Acute toxicity and patient-reported outcomes in anal canal cancer: results of a pilot study

Elizabeth Brown, BAAppSc (MRT-RT), PhD1, Emma Le Cornu, MedRadSc (RT), GCert HPri, MHMng (HServ)1, Thanh Bui, BAAppSc (MRT-RT), Anne Bernard, PhD2, Tao Mai, MBBS, FRANZCR, PhD1,3, & Jennifer Harvey, BSc (Hons), MBBS, FRANZCR1,3

1Radiation Oncology Princess Alexandra Hospital – Ipswich Road, Brisbane, Queensland, Australia
2QCIF Bioinformatics, Institute for Molecular Bioscience, University of Queensland, Brisbane, Queensland, Australia
3School of Medicine, University of Queensland, Brisbane, Queensland, Australia

Keywords
anal canal cancer, patient reported outcomes, toxicity, volumetric modulated arc therapy (VMAT)

Abstract
Introduction: Anal canal cancer (ACC) is uncommon. The gold standard of care is chemoradiotherapy treatment. However, this treatment is associated with considerable acute and late side effects. The aim of this pilot study was to evaluate acute toxicity and patient-reported outcomes (PRO) in these patients from planning to 3 months after treatment. Methods: Sixteen patients were recruited to this prospective observational study from March 2015 to December 2017. All patients received volumetric modulated arc therapy (VMAT) in 30#. Toxicity data were graded by a Radiation Oncologist using the Common Terminology Criteria for Adverse Effects (CTCAE) version 4 at planning, weekly during treatment, 6-week and 3-month post-treatment. PRO data were collected using the EORTC QLQ C30 and CR29 questionnaires completed by patients at planning, mid and end treatment and 3-month post-treatment. Results: The majority of toxicity and PRO items peaked in severity at the end of treatment (week 6). Skin was the only item where >50% of patients had ≥ grade 2 toxicity at any point with 75% having ≥ grade 2 at week 6. Patient-reported embarrassment significantly increased over time (P < 0.001). No meaningful relationships were found between PRO and CTCAE results. Conclusion: After reaching their maximum severity at the end of treatment, the majority of toxicity and PRO items approached baseline levels by 3-month post-treatment. The results of this study suggest that PROs are an important complementary tool to CTCAE and provide greater understanding of patients’ perception of treatment side effects.
that comes directly from the patient (i.e. without the interpretation of the patient’s responses by a physician or anyone else), including disease symptoms, patient functioning and QoL. PROs can provide important insight into and understanding of how treatment and its side effects influences a patient’s day-to-day life. The collection of PROs, in addition to clinician-rated toxicity, is steadily being incorporated into clinical practice and trials to provide a more holistic picture of how treatment impacts patients. However, there is further work to be done to gain a deeper understanding of the relationship between these measures for different cancer sites. As such, the aim of this prospective exploratory pilot study was to collect dosimetry, toxicity and PRO data from planning through to three-year post-treatment completion for patients receiving VMAT treatment for ACC. This paper will specifically focus on the results of the acute phase of the study, covering the time period from planning to three-month post-treatment completion.

**Methods**

**Patients**

Between March 2015 and December 2017, all patients presenting for radical CRT for ACC were invited to participate in the study. Patients were eligible for inclusion if they were over 18 years of age, had a sufficient knowledge of English and adequate cognitive function to complete the questionnaires, had histologically confirmed squamous cell carcinoma or basaloid carcinoma of the anus, had T2-4 disease and were intended to receive VMAT treatment to all pelvic nodal groups up to the L5-S1 interspace. Patients were excluded if they had evidence of metastatic disease at the time of diagnosis, had prior pelvic surgery or radiation therapy and had connective tissue disorders or acquired immunodeficiency syndrome (AIDS). All patients signed a written consent form to participate in the study. Ethics approval for the conduct of this study was granted by the Metro South Human Research Ethics Committee.

**CT simulation, planning and treatment**

All patients were planned with a comfortably full bladder, voiding their bladder 40 min prior to the CT session and then drinking 500 mL of water. The acceptability of the bladder volume was determined by the Radiation Oncologist upon viewing the CT scan. Patients were positioned supine with foot stocks to separate their legs. Bolus was applied as required.

Target volume contouring was in accordance with The Australian Gastro-Intestinal Trials Group (AGITG) guidelines. The gross tumour volume (GTV) included the gross disease as defined on clinical digital examination, examination under anaesthesia, CT, magnetic resonance imaging (MRI) and positron emission tomography (PET). The high dose clinical target volume (CTV) included the GTV, entire anal canal and 1–2 cm expansion (except in bone or air). The elective CTV also included all elective lymph node groups (mesorectum, presacral space, internal and external iliac lymph nodes, inguinal). The planning target volume (PTV) was generated by applying a 0.7-cm planning margin to the CTVs. PTV volumes generated for the optimization process were cropped 0.3 cm from the skin surface unless the use of bolus had been specified in that area.

OARs were delineated according to RTOG guidelines except for the small bowel. OAR included the femoral head and neck, urinary bladder, small bowel, external genitalia and bone marrow. Small bowel delineation followed the definition reported by Devisetty and colleagues.

All patients were planned with a VMAT simultaneous integrated boost technique (SIB). Gross disease received a total dose of 54Gy delivered over 30 fractions. Elective lymph nodes received 45Gy over 30 fractions. OAR dose constraints were based on the RTOG 05–29 with some modifications (Table 1). The primary objective was to achieve target volume coverage with OAR being prioritised as per the order presented in Table 1.

VMAT treatment was delivered using two full arcs and was planned using the Pinnacle treatment planning system (version 14, Philips Radiation Oncology Systems, Fitchburg, WI, USA). Patients were not planned to receive a break during treatment; however, if treatment

| OAR            | Dose constraint |
|----------------|----------------|
| Small bowel    | V30Gy ≤ 350 cc  |
|                | V35Gy ≤ 150 cc  |
|                | V45Gy ≤ 20 cc   |
|                | V50Gy = 0 cc    |
| Left and right femoral heads | V40Gy ≤ 35%   |
|                | V44Gy ≤ 5%      |
| Bone marrow    | V30Gy ≤ 50%     |
|                | V40Gy ≤ 35%     |
|                | V50Gy ≤ 5%      |
| External genitalia | V20Gy ≤ 50%  |
|                | V30Gy ≤ 35%     |
|                | V40Gy ≤ 5%      |
| Bladder        | V35Gy ≤ 50%     |
|                | V40Gy ≤ 35%     |
|                | V50Gy ≤ 5%      |

OAR, organ at risk.
interruption or cessation occurred, the reason for this was documented.

Chemotherapy

The standard chemotherapy regimen employed consisted of 2 cycles of Flurouracil (5-FU) (1000 mg/m²) given over 96 h continuous infusion in weeks 1 and 5 and 1 cycle of Mitomycin C (MMC) (10 mg/m²) in week 1.

Toxicity and PRO data collection

Clinician-rated toxicity was recorded by the treating Radiation Oncologist using the NCI – Common Terminology Criteria for Adverse Effects (CTCAE) version 4 at baseline (planning session), weekly throughout radiation therapy treatment, six-week and three-month post-treatment.

PRO data were collected using the EORTC QLQ C30 (core) and CR29 (colorectal) questionnaires completed by patients at planning (baseline), mid and end treatment and 3-month post-treatment. Table 2 outlines when each assessment was undertaken. The EORTC QLQ-C30 questionnaire assesses functional and symptom aspects of health-related QoL, and the QLQ-CR29 assesses colorectal QoL. The QLQ-CR29 module specifically addresses body image, urinary symptoms, pain, anorectal and sexual functions. A scale from 1 to 4 is used to rate each question except for the Global Health scale which is 1 to 7. All QLQ-C30 and CR29 scores were linearly adjusted to range scores from 0 to 100. A high score on Global Health status/QoL and function scales indicates a higher level of functioning. However, a high score on symptom scale indicates a high degree of the symptom.

Statistics

Descriptive statistics for continuous data were presented using mean and standard deviation (SD) when data were normally distributed or median and inter-quartile range (IQR) when normality was not met. Normality was assessed using Shapiro–Wilk test where appropriate. Categorical data were described using frequencies and percentages. A Linear Mixed Model (LMM) analysis with time (baseline, 6-week post-treatment and 3-month post-treatment) as a fixed effect and patient as random intercept effect was performed to assess the difference in each PRO item between time points. When significant difference was found, post hoc tests with adjustment for multiple testing were performed. Estimates and standard errors were presented along with P-values and adjusted (adj.) P-values. Toxicity results were further categorised into two groups (those < Grade 2 vs ≥ Grade 2) and PROs were compared between the two groups using t-tests. Statistical analyses were performed using R statistical software and P-values <0.05 were considered significant.

Results

Patient characteristics

Over the study period, 16 patients consented to participate. Patient demographics are displayed in Table 3. The majority of patients were female (68.7%) with SCC being the predominant pathology (93.8%). Most patients received a prescription dose of 54Gy in 30# (93.8%) and one patient required an interruption in treatment as a result of bladder issues.

All patients completed the QoL questionnaires at baseline and week 6 of radiation therapy treatment. Of the 16 patients, 15 (93.75%) completed both questionnaires at week 4 of treatment and at 3-month post-treatment completion, all patients completed the QLQ-C30 questionnaire and 15 (93.75%) completed the QLQ-CR29 questionnaire. All patients completed the questionnaires without help. The majority of questions at each time point were completed excepting the

Table 2. Schedule of assessments.

| Form                | Planning | Wk 1 | Wk 2 | Wk 3 | Wk 4 | Wk 5 | Wk 6 | 6 weeks post | 3 months post | 6 months post | 12 months post | 24 months post | 36 months post |
|---------------------|----------|------|------|------|------|------|------|--------------|---------------|---------------|----------------|----------------|---------------|
| NCI-CTCAE v4.0      | ✓✓       | ✓✓   | ✓✓   | ✓✓   | ✓✓   | ✓✓   | ✓✓   | ✓✓           | ✓✓            | ✓✓            | ✓✓             | ✓✓             | ✓✓            |
| EORTC QLQ-C30       | ✓✓       | ✓✓   | ✓✓   | ✓✓   | ✓✓   | ✓✓   | ✓✓   | ✓✓           | ✓✓            | ✓✓            | ✓✓             | ✓✓             | ✓✓            |
| EORTC-CR29          | ✓✓       | ✓✓   | ✓✓   | ✓✓   | ✓✓   | ✓✓   | ✓✓   | ✓✓           | ✓✓            | ✓✓            | ✓✓             | ✓✓             | ✓✓            |

CTCAE, Common Terminology Criteria for Adverse Effects; EORTC, European Organisation for Research and Treatment of Cancer; NCI, National Cancer Institute.
questions regarding sexuality which many patients left blank.

**Dosimetric information**

Relevant dosimetric information is displayed in Table 4. PTV coverage was acceptable for all patients. All mean OAR tolerance doses/values were below the specified dose constraints except the small bowel V50 parameter. Of all OAR tolerances, the small bowel was the most exceeded with 2 patients (12.5%) exceeding the V30 constraint and 3 patients (18.75%) exceeding the V50 constraint.

**Clinician-reported toxicity**

As displayed in Figure 1, the majority of toxicity items peaked in severity at the end of treatment and approached baseline levels by 3-month post-treatment. Skin was the only item where more than 50% of patients had greater than grade 2 toxicity at any time point during treatment with 75% of patients having greater than grade 2 at the end of treatment. Constipation improved from planning to the end of treatment with a 43.75% decrease in toxicity rated as ≥2.

---

**Table 3. Patient characteristics.**

| Parameter                  | N (%)          |
|----------------------------|----------------|
| Gender                     |                |
| Male                       | 5 (31.3%)      |
| Female                     | 11 (68.7%)     |
| Mean (±SD) age (years)     | 65.5 (±9.7)    |
| Range                      | 46.6–81        |
| Diagnosis                  |                |
| SCC                        | 15 (93.8%)     |
| Basaloid                   | 1 (6.2%)       |
| T stage                    |                |
| 1                          | 2 (12.5%)      |
| 2                          | 5 (31.3%)      |
| 3                          | 4 (25%)        |
| 4                          | 5 (31.3%)      |
| N stage                    |                |
| 0                          | 8 (50%)        |
| 1                          | 2 (12.5%)      |
| 2                          | 2 (12.5%)      |
| 3                          | 4 (25%)        |
| Prescription               |                |
| 54Gy/30#                   | 15 (93.8%)     |
| 50.4Gy/28#                 | 1 (6.2%)       |
| Bolus applied              |                |
| Yes                        | 1 (6.3%)       |
| No                         | 15 (93.7%)     |
| Treatment interruption     |                |
| Yes                        | 1 (6.2%)       |
| No                         | 15 (93.8%)     |

SCC, squamous cell carcinoma; SD, standard deviation.

**Table 4. Dosimetric information.**

| Variable                  | Mean (±SD)       |
|----------------------------|------------------|
| PTV 45Gy D98              | 42.14Gy (0.85)   |
| PTV 54Gy D98              | 51.51Gy (0.90)   |
| Small bowel V30           | 229.29 cc (114.92) |
| Small bowel V50           | 3.24 cc (9.14)   |
| Bone marrow V30           | 41.61% (27.73)   |
| Bone marrow V50           | 0.14% (0.37)     |
| External genitalia V20    | 43.06% (6.82)    |
| External genitalia V40    | 2.73% (6.01)     |
| Bladder V35               | 39.10% (12.10)   |
| Bladder V50               | 3.47% (7.50)     |

PTV, planning target volume; SD, standard deviation.

---

**PRO**

Figure 2 displays the average (±standard error) results of the QLQ-C29 questionnaire which specifically assesses colorectal QoL. The 4-week post-baseline data were not included in the analysis in order to align with previously published literature in the area but is presented in the figures for visualisation purposes. Similar to toxicity, the majority of radiation (Fig. 2A) and chemotherapy (Fig. 2B) PROs peaked in severity at end of treatment (week 6) and started to approach baseline levels 3-month post-treatment. Patient-reported painful skin levels significantly increased between baseline and end of treatment (adj. \( P = 0.02 \)) and then significantly decreased, approaching baseline levels, at 3-month post-treatment (adj. \( P < 0.001 \)). Chemotherapy-related factors (Fig. 2B), including hair loss, dry mouth, bloating and taste, were affected during treatment but started to approach baseline levels by the 3-month post-treatment time point. Functional QoL (Fig. 2C) measures showed differing trajectories. Anxiety was minimally altered throughout the time period, however, a trend towards a decline in body image from baseline to 3-month post-treatment was observed with a decrease in mean score from 89.58 (±16.47) to 70.63 (±28.36) (\( P = 0.06 \)). Of note, the level of embarrassment significantly increased from baseline to 3-month post-treatment (adj. \( P < 0.001 \)).

Figure 3 demonstrates the average (±standard error) results of the QLQ-C30 questionnaire which assesses functional and symptom aspects of health-related QoL. The Global Health status displayed a moderate deterioration during treatment, returning to baseline levels at 3-month post-treatment (Fig. 3A). The functioning domains of role, social and physical all decreased slightly by the end of treatment but then increased approaching baseline levels by 3-month post-treatment completion (Fig. 3A). With respect to symptom scales (Fig. 3B), most showed slight increases in
severity during treatment with a return to baseline levels at 3-month post-treatment. The exceptions to this were diarrhoea and constipation. Constipation demonstrated a considerable decrease between baseline and 3-month post-treatment (mean 37.78 ± 39.57 vs 14.29 ± 17.12, adj. $P = 0.04$), and diarrhoea showed a significant increase between baseline and the end of treatment (mean 8.89 ± 26.63 vs 50.00 ± 36.51, adj. $P < 0.001$).

No meaningful relationships were found between clinician-reported toxicity and PRO data. However, a greater frequency of increased PRO scores in the toxicity areas of painful skin, diarrhoea and faecal incontinence were observed in comparison with clinician-reported toxicity.

**Discussion**

This study found that both clinician-reported toxicity and PROs peaked at the end of treatment then approached baseline levels by 3-month post-treatment. This trajectory is similar to other studies investigating toxicity with modulated, highly conformal techniques in ACC.\(^{16-18}\)

However, clinician-reported toxicity in this study appeared more favourable than other studies with all items, excepting skin, having less than half of patients experiencing greater than or equal to grade 2 toxicity. The severity of dermatological toxicities reported in this study is in line with other similar studies. The RTOG 0529 trial\(^5\) investigating 52 ACC patients, recorded 73\% grade 2+ skin toxicity and Kronborg et al. reported 68\% grade 2+ radiation dermatitis in 100 patients.\(^{10}\) This compares well with the current study where 75\% of patients experienced grade 2+ skin toxicity. However, we found only one patient (6.25\%) experienced grade 3 dermatological toxicity, considerably less than RTOG 0529 who reported 23\% of patients experiencing grade 3+.\(^5\) Additionally, the frequency of patients experiencing grade 2 diarrhoea was also considerably less than other studies with only one (6.25\%) patient rated as having grade 2 diarrhoea at the end of radiation therapy treatment. This is in comparison with the RTOG 0529 trial\(^5\) that reported 34.6\% of patients experiencing grade 2+ toxicity and Kronborg et al. reporting 34.6\%.\(^{10}\) Possible explanations for this could include the slightly

---

![Figure 1. Clinician-related toxicity rated ≥2 across time.](image-url)
Figure 2. EORTC QLQ-CR29 questionnaire results (average score with standard errors). (A) Radiation side effects, (B) chemotherapy side effects and (C) functional quality of life measures.

Figure 3. EORTC QLQ-C30 questionnaire results (average score with standard errors). (A) Functional domains and (B) symptom scales.
lower prescription dose used in this study, and the lower dose delivered to gastrointestinal OAR.

The current study also found few treatment interruptions were required with only one patient having a break during treatment as a result of bladder issues. The frequency of required treatment breaks varies considerably in the literature with studies employing modulated techniques reporting frequencies ranging from 2% to 71.4%. Despite these differences, this study adds to the evidence supporting the benefits of highly conformal modulated techniques in this patient cohort to reduce acute toxicity.

The need to include PROs in clinical studies has become increasingly evident due the association that has been found with survival and the rich information they provide. No meaningful relationships were found between clinician-reported toxicity and PROs in this study. This could be a result of the small sample size of this study as well as the low levels of severe toxicity recorded. A similar study conducted by Kronborg and colleagues found a high frequency of PRO scores and a weak agreement between toxicity and PROs. Similar to Kronborg’s study, we also found a greater frequency of increased PRO scores in the toxicity areas of sore skin, diarrhoea and faecal incontinence. Supporting this finding was the results of a study conducted by Tom and colleagues who investigated the prevalence of PROs for gastrointestinal symptoms in 78 patients with ACC. They also found that patients were more likely to report the prevalence of symptoms when compared to clinicians with results showing good agreement between clinician-reported toxicity and PROs for diarrhoea but poor agreement for proctitis. These studies all support the importance of PROs as complementary tools evaluating patient symptoms and outcome during and after treatment for ACC. This study found that the majority of toxicity and PRO items peaked in severity at the end of treatment and approached baseline levels by 3-month post-treatment. The symptoms and side effects of ACC can be private and embarrassing, negatively impacting a person’s self-confidence. In a study investigating the QoL of long-term survivors of ACC with normative data, Bentzen et al. found that social and role functioning was reduced in 128 long-term ACC survivors with pelvic side effects such as diarrhoea and buttock pain, often perceived by people as private and embarrassing. Embarrassment, depression and distress have not been extensively investigated in ACC, but the results of these studies suggest that this needs to be investigated in more depth to enable us to gain a better understanding of how ACC treatment and its associated side effects holistically affects a person both in the short and long term.

This study had its limitations. As it was designed as an exploratory pilot study, only a small number of patients were included. This restricted its ability to determine meaningful relationships and make definitive statements and as such, the findings would need to be validated in a larger cohort. However, our results show reasonable concordance with others reported in literature providing some level of confidence in its indications. We were also unable to conduct any analysis on sexual function due to the low number of patients who completed these questions. It should be noted that the majority of patients were female which may have influenced the PRO results, potentially limiting its generalisation to males. Future studies should incorporate the use of the new EORTC QLQ-ANL27 questionnaire which is currently under Phase IV testing. This questionnaire has been developed to more specifically address QoL issues experienced by ACC patients and will provide a more detailed insight into how treatment impacts these patients. Future work should also further investigate the impact and trajectory of treatment-related embarrassment in this patient cohort to assist in developing evidence-based strategies to provide better support.

Conclusion

This study found that the majority of toxicity and PRO items peaked in severity at the end of treatment and approached baseline levels by 3-month post-treatment. Although no relationships between toxicity and PRO data were able to be determined, the results do support the idea that PROs are an important complementary tool in the management of ACC patients with and enables a greater understanding of the effect of treatment side effects on the person and their day-to-day life.

Acknowledgements

The authors wish to acknowledge the support of the Princess Alexandra Hospital Radiation Oncology management and staff in the conduct of this study. They also wish to express their appreciation to the patients who so willingly gave their time to participate in the study.

Conflict of interest

The authors have no conflicts of interest to declare.
References

1. Glynne-Jones R, Renehan A. Current treatment of anal squamous cell carcinoma. *Hematol Oncol Clin North Am* 2012; 26: 1315–50.
2. Glynne-Jones R, Nilsson PJ, Aschele C, et al. Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *Radiother Oncol* 2014; 111: 330–9.
3. Mitchell MP, Abboud M, Eng C, Beddar AS, Krishnan S, Delcos ME, Crane CH, Das P. Intensity-modulated radiation therapy with concurrent chemotherapy for anal cancer: outcomes and toxicity. *Am J Clin Oncol* 2014; 37: 461–6.
4. Milano MT, Jani AB, Farrey KJ, Rash C, Heimann R, Chmura SJ. Intensity-modulated radiation therapy (IMRT) in the treatment of anal cancer: toxicity and clinical outcome. *Int J Radiat Oncol Biol Phys* 2005; 63: 354–61.
5. Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity-modulated radiation therapy in combination with 5-Fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. *Int J Radiat Oncol Biol Phys* 2013; 86: 27–33.
6. Yordanov K, Cima S, Richetti A, et al. Concurrent chemoradiation with volumetric modulated Arc therapy of patients treated for anal cancer—acute toxicity and treatment outcome. *J Gastrointest Oncol* 2017; 8: 361–7.
7. Shridhar R, Shibata D, Chan E, Thomas CR. Anal cancer: Current standards in care and recent changes in practice. *CA Cancer J Clin* 2015; 65: 139–62.
8. Administration USDoHaHSFaD. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. U.S. Department of Health and Human Services Food and Drug Administration, Rockville, MD, 2009.
9. Tom A, Bennett AV, Rothenstein D, Law E, Goodman KA. Prevalence of patient-reported gastrointestinal symptoms and agreement with clinician toxicity assessments in radiation therapy for anal cancer. *Qual Life Res* 2018; 27: 97–103.
10. Kronborg C, Serup-Hansen E, Lefeve R, et al. Prospective evaluation of acute toxicity and patient reported outcomes in anal cancer and plan optimization. *Radiother Oncol* 2018; 128: 375–9.
11. Ng M, Leong T, Chander S, et al. Australasian Gastrointestinal Trials Group (AGITG) contouring atlas and planning guidelines for intensity-modulated radiotherapy in anal cancer. *Int J Radiat Oncol Biol Phys* 2012; 83: 1455–62.

12. Devisetty K, Mell LK, Salama JK, et al. A multi-institutional acute gastrointestinal toxicity analysis of anal cancer patients treated with concurrent intensity-modulated radiation therapy (IMRT) and chemotherapy. *Radiother Oncol* 2009; 93: 298–301.
13. Institute NC. Common Terminology Criteria for Adverse Events (CTCAE), U.S. Department of Health and Human Services. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm. 2021. Accessed 11th November, 2021.
14. Cancer EOfRTo. Quality of Life questionnaires. EORTC. Available from: https://qol.eortc.org/questionnaires/. 2022. Accessed 11th November, 2021.
15. R: A language and environment for statistical computing. R Foundation for Statistical Computing [computer program], Vienna, Austria, 2020.
16. Joseph K, Vos L, Warkentin H, et al. Patient reported quality of life after helical IMRT based concurrent chemoradiation of locally advanced anal cancer. *Radiother Oncol* 2016; 120: 228–33.
17. Han K, Cummings BJ, Lindsay P, et al. Prospective evaluation of acute toxicity and quality of life after IMRT and concurrent chemotherapy for anal canal and perianal cancer. *Int J Radiat Oncol Biol Phys* 2014; 90: 587–94.
18. Tournier-Rangeard L, Mercier M, Peiffert D, et al. Radiochemotherapy of locally advanced anal canal carcinoma: Prospective assessment of early impact on the quality of life (randomized trial ACCORD 03). *Radiother Oncol* 2008; 87: 391–7.
19. Gotay CC, Kawamoto CT, Bottomley A, Efficace F. The prognostic significance of patient-reported outcomes in Cancer Clinical Trials. *J Clin Oncol* 2008; 26: 1355–63.
20. Quinten C, Maringwa J, Gotay CC, et al. Patient self-reports of symptoms and clinician ratings as predictors of overall cancer survival. *J Natl Cancer Inst* 2011; 103: 1851–8.
21. Atkinson TM, Ryan SJ, Bennett AV, et al. The association between clinician-based common terminology criteria for adverse events (CTCAE) and patient-reported outcomes (PRO): a systematic review. *Supportive Care Cancer* 2016; 24: 3669–76.
22. Bentzen AG, Balteskard L, Wander EH, et al. Impaired health-related quality of life after chemoradiotherapy for anal cancer: late effects in a National Cohort of 128 survivors. *Acta Oncol* 2013; 52: 736–44.
23. Sodergren SCJC, Gilbert A, Tomaszewski KA, et al. Phase I–III development of the EORTC QLQ-ANL27, a health-related quality of life questionnaire for anal cancer. *Radiother Oncol* 2018; 126: 222–8.