UK National cohort of anal cancer treated with intensity modulated radiotherapy: One-year oncological and patient reported outcomes

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Abstract

Background

Concurrent chemoradiotherapy is standard treatment for anal cancer. Following national UK implementation of intensity-modulated radiotherapy (IMRT) this prospective, national cohort evaluates the 1-year oncological outcomes and patient-reported toxicity outcomes (PRO) after treatment.

Materials and Methods

A national cohort of UK cancer centres implementing IMRT was carried out between February to July 2015. Cancer centres provided data on oncological outcomes including survival, and disease and colostomy status at 1-year. EORTC-QLQ core (C30) and colorectal (CR29) questionnaires were completed at baseline and 1-year follow-up. The PRO scores at baseline and 1-year were compared.

Results

40 UK Cancer Centres returned data with a total of 187 patients included in the analysis. 92% received mitomycin with 5-flurouracil or capecitabine. 1-year overall survival was 94%; 84% were disease-free and 86% colostomy-free at 1-year follow up. At 1-year, PRO results found significant improvements in buttock pain, blood and mucous in stools, pain, constipation, appetite loss, and health anxiety compared to baseline. No significant deteriorations were reported in diarrhoea, bowel frequency, and flatulence. Urinary symptom scores were low at 1-year. Moderate impotence symptoms at baseline remained at 1-year and a moderate deterioration in dyspareunia reported.

Conclusions

With national anal cancer IMRT implementation, at this early pre-defined time point, 1-year oncological outcomes were reassuring and result in good disease-related symptom control. 1-year symptomatic complications following CRT for anal cancer using IMRT techniques appear to be relatively mild. These PRO results provide a basis to benchmark future studies.

Introduction

Concurrent chemoradiotherapy is the standard of care for anal cancer treatment[1, 2]. In 2012, the UK department of health recommended implementation of intensity modulated radiotherapy (IMRT) (including volumetric modulated arc therapy (VMAT) and tomotherapy) with the aim of reducing toxicity from radiotherapy through sculpting of the beams and dose[3]. Within clinical trials, radiotherapy protocol deviations are known to impact on treatment failure and oncological outcomes[4]. Therefore, to optimise implementation of IMRT in a rare cancer, the Royal College of Radiologists supported the development of a national protocol and implementation strategy[5]. This national cohort was carried out with the aim of collecting prospective data to investigate IMRT delivery[6], to assess early toxicity[7], oncological outcomes and health-related quality of life (HRQOL).

A small number of studies in anal cancer, including prospective phase II trials, have reported on improved disease outcomes and treatment-related acute toxicity with the introduction of IMRT techniques[8-11]. Cross-sectional studies using patient-reported outcomes (PROs) have found patients report long-term toxicity related to bowel, urinary and sexual dysfunction post-treatment[12, 13]. However, there is a lack of prospectively collected PROs

measuring toxicity and HRQOL following anal cancer chemoradiotherapy from both IMRT and conformal techniques[13]. Baseline PRO data is important to be able to establish the true symptomatic benefit of treatment and to distinguish between toxicity and pre-morbid symptoms. In addition, there is also a lack of data outside of single-centre series. This paper presents the prospective evaluation of the impact of IMRT on patient-reported toxicity including HRQOL at 1-year in a national anal cancer cohort supplemented with oncological outcomes.

Materials and Methods

Prospective data collection from all UK National Health Service (NHS) cancer centres (n=56) in patients with a diagnosis of anal cancer starting IMRT over a 6-month period from 9 February to 27 July 2015 was requested. Full details are reported elsewhere[6]. Data collection was performed by the RCR as part of a national prospective cohort program in which approval was obtained by each NHS institution's research and governance board with a pre-planned 1-year follow-up schedule.

Patient demographic data at baseline included age, gender, stoma status, HIV and smoking status. Tumour and treatment information included TNM staging, radiotherapy dose and fractionation and concurrent chemotherapy schedule. Acute toxicity data was collected weekly during treatment using CTCAEv4[14] and reported grade 3/4 toxicity in any category used in the analysis. Full details of demographics and acute toxicity have been reported previously[6].

Patients were invited to complete the validated European Organisation for Research and Treatment of Cancer QOL questionnaires (EORTC-QLQ) core module (C30) and colorectal cancer module (CR29)[15, 16]. An anal cancer-specific module was not available at the time of recruitment[17]. The C30 is a generic questionnaire including items on overall HRQOL, physical, role, social, emotional and cognitive function as well as generic symptoms affecting cancer patients including fatigue, diarrhoea and pain. CR29 addresses disease-specific concerns including bowel, urinary and sexual symptoms.

PRO collection was coordinated by clinical teams at each cancer centre and patients were invited to complete paper questionnaires at two timepoints – baseline (prior to or on day 1 of starting radiotherapy) and at 1-year. Invitations to report 1-year follow up data were sent between 14 July 2016 and 18 November 2016 via three email reminders to clinical teams (Range 353-648days). Paper questionnaires were either handed out at clinic appointments for completion or sent to patients in the post with a return (stamped) envelope at the discretion of the clinical team. Resources for this national program were restricted.

Descriptive and regression analyses were performed using Stata v13.1[18]. Descriptive statistics were used to describe patient, clinical and tumour characteristics. Descriptive analysis was performed on 1-year oncological outcomes as event rates were too low to carry out more extensive analyses. Disease-free status was defined as disease that had achieved a complete response and not demonstrated recurrence[19] and missing data explored using logistic regression.

Exploratory analyses of EORTC QLQs and handling of missing data were performed according to EORTC guidelines, using a process of imputing missing values in scaled responses[20]. All item responses from the PROs were converted from a four-point Likerttype scale through a linear transformation onto a 0-100 scale. Higher scores for symptom items reflect more severe symptoms (i.e. 'not at all'=0; 'a little'=33.3; 'quite a bit'=66.6; 'very much'=100); higher scores for function items reflect a better level of functioning[20]. A minimum important difference (MID) was classified as a small change in scores from 5 to 10 points, moderate differences as a change up to 20 points and large differences as a change in scores of >20[21].

Mean and paired differences between baseline PRO scores and 1-year follow-up were evaluated. A two-sided t-test was used to evaluate statistical significance with a p-value <0.01 deemed to be significant, after Bonferroni correction for multiple comparisons. Multivariable linear regression analysis was performed to evaluate the impact of age, gender, acute (any) grade 3/4 toxicity, tumour stage and nodal stage on PRO items ($p<0.01$). Reasons for missing PRO data at baseline and 1-year follow up were explored using multivariable logistic regression, including age, gender, disease status, cancer centre, T stage and baseline PRO completion rates as confounders. An exploratory analysis compared mean PRO scores (for pre-defined PRO items taken from CORMAC core outcome set) at baseline and 1-year by risk groups; early stage T1/2N0 versus locally advanced T3/4 and/or N+[19, 22].

Results

Patient characteristics

1-year follow up data was collected in 40 UK Cancer Centres (71%), with numbers of participants included from each centre ranging from 1-13 participants (Median 4 per centre). Patient and tumour characteristics are summarised in Table 1 and 2 respectively. All 187 patients who received radical (curative intent) IMRT were included in this analysis, including patients who received full dose IMRT adherent to UK guidance (n=157)[6], those who received full dose IMRT not strictly adherent to UK guidance (n=23) and those receiving reduced dose IMRT (n=7) (see supplementary figure). Median radiotherapy dose received was 53.2Gy in 28 fractions(F) (Range 30-53.2Gy in 10-30F); T1/2 received median dose 50.4Gy in 28F (Range 30-54Gy in 10-30F) and T3/4 received median dose 53.2Gy in 28F (Range 40-54Gy in 15-30F). The majority of patients (n=153) completed full dose chemotherapy (n=27 dose reduced/omitted secondary to toxicity; n=7 no chemotherapy given) (see [6] for more details).

1-year survival data was available for 109 (58.2%) patients during follow-up. At 3-months no patients were known to have died. At 6-months 2 deaths were known to have occurred - both patients had residual local disease at 3-months. At 1-year, 6 patients in total had died - 94% 1-year overall survival. All 6 patients had evidence of local or distant disease, with 4 patients with residual local disease reported at 3-months. Disease-free survival status was available on 107 patients (57.2%) (2 patients were alive with unknown disease status). At 1year, 84 were disease-free (78.5%), and 13 had local disease failure reported (5 underwent salvage surgery; 5 local regional failure; 3 LRR and metastatic disease) (12.1%). Table 3

presents 1-year oncological outcomes by patient, treatment and disease characteristics. The event rate (6 deaths) was too low to comment on any trends in the data. 86% of patients were colostomy-free at 1-year (n=97/113). In regards missing data, centres either returned oncological outcome data or did not return any.

Exploratory PRO and HRQOL analysis

A total of 121 (65%) of patients reported some PRO data at either time-point, with 115 (61%) completing at least one PRO item at baseline and 57 (30%) at 1-year. 103 (55%) had complete data across all subscales at baseline and 54 (29%) at 1-year follow up. 43 (23%) of patients have complete subscale data at both time-points. No patient, clinical or tumour characteristics predicted missing PRO data. At baseline, only cancer centre appeared to predict missing questionnaires reflecting the administration approach to PRO data collection ($p=0.02$). At 1-year, there were no significant predictors of missing questionnaire data.

Table 4 describes the PRO mean scores at baseline and 1-year follow-up and mean and paired differences. Pain, constipation, appetite loss, anxiety, blood and mucous in stools, and buttock pain were all significantly improved at 1-year (mean differences). On review of MID between scores at baseline and 1-year, only dyspareunia showed a moderate clinical deterioration in mean scores (14.5 to 29.5). Otherwise moderate improvements were noted for role and emotional functioning and symptom scores: pain, constipation, appetite loss, anxiety, blood and mucous in stools. A large improvement in buttock pain from baseline was reported.

In terms of 1-year toxicity, it is reassuring that there was no clinically significant deteriorations reported with PRO items on diarrhoea, bowel frequency, flatulence, urinary frequency or impotence. Mean scores at 1-year for all bowel items ranged between 19.1 to 38.8 correlating to a patient reporting a 'mild' symptom[23]. Stoma scores are not included due to low numbers of patients reporting (n=13 at baseline and n=6 at 1-year).

The sample size for sexual toxicity items was small as only 34% of women reported on symptoms (n=46) and 50% of men (n=26). However, impotence scores for men remained relatively poor (mean score 46.6 – moderate symptoms) at 1-year but did not significantly deteriorate after treatment. For women, dyspareunia showed a moderate deterioration in mean scores but overall the 1-year mean score (29.4) relates to 'mild' symptoms.

The items with the most severe symptom mean scores at 1-year were flatulence, impotence, libido (for both men and women), and health anxiety. Although, both health anxiety and female libido showed a moderate and small improvement, respectively, from baseline scores. All other changes were minor. In regards HRQOL and function, moderate improvements at 1-year were noted for role and emotional functioning.

Regression analysis on predictors of significant PRO change between baseline and 1-year found change in pain scores was predicted by gender, with women reporting less of an improvement in pain scores over time (p=0.004); and acute G3/4 toxicity, with patients reporting a greater improvement in pain scores if they had reported any G3/4 toxicity during treatment or if this data was unknown as compared to patients with no G3/4 toxicity

(p=0.007). Similarly, change in buttock pain scores found women reporting less improvement in pain over time (p=0.01).

The exploratory analysis by risk groups (supplementary file), found locally advanced tumours have poorer baseline scores but report relatively greater improvements in function and cancer symptoms. In comparison, patients with early stage tumours are less compromised by cancer-related issues at baseline but have a proportionally greater change in scores by 1-year representing more toxicity-related issues.

Discussion

To our knowledge this is the largest, multicentre prospective cohort of 1-year oncological outcomes including PRO assessment of anal cancer patients treated with curative intent IMRT. The results provide a comprehensive evaluation of patients treated in routine practice in the UK.

The 1-year oncological outcomes found patients to have reassuringly high overall (94%), disease-free (84%) and colostomy-free (86%) survival in line other prospective studies of IMRT and randomised studies of conformal radiotherapy in anal cancer[2, 9, 24].

The toxicity rates for all symptoms are generally low and improvements in disease-related symptoms, such as buttock pain and per rectal bleeding, significant. Importantly at 1-year, there were no significant deteriorations seen in bowel toxicity items including diarrhoea, bowel frequency, and flatulence, although flatulence symptom scores remained moderately

severe (40.2). Urinary symptoms also did not significantly deteriorate at 1-year, although studies of pelvic radiotherapy with longer follow up have found that whilst bowel symptoms may improve after 1-year, urinary symptoms may deteriorate over a longer timeframe[26]. Whilst the sample for patients reporting on sexual function is small, it is important to note that dyspareunia deteriorated moderately at 1-year; and impotence symptom scores remained moderately severe, with a relatively greater deterioration seen in earlier cancers.

The 1-year PRO toxicity scores are similar to those reported in single-centre series of patients treated with IMRT[9, 27]. Although the use of different questionnaires and quality of reporting can make it challenging to directly compare results with other studies, the rates of late toxicity for bowel and erectile function using IMRT appear to be lower than crosssectional series of patients treated with conformal techniques[28-31]. These findings are likely to reflect the sculpted dose around bowel and penile bulb structures resulting in reduced dose anteriorly[32]. For example, within the current study at 1-year patients reported mild diarrhoea symptoms (mean 16.4; SD22.0). Similarly, contemporary studies of patients treated with IMRT report mild symptoms with mean scores ranging from 12-22.8[9, 27]. In comparison, older studies have reported moderate diarrhoea symptom scores with mean scores between 27-34.6[28, 30, 31, 33]. Similarly, large to moderate improvements using IMRT are observed with symptoms of flatulence, faecal incontinence and impotence[27, 30, 31]. Our rates of dyspareunia, urinary frequency and incontinence were similar to results from previous conformal and IMRT studies. Vaginal doses remain high as the structure is directly adjacent to the high dose tumour volume, whilst bladder symptoms

may be more reflective of pre-morbid symptoms as minimal change was observed from baseline[34, 35].

The exploratory analysis lends credence to the need to improve symptoms with a significant impact on QOL, such as flatulence, dyspareunia and impotence, and this should be a target for future studies de-escalating dose in patients with low-risk anal cancer[22]. Indeed, these data provide a benchmark to test improvements in PRO from reduced dose IMRT in early stage disease and to assess any potential 'cost' in PRO from efforts to improve locoregional control in advanced disease with increasing radiotherapy doses, as is being tested in the ongoing platform trial, PLATO (personalizing anal cancer radiotherapy dose; registry no. ISRCTN88455282)[22].

Due to the restricted resources available for national programs, there are missing data for both PRO and oncological outcomes, more so at 1-year follow-up. The event rate therefore could be underestimated although PRO scores and oncological event rates were similar to expected. This demonstrates the limitations of unfunded multi-centre national audit programs. However, it is reassuring than no patient, clinical or tumour characteristics appeared to predict missing data. Only centres failing to return data appears to be in effect, which provides a strong argument in support of the reliability of these results. The authors also acknowledge that 1-year is an early timepoint in follow-up. A further limitation is standardised quality assurance for IMRT implementation and delivery. At the time of patient recruitment, no validated anal cancer specific PRO existed and therefore as in other studies, the EORTC-QLQ CR29 was used for evaluation. Whilst this provides good quality data, a

number of important long-term toxicity issues are missing; of particular note, symptoms related to bowel urgency, toilet dependency, and vaginal symptoms such as vaginal dryness and stenosis. These issues are present in the newly developed EORTC-QLQ ANL27, which is currently under phase IV international validation testing and included in the PLATO trial[17, 36]. Future studies should use the EORTC-QLQ ANL27 to provide an accurate understanding of patient disease and toxicity burden [37] and prioritise a priori selection of key PRO items highlighted in CORMAC, the anal cancer core outcome set, for hypothesis testing[19].

Conclusions

In comparison to other studies reporting PRO and HRQOL in anal cancer, our study provides PRO data in a multicentre prospective setting. The effective implementation of IMRT in a national setting was reported previously[6]. At 1-year, early oncological outcomes were reassuring and result in good disease-related symptom control measured with PROs. In comparison to historical series of conformal radiotherapy, these results also suggest benefits in the reduction of bowel and male sexual dysfunction at 1-year. These findings, as well as providing prospective PRO toxicity data to better understand patient experience, may also provide the basis for benchmarking future studies.

Conflict of Interest statement

None declared

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References

1. Northover J, Glynne-Jones R, Sebag-Montefiore D, James R, Meadows H, Wan S, et al. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I). British journal of cancer. 2010;102(7):1123-8.
2. James RD, Glynne-Jones R, Meadows HM, Cunningham D, Myint AS, Saunders MP, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, openlabel, 2 x 2 factorial trial. The lancet oncology. 2013;14(6):516-24.
3. Department of Health Cancer Policy Team. Radiotherapy in England, 2012. Available at https://www.gov.uk/government/publications/radiotherapy-services-in-england-2012 (accessed 6 March 2019).
4. Ohri N, Shen X, Dicker AP, Doyle LA, Harrison AS, Showalter TN. Radiotherapy protocol deviations and clinical outcomes: a meta-analysis of cooperative group clinical trials. Journal of the National Cancer Institute. 2013;105(6):387-93.
5. Muirhead R, Adams RA, Gilbert DC, Glynne-Jones R, Harrison M, Sebag-Montefiore D, et al. Anal cancer: developing an intensity-modulated radiotherapy solution for ACT2 fractionation. Clin Oncol (R Coll Radiol). 2014;26(11):720-1.
6. 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 (R Coll Radiol). 2017;29(3):188-97.
7. Jones CM, Adams R, Downing A, Glynne-Jones R, Harrison M, Hawkins M, et al. Toxicity, Tolerability, and Compliance of Concurrent Capecitabine or 5-Fluorouracil in Radical Management of Anal Cancer With Single-dose Mitomycin-C and Intensity Modulated Radiation Therapy: Evaluation of a National Cohort. International journal of radiation oncology, biology, physics. 2018;101(5):1202-11.
8. Kachnic LA, Winter K, Myerson RJ, Goodyear MD, Willins J, Esthappan J, 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. International journal of radiation oncology, biology, physics. 2013;86(1):27-33.
9. Han K, Cummings BJ, Lindsay P, Skliarenko J, Craig T, Le LW, et al. Prospective evaluation of acute toxicity and quality of life after IMRT and concurrent chemotherapy for anal canal and perianal cancer. International journal of radiation oncology, biology, physics. 2014;90(3):587-94.

10. Joseph K, Nijjar Y, Warkentin H, Schiller D, Tankel K, Usmani N, et al. Prospective phase II study of tomotherapy based chemoradiation treatment for locally advanced anal cancer. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2015;117(2):234-9.
11. Salama JK, Mell LK, Schomas DA, Miller RC, Devisetty K, Jani AB, et al. Concurrent chemotherapy and intensity-modulated radiation therapy for anal canal cancer patients: a multicenter experience. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(29):4581-6.
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):8229.
13. Sodergren SC, Vassiliou V, Dennis K, Tomaszewski 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. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2015.
14. CTCAE. Common Terminology Criteria for Adverse Events (CTCAE). US Department of Health and Human Services. National Institutes of Helath National Cancer Institute Version 40. 2009;May 28 2009 (v4.03):June 14 2010.
15. Whistance RN, Conroy T, Chie W, Costantini A, Sezer O, Koller M, et al. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess healthrelated quality of life in patients with colorectal cancer. Eur J Cancer. 2009;45(17):3017-26.
16. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute. 1993;85(5):365-76.
17. 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. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2018;126(2):222-8.
18. StataCorp. 2013. Stata Statistical Software: Release 13.1. College Station, TX: StataCorp LP.
19. Fish R, Sanders C, Adams R, Brewer J, Brookes ST, DeNardo J, et al. A core outcome set for clinical trials of chemoradiotherapy interventions for anal cancer (CORMAC): a patient and health-care professional consensus. Lancet Gastroenterol Hepatol. 2018;3(12):865-73.
20. Fayers P, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. EORTC QLQC30 scoring manual. Brussels, Belgium: European Organisation for Research and Treatment of Cancer; 1999.
21. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1998;16(1):139-44.
22. Sebag-Montefiore D, Adams R, Bell S, Berkman L, Gilbert DC, Glynne-Jones R, et al. The Development of an Umbrella Trial (PLATO) to Address Radiation Therapy Dose

Questions in the Locoregional Management of Squamous Cell Carcinoma of the Anus. International Journal of Radiation Oncology • Biology • Physics. 2016;96(2):E164-E5.
23. Snyder C, Smith K, Holzner B, Rivera YM, Bantug E, Brundage M, et al. Making a picture worth a thousand numbers: recommendations for graphically displaying patientreported outcomes data. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2019;28(2):345-56.
24. Kachnic LA, Tsai HK, Coen JJ, Blaszkowsky LS, Hartshorn K, Kwak EL, et al. Dosepainted intensity-modulated radiation therapy for anal cancer: a multi-institutional report of acute toxicity and response to therapy. International journal of radiation oncology, biology, physics. 2012;82(1):153-8.
25. Glynne-Jones R, Sebag-Montefiore D, Meadows HM, Cunningham D, Begum R, Adab F, et al. Best time to assess complete clinical response after chemoradiotherapy in squamous cell carcinoma of the anus (ACT II): a post-hoc analysis of randomised controlled phase 3 trial. The lancet oncology. 2017;18(3):347-56.
26. Barraclough LH, Routledge JA, Farnell DJ, Burns MP, Swindell R, Livsey JE, et al. Prospective analysis of patient-reported late toxicity following pelvic radiotherapy for gynaecological cancer. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2012;103(3):327-32.
27. Joseph K, Vos LJ, Warkentin H, Paulson K, Polkosnik LA, Usmani N, et al. Patient reported quality of life after helical IMRT based concurrent chemoradiation of locally advanced anal cancer. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2016;120(2):228-33.
28. Jephcott CR, Paltiel C, Hay J. Quality of life after non-surgical treatment of anal carcinoma: a case control study of long-term survivors. Clin Oncol (R Coll Radiol). 2004;16(8):530-5.
29. Welzel G, Hagele V, Wenz F, Mai SK. Quality of life outcomes in patients with anal cancer after combined radiochemotherapy. Strahlentherapie und Onkologie. 2011;187(3):175-82.
30. Bentzen AG, Balteskard L, Wanderas EH, Frykholm G, Wilsgaard T, Dahl O, 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(4):736-44.
31. Provencher S, Oehler C, Lavertu S, Jolicoeur M, Fortin B, Donath D. Quality of life and tumor control after short split-course chemoradiation for anal canal carcinoma. Radiat. 2010;5:41.
32. Olsen JR, Moughan J, Myerson R, Abitbol A, Doncals DE, Johnson D, et al. Predictors of Radiation Therapy-Related Gastrointestinal Toxicity From Anal Cancer Dose-Painted Intensity Modulated Radiation Therapy: Secondary Analysis of NRG Oncology RTOG 0529. International journal of radiation oncology, biology, physics. 2017;98(2):400-8.
33. Welzel G, Hagele V, Wenz F, Mai SK. Quality of life outcomes in patients with anal cancer after combined radiochemotherapy. Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al]. 2011;187(3):175-82.
34. Son CH, Law E, Oh JH, Apte AP, Yang TJ, Riedel E, et al. Dosimetric Predictors of

Radiation-Induced Vaginal Stenosis After Pelvic Radiation Therapy for Rectal and Anal Cancer. International journal of radiation oncology, biology, physics. 2015;92(3):548-54.

35. Yahya N, Ebert MA, Bulsara M, Haworth A, Kennedy A, Joseph DJ, et al. Dosimetry, clinical factors and medication intake influencing urinary symptoms after prostate radiotherapy: An analysis of data from the RADAR prostate radiotherapy trial. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2015;116(1):112-8.

36. ISRCTN Registry. PLATO - Personalising anal cancer radiotherapy dose. ISRCTN88455282 https://doi.org/10.1186/ISRCTN88455282. (Accessed 13 March 2019 at http://www.isrctn.com/ISRCTN88455282q=&filters=conditionCategory:Cancer&sort=&offset=9&totalResults=1850&page=1&pageSize=10&searchType=basic-search).

37. Sodergren SC, Gilbert A, Darlington AS, Vassiliou V, Group EQoL. Anal Cancer: Putting Health-Related Quality of Life at the Forefront. Clin Oncol (R Coll Radiol). 2019;31(2):69-71.