) OR "Late toxicity") OR "late radiation tissue injury") OR "late adverse effects"))))) AND ((((("sexual dysfunction")

or "dysparenuria") OR "erectile dysfunction") OR "sexual rehabilitation)))) = 15 hits heraf flere relevante (og et væsentligt overlap)

3) Final search for quality of life:

((((("anal cancer") OR "anal tumor") OR "pelvic cancer") OR "pelvic tumor")))) AND ((((radiotherapy) OR radiation) OR chemoradiation) OR Chemoradiotherapy) OR CRT))))) AND ((((((("late effects") OR survivorship) OR "Late toxicity") OR "late radiation tissue injury") OR "late adverse effects"))))) AND ((("quality of life") or "QoL") OR "psychosocial")))

4) Final search for pain:

((((("anal cancer") OR "anal tumor") OR "pelvic cancer") OR "pelvic tumor")))) AND ((((radiotherapy) OR radiation) OR chemoradiation) OR Chemoradiotherapy) OR CRT))))) AND ((((((("late effects") OR survivorship) OR "Late toxicity") OR "late radiation tissue injury") OR "late adverse effects"))))) AND (((((("chronic pain") or "pain") OR "pelvic pain")OR "Accelerated bone loss") OR insufficiens fracture")))))

5) Final search for treatment/ algorithms

((((("anal cancer") OR "anal tumor") OR "pelvic cancer") OR "pelvic tumor")))) AND ((((radiotherapy) OR radiation) OR chemoradiation) OR Chemoradiotherapy) OR CRT))))) AND ((((((("late effects") OR survivorship) OR "Late toxicity") OR "late radiation tissue injury") OR "late adverse effects"))))) AND ((((treatment) OR "treatment model") OR care) OR rehabilitation))))

Extra search “pelvic radiation disease:

Search: ((((("anal cancer") OR "anal tumor") OR "pelvic cancer") OR "pelvic tumor")))) AND ((((radiotherapy) OR radiation) OR chemoradiation) OR Chemoradiotherapy) OR CRT))))) AND ((((((("late effects") OR survivorship) OR "Late toxicity") OR "late radiation tissue injury") OR "late adverse effects"))))) AND (("pelvic radiation disease") OR "pelvic organ disease"))

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