Clinical Oncology 31 (2019) 69–71

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Editorial

Anal Cancer: Putting Health-Related Quality of Life at the Forefront

S.C. Sodergren *, A. Gilbert †‡, A.-S. Darlington *, V. Vassiliou §, on Behalf of the EORTC Quality of Life Group

* School of Health Sciences, University of Southampton, Southampton, UK
† Leeds Radiotherapy Research Group, Leeds Institute of Cancer and Pathology, University of Leeds, Leeds, UK
‡ Leeds Cancer Centre, St James's University Hospital, Leeds, UK
§ Bank of Cyprus Oncology Centre, Nicosia, Cyprus

Received 28 August 2018; accepted 10 October 2018

Anal carcinomas are rare, accounting for 2% of all gastrointestinal malignancies, and are related to human papillomavirus [1,2]. In the last three decades there has been an increase in incidence, with females three times more likely to be diagnosed than men [1,2]. Concurrent chemoradiotherapy (CRT) is the standard of care for most patients, with 5-year survival rates of over 75% [3]. Although patients experience high cure rates, treatment-related toxicity can be a chronic and debilitating disease state. Patients are prone to specific toxicities, such as bowel, urinary and sexual dysfunction, given the high dosage of radiotherapy delivered and sensitive areas irradiated. These toxicities can prompt unintended treatment breaks and radiation dose reduction, leading to suboptimal disease-related outcomes. Furthermore, they also impact on the patient's health-related quality of life (HRQoL), not only in the short term, but also well beyond treatment.

Alternative treatment regimens supporting more favourable toxicity profiles are continuously being investigated. Precision radiotherapy techniques, such as volume-modulated arc therapy and intensity-modulated radiation therapy, are now standard of care in most radiotherapy centres [4]. With improvements in the accuracy of radiotherapy delivery achieved by these techniques, current research is concerned with the identification of optimal radiotherapy dose. The option of dose escalation for high-risk patients and dose de-escalation for lower-risk patients with anal cancer has become an important research question, addressed in the current PLATO trial (PersonaLizing Anal cancer radioTherapy dOse, incorporating ACT3, ACT4 and ACT5) [5]. As reduction (or no deterioration) in treatment-related morbidity will be one of the key outcomes of PLATO and future trials, it is key that patient experience of symptomatic toxicity and HRQoL are accurately measured using patient-reported outcome (PRO) measures.

Given that treatment-related morbidity is the hallmark of the anal cancer patient experience and forms an integral part of the treatment decision criteria, it is surprising that it is not systematically documented in this patient group as part of routine care [6]. Reasons for this include restricted options for HRQoL measurement in anal cancer patients with a focus on pre-morbid conditions rather than treatment-related effects [7] and no general consensus on core PRO sets [8]. In addition, within the context of clinical trials, quality of reporting has been recognised as inconsistent and inclusion of PROs within clinical trials is now accepted as the gold standard for the measurement of symptomatic patient experience [7]. Our review of existing PRO measures used with patients with anal cancer [6] revealed that the specific treatment-related effects experienced by this patient group are either overlooked completely or inadequately represented by the measures used, including the European Organization for Research and Treatment of Cancer (EORTC) colorectal cancer-specific module (EORTC QLQ-CR29) [9].

In 2013, the EORTC Quality of Life Group, renowned for its development of disease- and treatment-specific HRQoL measures, supported the development of an anal cancer module to supplement the core EORTC HRQoL questionnaire (EORTC QLQ-C30). Its aim is to assess the HRQoL of anal cancer patients managed with radical CRT. This process follows four key phases of development: (1) generation of HRQoL issues through a systematic review of the literature and interviews with patients and healthcare professionals (HCPs); (2) selection of questionnaire items; (3) an initial pilot testing of the questionnaire; and (4) a larger validation study.

Address for correspondence: S.C. Sodergren, University of Southampton, Southampton, UK.
E-mail address: S.C.Sodergren@soton.ac.uk (S.C. Sodergren).

https://doi.org/10.1016/j.clon.2018.10.010

Our systematic review of HRQoL assessment in anal cancer covered 152 publications from 2006 to 2014 [6] and included 11 studies that used a formal assessment of HRQoL. In order to add to our list of issues captured from the literature, we interviewed 53 patients with anal cancer and 34 HCPs with expertise in the disease field. Patients and HCPs were representative of different language and cultural settings and patients were recruited across the disease and treatment spectrum, ensuring that both acute and late effects (up to 5 years) were identified. In total, 197 initial issues were generated. These were condensed and operationalised into a 65-item questionnaire using the EORTC Quality of Life Group item library, optimising content validity. Of these questions, 23 described novel issues, not covered by existing EORTC modules. The draft 65-item questionnaire was pilot tested and reviewed for relevance and importance by an additional 100 patients from eight countries. This initial testing resulted in the removal and rewording of questions, resulting in a 27-item questionnaire, the EORTC QLQ-ANL27 [10], covering four areas (domains) of HRQoL concern: bowel, pain or discomfort (relating to both skin and bowel problems), sexual function (male and female) and stoma, as well as five single questions: frequent urination, keeping clean, proximity to toilet, lower limb oedema and planning activities (Table 1). Having completed phase III, the EORTC QLQ-ANL27 module is now available for use in clinical trials (http://groups.eortc.be/qol/). A larger phase IV international validation study to confirm its psychometric properties is now underway.

In summary, our research confirmed that patients suffer significant acute and late side-effects of treatment impacting on activities of daily living, including bowel, urinary and sexual function, as well as radiotherapy-related skin reactions and lymphoedema [10]. Our review of the literature [6] identified bowel problems, in particular diarrhoea, as a commonly reported side-effect of treatment for anal cancer [11,12]. However, in addition to diarrhoea, bowel frequency and incontinence, other issues, such as bowel urgency, toilet dependency and tenesmus, were also important issues reported by patients and clinicians not covered by existing measures [6]. Inclusion of questions related to having a stoma were also felt to be important. Although only a minority of patents will undergo a stoma placement, the HRQol issues surrounding having a stoma are well documented [13]. Alongside bowel problems, sexual dysfunction is also recognised as a common concern of patients with anal cancer [11,12]. Female patients encounter dyspareunia, vaginal dryness, pelvic pain and vaginal stenosis. In males, impotence is a potential complication [12]. Acute skin toxicity in the radiation field causes a burning sensation and severe discomfort and pain, which is exacerbated by movement, sleeping, micturition and defaecation. These issues are not adequately covered by the EORTC QLQ-CR29 module or the radiation proctitis module (EORTC QLQ-PRT21) [14]. Urinary frequency was the main urinary issue reported in the literature and by patients. Lower limb lymphoedema is a relatively uncommon but serious late complication resulting from the irradiation of the pelvic and inguinal nodal regions. Symptoms of lymphoedema were not addressed in existing questionnaires used with patients with anal cancer.

Table 1
Issues included in the EORTC QLQ-ANL27 and hypothesised conceptual scales

Conceptual scale	Issues
Bowel	Flatulence
	Bowel incontinence
	Frequent defecation
	Bowel urgency
	Sensation of inability to effectively empty bowels
Pain/discomfort/skin reaction	Painful bowel movements
	Pain or discomfort in the anus or anal opening
	Pain while sitting
	Discomfort in certain positions (e.g. lying down)
	Soreness in treatment area
	Itchy/irritated skin in treated areas
Stoma	Skin reaction around stoma site
	Leakage of stools from stoma bag
	Unintentional release of gas/flatulence from stoma bag
Sexual	*General*
	Sexual interest
	Affected sex life
	Painful sexual intercourse
	Male
	Impotence
	Female
	Vaginal dryness
	Vaginal narrowing
	Vaginal pain
Individual items	Frequent urination
	Keeping clean
	Proximity to toilet
	Lower limb oedema
	Planning activities

The EORTC QLQ-ANL27 module [10] is the first questionnaire of its kind to measure the specific disease and treatment effects of anal cancer managed with radical CRT. It is designed for use in clinical trials as well as in routine clinical practice. The EORTC QLQ-ANL27 is currently used to assess HRQoL and symptomatic toxicity for all anal cancer patients enrolled in the PLATO trial [5]. The EORTC QLQ-ANL27 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. Thus, this recognition of concerns can prompt HCPs to provide the necessary support (practical or psychological) to patients, which will probably confer HRQoL benefits as well as potentially impacting on disease outcome [15,16]. It is recognised that issues such as those measured by the EORTC QLQ-ANL27 will probably be under-reported in the current literature, especially those of a sensitive nature, such as problems relating to bowel or sexual function [17,18], which

might not necessarily come up during clinical assessments and are not adequately addressed by current measures. The EORTC QLQ-ANL27 aims to address this issue.

The EORTC QLQ-ANL27 also addresses a major shortfall in the measurement of the burden imposed by anal cancer and its treatment at a time when measuring patient experience is deemed essential rather than just an addition to other areas of primary interest, such as disease outcome [15,19]. The EORTC QLQ-ANL27 offers detailed, relevant data on both acute and chronic disease and treatment-related effects from the perspective of the patient; informative both for clinicians and patients themselves, as well as essential for supporting claims regarding improved treatment schedules.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The authors would like to thank Professor Colin Johnson for his assistance in preparing the manuscript. We would also like to thank our collaborators on the EORTC QLQ-ANL27 module development. The EORTC QLQ-ANL27 module development project is funded by the EORTC Quality of Life Group. The grant was awarded to Professor Colin Johnson, Associate Professor Anne Sophie Darlington and Dr Vassilios Vassiliou.

References

[1] Aggarwal A, Duke S, Glynne-Jones R. Anal cancer: are we making progress? *Curr Oncol Rep Rep* 2013;15(2):170–181. https://doi.org/10.1007/s11912-013-0296-6.

[2] Jemal A, Simard EP, Dorell C, Noone A-M, Markowitz LE, Kohler B, *et al*. Annual report to the nation on the status of cancer, 1975–2009, featuring the burden and trends in human papillomavirus (HPV)-associated cancers and HPV vaccination coverage levels. *J Natl Cancer Inst* 2013;105:175–201.

[3] Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson AB, Thomas CR, *et al*. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. *JAMA* 2008;299(16):1914–1921. https://doi.org/10.1001/jama.299.16.1914.

[4] Muirhead R, Drinkwater K, O'Cathail SM, Adams R, Glynne-Jones R, Harrison M, *et al*. Initial results from the Royal College of Radiologists' UK National Audit of Anal Cancer Radiotherapy 2015. *Clin Oncol* 2017;29(3):188–197.

[5] PLATO Trial. PersonaLising anal cancer radioTherapy dOse – incorporating ACT3, ACT4 and ACT5. Available at: http://medhealth.leeds.ac.uk/info/430/solid_tumours/2210/plato. [Accessed 9 July 2018].

[6] Sodergren SC, Vassiliou V, Dennis K, Tomaszewsk KA, Gilbert A, Glynne-Jones R, *et al*. Systematic review of the quality of life issues associated with anal cancer and its treatment with radiochemotherapy. *Support Care Cancer* 2015;23(12):3613–3623.

[7] Glynne-Jones R, Adams R, Lopes A, Meadows H. Clinical endpoints in trials of chemoradiation for patients with anal cancer. *Lancet Oncol* 2017;18:e218–e227.

[8] Fish R, Sanders C, Williamson PR, Renehan AG. Core outcome research measures in anal cancer (CORMAC): protocol for systematic review, qualitative interviews and Delphi survey to develop a core outcome set in anal cancer. *BMJ Open* 2017;7:e018726. https://doi.org/10.1136/bmjopen-2017-018726.

[9] Whistance RN, Conroy T, Chie W, Sezer O, Koller M, Johnson CD, *et al*, European Organisation for the Research and Treatment of Cancer Quality of Life Group. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer. *Eur J Cancer* 2009;45(17):3017–3026. https://doi.org/10.1016/j.ejca.2009.08.014.

[10] Sodergren SC, Johnson CD, Gilbert A, Tomaszewski KA, Chu W, Chung HT, *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(2):222–228. https://doi.org/10.1016/j.radonc.2017.11.018.

[11] Allal AS, Sprangers MA, Laurencet F, Reymond MA, Kurtz JM. Assessment of long-term quality of life in patients with anal carcinomas treated by radiotherapy with or without chemotherapy. *Br J Cancer* 1999;80(10):1588–1594.

[12] Das P, Cantor SB, Parker CL, Zampieri JB, Baschnagel A, Eng C, *et al*. Long-term quality of life after radiotherapy for the treatment of anal cancer. *Cancer* 2010;116(4):822–829. https://doi.org/10.1002/cncr.24906.

[13] Downing A, Morris EJA, Richards M, Corner J, Wright P, Sebag-Montefiore D, *et al*. Health-related quality of life after colorectal cancer in England: a patient-reported outcomes study of individuals 12 to 36 months after diagnosis. *J Clin Oncol* 2015;33(6):616–624.

[14] Spry N, Halkett G, Aoun S, Spry J, Yeoh EN, Spry G, *et al*. Development of an EORTC module to assess the quality of life of patients with proctitis following pelvic radiotherapy for malignancy. *Int J Radiat Oncol Biol Phys* 2008;72(2):522–528.

[15] Basch E, Deal AM, Dueck AC, Scher HI, Kris MG, Hudis C, *et al*. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. *JAMA* 2017;318(2):197–198.

[16] Velikova G, Booth L, Smith AB, Brown PM, Lynch P, Brown JM, *et al*. Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. *J Clin Oncol* 2004;22(4):714–724.

[17] Boyce M, Browne GP, Greenhalgh J. The experiences of professionals with using information from patient-reported outcome measures to improve the quality of healthcare: a systematic review of qualitative research. *BMJ Qual Saf* 2014;23(6):508–518.

[18] Flynn KE, Reese JB, Jeffery DD, Abernethy AP, Lin L, Shelby RA, *et al*. Patient experiences with communication about sex during and after treatment for cancer. *Psycho-oncology* 2012;21(6):594–601. https://doi.org/10.1002/pon.1947.

[19] US Department of Health and Human Services Food and Drug Administration. Guidance for industry: patient report outcome measures: use in clinical medical product development to support labelling claims: draft guidance. *Health Qual Life Outcome* 2006;4:79.