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Systematic Review of the Quality of Life issues associated with Anal Cancer and its treatment with Radiochemotherapy

Running Title: Quality of Life in Anal Cancer

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Abstract

Purpose

Radiochemotherapy is the standard of care for the treatment of anal carcinoma achieving good loco-regional control and sphincter preservation. This approach is however associated with acute and late toxicities including haematological, skin, bowel function and genito-urinary complications. This paper systematically reviews studies addressing the quality of life (QoL) implications of anal cancer and radiochemotherapy. The paper also evaluates how QoL is assessed in anal cancer.

Methods

Medline, EMBASE, CINAHL, PsycInfo, Web of Science and the Cochrane Library were searched for publications (1996-2014) reporting the effects on patients of anal cancer and radiochemotherapy.

Results

Of the 152 papers reporting treatment-related effects on patients, only 11 provided a formal assessment of QoL. In the absence of an anal cancer specific measure, QoL was assessed using generic cancer instruments such as the core EORTC quality of life questionnaire (EORTC QLQ-C30) or colorectal cancer tools such as the EORTC QLQ-CR29. Bowel function, particularly diarrhoea, and sexual problems were the most commonly reported QoL concerns. The review of QoL issues of anal cancer patients treated with radiochemotherapy is limited by the QoL assessment measures used. It is argued that certain treatment-related toxicities, for example skin-induced radiation problems are overlooked or inadequately represented in existing measures.

Conclusions

This review emphasises the need to develop an anal cancer specific QoL measure and to incorporate QoL as an outcome of future trials in anal cancer. The results of this review are informative to clinicians and patients in terms of treatment decision making.

Keywords

Anal cancer, radiochemotherapy, quality of life, toxicities

1. Introduction

Background

Anal carcinoma is an uncommon malignancy accounting for 2% of all gastrointestinal malignancies and 10% of all anorectal malignancies, but with increasing incidence over the past 25 years and higher incidence seen in women [1,2]. Historically, anal cancer was regarded as a surgical disease treated by local excision or abdominoperineal resection (APR) with radiotherapy reserved for salvage or palliation. The landmark report of three cases by Nigro in 1974 [3] demonstrated complete responses after low-dose radiotherapy combined with mitomycin-C (MMC) and 5-fluorouracil (5-FU) without surgical intervention. Subsequent trials [4-6] showcased the superiority of this treatment regimen over radiotherapy alone or radiotherapy with only 5-FU using different endpoints such as local control, recurrence free survival, progression free survival, colostomy free survival or overall survival and thus radiotherapy with MMC and 5FU became the standard of care. Follow-up phase III trials failed to demonstrate benefits of alternative treatments schedules such as replacing MMC with cisplatin [7-9]. 5 year disease-free survival rates are reported as approximately 65% [8].

This approach has improved loco regional control with the majority of patients benefiting from sphincter preservation, however clinician-reported acute grade 3 or 4 toxicities can be as high as 80% [10] with severe late effects recorded in about 10% patients [8]. Radiation dose has been identified as one of the most significant factors influencing adverse late effects [11]. Thus, alternative radiation treatment schedules tailored to reduce toxicities without compromise of disease control have been investigated, including the delivery of lower dose radiotherapy [12], continuous vs. split course treatments [13], brachytherapy [14], and the introduction of Intensity-modulated radiation therapy (IMRT) as an alternative to the conventional conformal radiation therapy (CRT) [15,16]. The current clinical practice guidelines for anal cancer recommend radiation doses of at least 45-50 Gray (Gy) with boost doses between 15 and 20 Gy , thus the study and management of late toxicities is clearly pertinent [11]. Toxicities can result in unintended treatment breaks and radiation dose-reduction, leading to unfavourable disease-related outcomes as well as impacting on quality of life (QoL). Although toxicities have been extensively described using objective indices, little has been written using patient reported outcome measures on the effect of toxicities on health related Quality of Life (QoL) of radiochemotherapy for anal cancer.

QoL 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 [17]. While a patient's physical health, including symptoms experienced as a result of disease and treatment impacts on QoL judgements, the patient's response in terms of coping strategies, goals and expectations from treatment significantly affects their perception of QoL [18]. Therefore assumptions regarding QoL cannot be made from an inspection of toxicity grades; only the patient can provide an accurate estimate of QoL [19].

Assessment of QoL is well established in rectal cancer with a repertoire of measures specifically tailored to the concerns of this patient group, such as the European Organisation for Research and Treatment of Cancer EORTC Colorectal Cancer Specific Quality of Life Questionnaire (EORTC QLQ-CR29) [20] and the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) [21]. However toxicities for anal cancer patients are likely to differ from rectal cancer given their different treatment modalities and the specific needs of anal cancer patients have not been well studied.

The current paper aims to review the published literature to clarify the QoL issues reported by patients with anal cancer undergoing radiochemotherapy. We also provide an overview of the effect of acute and chronic toxicities resulting from anal cancer and its treatment on QoL.

2. Methods

The protocol for this systematic review was informed by the Centre for Reviews and Dissemination Guidance for undertaking reviews in health care [22] and the reporting follows the Preferred Reporting Items of Systematic reviews and Meta-Analyses (PRISMA) guidelines [23]. The protocol is available from the authors.

2.1. Search strategy and criteria for considering studies

Our search for publications reporting patients treated with radiochemotherapy for anal cancer extended from January 1996 to March 2014. Medline, EMBASE, CINAHL, PsycInfo, Web of Science and the Cochrane Library Databases were searched. The search process was verified by a medical librarian. Anal cancer and its synonyms were entered as search terms combined with terms relating to treatment as well as the general terms of QoL and its variants using Boolean logic rules (Table 1). We included randomised controlled trials (RCTs), prospective

trials, reviews of cohorts of patients, meta-analyses and reviews documenting QoL issues or toxicities following radiotherapy (CRT, IMRT, brachytherapy) with or without chemotherapy (5-FU, MMC, CDDP, capecitabine). Reports of conference proceedings, abstracts and case reports were excluded. Publications including anal cancer patients alongside other patient groups as well as those treated by surgery alone were also excluded.

Using these criteria, papers were selected for review based on titles and abstracts. SS screened all papers while KT and KD each independently reviewed half the records. Papers selected by either reviewer were included.

Table 1. Search terms applied

Area	**Terms**
Anal Cancer	Anus neoplasm (MeSH term) Anal neoplasm Anal cancer Anus cancer Anal carcinoma Anus carcinoma (no hits) Anal canal cancer Anal canal carcinoma Anal tumour Anus tumour (no hits) Anal intraepithelial neoplasia Anal canal intraepithelial neoplasia Anal squamous intraepithelial lesions Anal squamous cell carcinoma Anal cloacogenic carcinoma (no hits)

	Cloacogenic carcinoma of the anal canal
Treatments Radiochemotherapy Stoma	Chemoradiotherapy Radiochemotherapy Chemoradiation Chemotherapy Radiotherapy Combined modality therapy Antineoplastic chemotherapy Antineoplastic agents Colostomy Surgical stoma (Exp Stoma and stoma bag)
Health-related quality of life	Quality of Life QOL Health related quality of life HRQOL Subjective health status Patient reported outcome Patient based outcome Patient reported outcome measure PROM Self report Side effect Toxicity

	Adverse effect Adverse event Safety Complication Dysfunction Disturbance Disorder Impairment Complaint Symptom

2.2. Methods of evaluation and data extraction

SS read the full text version of selected papers and extracted the relevant data onto a data extraction form. For each publication that provided first hand data on the effects on patients of anal cancer and its treatment, a record was made of the type of study, outcome measures and QoL or toxicity data. We noted all toxicities (acute and late), complications, adverse events or QoL. The data extraction forms were verified by an independent reviewer (KD). This review is primarily concerned with papers reporting QoL as an outcome using formal methods, specifically patient reported outcome measures. Reviews, reports and meta-analyses were considered for descriptive and cross-referencing purposes but not for data extraction to avoid duplication. We recorded the quality of QoL reporting, QoL measures used, QoL issues reported and factors identified as impacting on QoL. A descriptive synthesis of the data was used because of the heterogeneity of studies in terms of research focus, treatments assessed, measures used and time of assessment. The quality of reporting QoL outcomes was assessed using a modified version of the checklist developed by Efficace and colleagues [24].

3. Results

3.1. Literature search

The selection process generated 1063 hits (Figure 1). Screening identified 307 (29%) papers for review with agreement between reviewers for 886 (83%) papers. Altogether 114 papers were subsequently rejected on the basis of subject matter (providing no account of the effects of anal cancer and its treatment n=75), disease area (inclusion of patients without a diagnosis of anal cancer n=15) or type of publication (reports of single cases n=24). Thus, 193 papers were eligible for data extraction, of which, 36 were reviews, 4 reports/management guidelines and 1 provided a meta-analysis. Primary source data were provided by 152 publications, of which, 123 (81%) were case series, typically retrospective in nature and 29 (19%) described trials either of quasi-experimental design or RCTs. Sixteen papers reported the experiences of HIV positive patients.

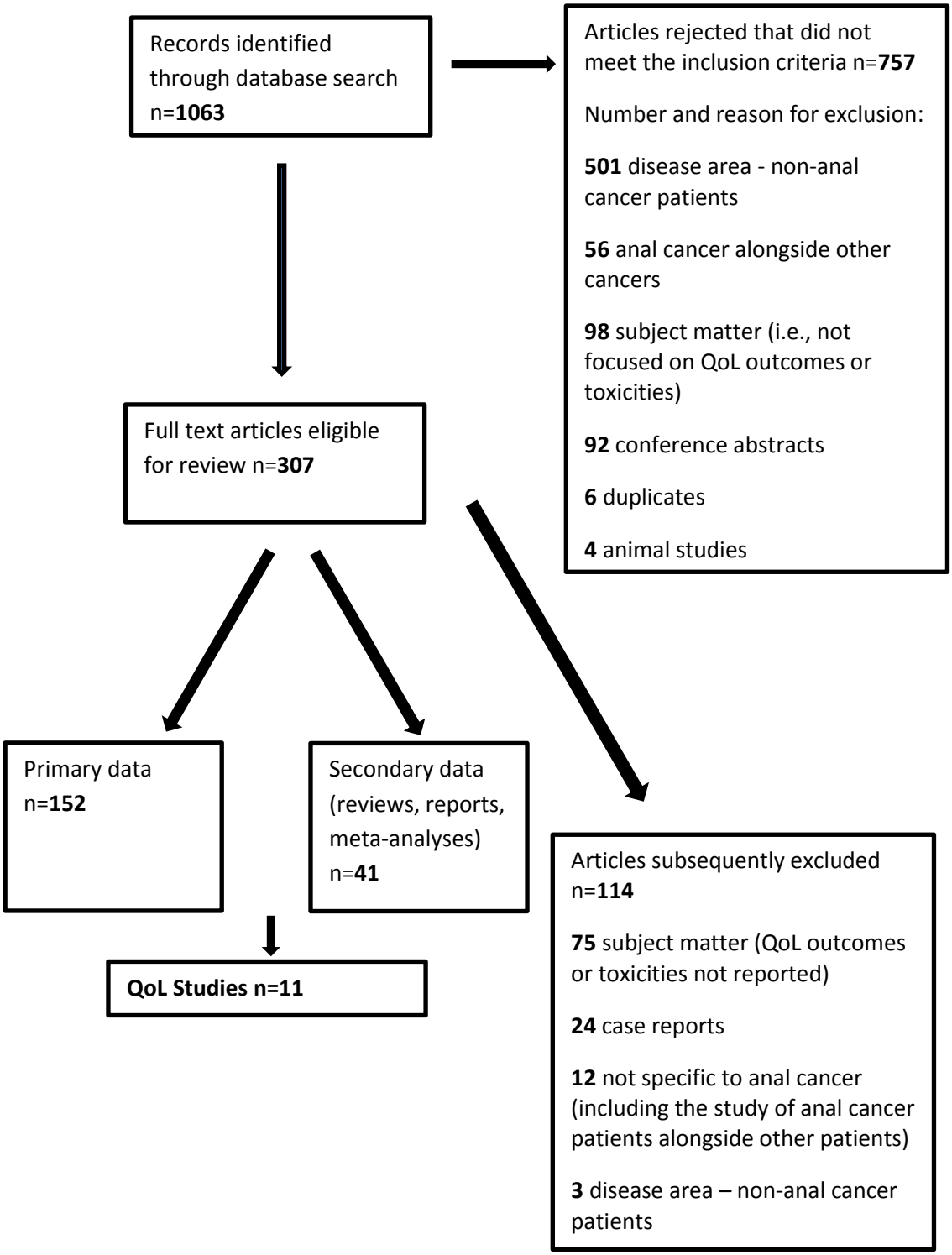

Figure 1. Flow chart of the paper selection process

3.2. Overview of toxicities

Toxicities are presented here to give context. This section is descriptive and brief as the overall focus of the paper is on QoL. Toxicities were an outcome measure in 147 papers. Toxicities were graded by clinicians according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTAE) [25] (n= 49 papers), criteria outlined by the Radiation Therapy Oncology Group (RTOG) / EORTC Morbidity Scoring System [26] (n=46), the Late Effects in Normal Tissues- Subjective Objective Management and Analytic (LENT-SOMA) Scales [27] (n=15), and the World Health Organisation (WHO) Morbidity Scoring System [28] (n=8). For 43 studies, a toxicity grading system was not identified or formally used.

Haematological complications such as neutropenia and leukopenia, were prevalent and were often described as severe and dose-limiting especially in patients treated with MMC and CDDP [8]. Skin reactions (radiation dermatitis and moist desquamation) were reported in almost all studies and were frequent; grade 3 or 4 acute skin toxicity was seen in 83% of patients reviewed by Provencher et al [29]. Other significant toxicities include pain, fatigue, genito-urinary complications, diarrhoea, incontinence and bone injury with the latter three recognised as common late complications [30-32]. Sexual functioning issues were not always assessed and were thus less commonly documented by clinicians. However, symptoms such as erectile dysfunction [33] and painful sexual intercourse [34] were significant late complications.

3.3. Quality assessment of QoL reporting

Of the 152 studies reviewed, 11 (7%) used patient reported tools to assess QoL associated with anal cancer and its treatment, which, for all patients involved chemotherapy and / or radiotherapy without surgery. No distinction was made between treatment-related and disease-related QoL issues. The first UK Anal Cancer Trial assessed QoL prospectively but was only published as a conference abstract [35]. This review focuses on the 11 studies published as full texts and these are outlined in Table 2. All studies except one adopted a cross-sectional design involving previously treated patients. Baseline QoL data were provided in one study that compared QoL of a sub-group of 199 patients at baseline and 2 months after treatment as part of the ACCORD 03 trial [36]. Six of the studies assessed QoL in the context of known group comparisons, for example according to age, sex, employment and marital status, treatment type and disease parameters [37,38,34,39,36,40,41]. Comparisons were also made

using reference values from published normative data from the general population or other disease groups [42,40,43,41,37,38] while two studies included matched healthy volunteers [42,44]. QoL was a primary end point for 9 studies and for 8 of these studies data on long-term QoL issues were provided with intervals between treatment and assessment varying from 2 years [38] to more than 12 years [44,40]. The prevalence of missing data (where reported) ranged from 32-40% [29,38].

Scores on the modified Efficace checklist ranged from 5 to 10, with a mean (standard deviation) score of 8.7 (1.7). Efficace and colleagues [24] recommend a score of at least 8 as a general indicator of high quality; only 2 (18%) studies did not satisfy this standard. Only 7 (64%) studies provided a rationale for their choice of measurement. In addition, Efficace et al. [24] identify the documentation of missing data as one of the high-priority concerns and only 2 (18%) studies satisfied this criterion.

Table 2. QoL Studies

First author and date of publication	Objective	Efficace checklist score (19)	Sample (number completed assessments and comparison group)	Treatment outline (numbers where cited)	QoL Measure	Key findings
Allal (1999) [37]	Long-term QoL in patients treated with radiotherapy or chemoradiotherapy	9	N=41 Comparison with Danish data (n=608)	Radiotherapy alone (n=11)EBRT with boost (EBRT boost n=10; brachytherapy boost n=31) Chemotherapy (n=30) 5-FU with MMC (n=39), leucovorin (n=1), cisplatin (n=1)	EORTC QLQ C-30; EORTC CR38 (2 additional questions: degree of satisfaction with anorectal function and treatment preference)	Long-term QOL was acceptable with the exception of diarrhoea and poorer sexual function (particularly in men). Late complications and anal dysfunction negatively influenced QoL.
Vordermark (1999) [40]	QoL in colostomy-free survivors treated with curative-intent radiation therapy or combined chemoradiotherapy and association with sphincter function	8	N= 22 Comparison with published results with healthy volunteers (n = 150) and patients with benign anorectal diseases (n = 325)	5-FU and MMC (n=16)	GIQLI	Overall QoL score was comparable to that of healthy volunteers and patients with less severe benign anorectal disorders. Completely continent patients had significantly higher QoL scores.

Vordermark (2001) [43]	QoL following chemoradiotherapy and intracavitary afterloading boost	6	N=14 Comparison with published results with healthy volunteers (n = 150) and patients with benign anorectal diseases (n = 325)	Radiotherapy: EBRT and intracavitaryafterloading boost Chemotherapy: 5-FU and MMC	GIQLI	Overall QoL score was slightly higher than the reference normative values for less benign diseases and only slightly lower than that of healthy volunteers.
Jephcott (2004) [44]	QoL following chemoradiotherapy	10	N=50 Comparisons with healthy volunteers (n=50)	Radiotherapy Chemotherapy: 5-FU and MMC (n=49), 5-FU alone (n=50)	EORTC QLQ C-30; EORTC CR38	Anal cancer survivors had poorer QoL compared with healthy volunteers and published norms as indicated by lower symptom scale scores in particular for fatigue, nausea, vomiting, dyspnoea, appetite loss, constipation and diarrhoea and sexual problems. Impairments to sexual enjoyment, physical, social, emotional and role function were also noted.
Oehler-Janne (2007) [39]	Compare outcomes (including QoL and toxicities) after pelvis EBRT followed by brachytherapy	5	N=17	EBRT with boost (EBRT or brachytherapy) Chemotherapy: 5-FU and MMC or CDDP	EORTC QLQ C-30; EORTC CR38	No significant differences in QoL according to treatment were identified

	boost after treatment break vs. EBRT boost without break in the treatment for anal cancer					
Tournier-Rangeard (2008) [36]	QoL before and 2 months after chemotherapy and / or radiotherapy as part of the ACCORD 03 Trial	10	N=119	Radiotherapy: EBRT with EBRT boost or brachytherapy boost Chemotherapy: Induction chemotherapy or concurrent chemoradiotherapy: 5-FU and CDDP	EORTC QLQ-C30 AS-CT	Compared to pre-treatment scores, patients reported significant improvement in their emotional function, global health status and satisfaction with intestinal functions. Gender and performance status (World Health Organisation criteria) influenced change in QoL scores.
Das (2010) [38]	Long-term QoL in anal cancer patients treated with radiotherapy or chemoradiotherapy	10	N=32 Comparisons with published results in the literature	Radiotherapy Chemotherapy: 5-FU with CDDP (n=23) (induction 5-FU and CDDP n=2), 5-FU and MMC (n=2), capcetabine and CDDP (n=6)	FACT-C MOS Sexual Problems Scale	QoL scores were favourable with the exception of bowel function issues (diarrhoea and bowel control) and sexual problems. Younger patients and those with a history of anxiety or depression or previous cancer had poorer QoL.
Provencher (2010)	QoL in patients	9	N=30	Radiotherapy	EORTC QLQ C-30;	Patients scored favourable

[29]	treated with short split course chemoradiotherapy			EBRT Chemotherapy: 5-FU and MMC	EORTC CR29	on all function scales. Urinary frequency, diarrhoea and sexual problems including erectile dysfunction, pain or discomfort during intercourse and low sexual interest were frequent issues. Other problems include fatigue, dyspnoea, pain and financial concerns.
Welzel (2011) [41]	QoL assessment of patients treated with chemoradiotherapy and identification of correlates of QoL	9	N=52. Comparisons with German normative data.	Radiotherapy Chemotherapy 5FU and MMC	EORTC QLQ C-30; EORTC CR38	Overall QoL was comparable to published norms, however, there was significant impairment on all functioning scales, in particular role, emotional and social functioning. Regarding the symptom and single items, stoma-related problems and sexual dysfunction were the most common, with impairments in fatigue, pain, dyspnoea, insomnia, constipation, diarrhoea and financial difficulties also recorded. Late toxicity, patient- or disease-related factors had minimal impact although

						fatigue was the strongest predictor of impaired QoL.
Bentzen (2013) [42]	Long-term QoL in anal cancer survivors treated with chemoradiotherapy	10	N= 128 Comparisons with Dutch and Norwegian normative data and healthy volunteers (n=269)	Radiotherapy: EBRT with chemotherapy: 5-FU with MMC and CDDP	EORTC QLQ C-30; EORTC CR29	Anal cancer survivors have significantly impaired social, role and sexual function. They also had notably higher scores for fatigue, dyspnoea, insomnia, anxiety, urinary frequency and incontinence, and bowel function issues (diarrhoea, flatulence, incontinence, buttock pain).
Fakhrian (2013) [34]	Chronic adverse events and QoL in patients following chemoradiotherapy	10	N=42	Radiotherapy Chemotherapy (n=39): 5-FU and MMC (n=37), 5-FU alone (n=1), MMC alone (n=1)	FACT-C	QoL scores were acceptable. Incidence of grade 3 chronic adverse events, particularly faecal incontinence, stool urgency and frequency and dyspareunia were associated with impaired QoL. Higher education and longer follow-up were associated with better QoL.

Key to measures

EORTC QLQ- C30: EORTC Core Questionnaire

EORTC QLQ- CR38 / CR29: EORTC Colorectal cancer specific quality of life module

FACT-C: Functional Assessment of Cancer Therapy-Colorectal

MOS: Medical Outcomes Study

AS-CT: Anal Sphincter Conservative Treatment Questionnaire

GIQLI: Gastrointestinal Quality of Life Index Questionnaire

3.4. QoL measures used

No anal cancer specific QoL measure was identified and no qualitative studies assessing QoL issues relevant to anal cancer patients were detected. QoL issues were captured using multi-dimensional generic tools designed to be appropriate for all cancer types such as the EORTC QLQ- C30 [45] (n=7 studies) [37,42,44,39,29,36,41], disease specific measures designed and validated for use with a specific patient group such as colorectal cancer patients (EORTC QLQ CR38/CR29 [20,46] (n=6) [37,42,44,39,29,41] and the FACT-C [21] (n=2) [38,34]) or more broadly relating to gastro-intestinal disease such as the Gastro-intestinal Quality of Life Index (GIQLI) [47] (n=2) [40,43], and symptom specific measures such as the Medical Outcomes Study (MOS) Sexual function scale[48] (n=1) [38] and the Anal Sphincter-Conservative Treatment Questionnaire (AS-CT)[49] (n=1) [36].

3.5. QoL issues

For 6 studies, overall or global QoL was summarised as acceptable and similar to normative data [37,29,40,43,41,34] with mean EORTC QLQ-C30 global QoL scores ranging between 60.4 [41] and 85.9 [39] (100 represents the best possible score), median FACT-C total scores (out of 136) ranging between 110 [34] and 108 [38] and mean GIQLI scores (out of 144) between 117 [43] and 114 [40].

Table 3 outlines the QoL issues identified by the studies. Symptom-related data replicate the findings from toxicity reports although bowel functioning issues, in particular diarrhoea, and sexual problems were the most commonly reported issues in the QoL literature and were presented as significant concerns in seven studies [37,42,38,34,44,29,41]. Allal et al. [37] reported a threefold increase in diarrhoea in their cohort compared with population norms while 31% of patients assessed by Das et al. [38] experienced diarrhoea “quite a bit” or “very much”. Das and colleagues also provided an assessment of sexual issues including declined sexual interest (reported in 65% patients) reduced enjoyment of sex (71%), difficulties getting aroused (72%), erectile dysfunction (67% of men who responded) and difficulties achieving orgasm (70% of women who responded) [38]. Comparisons between anal cancer patients and population norms have also highlighted difficulties in social and role functioning [42,41,44], as well as sexual [44,37,42], physical [44], cognitive [41], and emotional function [41,44] (Table 3).

Only one of the studies offered comparisons of QoL over time using a repeated measures design [36] and indicated improvement in QoL 2 months following treatment, especially in

global QoL, emotional function and symptom scores including insomnia, constipation, appetite loss and pain. Other studies have also observed improved QoL over time inferred from comparisons of patients at different follow-up points [34] [36]. By contrast, Welzel et al. reported poorer physical functioning with longer follow-up [41].

Table 3. Issues described by QoL studies

QoL Issue	**Study (First author and date of publication)**
Diarrhoea	Provencher (2010) [29], Fakhrian (2013) [34], Allal (1999) [37], Das (2010) [38], Welzel (2011) [41], Bentzen (2013) [42], Jephcott (2004) [44]
Constipation	Welzel (2011) [41], Jephcott (2004) [44]
Flatulence	Bentzen (2013) [42]
Bowel control / Faecal incontinence	Das (2010) [38]
Gastro-intestinal (general)	Welzel (2011) [41]
Nausea and vomiting	Jephcott (2004) [44]
Appetite loss	Jephcott (2004) [44]
Genito-urinary (general)	Welzel (2011) [41]
Increased urinary frequency	Provencher (2010) [29], Bentzen (2013) [42]
Urinary incontinence	Bentzen (2013) [42]
Sexual (general)	Provencher (2010) [29], Fakhrian (2013) [34], Allal (1999) [37], Welzel (2011) [41], Bentzen

	(2013) [42], Jephcott (2004) [44]
Painful sexual intercourse	Provencher (2010) [29], Fakhrian (2013) [34], Bentzen (2013) [42]
Reduced interest of enjoyment in sex	Provencher (2010) [29], Das (2010) [38], Bentzen (2013) [42], Jephcott (2004) [44]
Impotence	Provencher (2010) [29], Das (2010) [38], Bentzen (2013) [42]
Fatigue	Provencher (2010) [29], Welzel (2011) [41], Bentzen (2013) [42], Jephcott (2004) [44]
Insomnia	Welzel (2011) [41], Bentzen (2013) [42]
Pain	Provencher (2010) [29], Welzel (2011) [41], Bentzen (2013) [42]
Dyspnoea	Provencher (2010) [29], Welzel (2011) [41], Jephcott (2004) [44]
Anxiety	Bentzen (2013) [42]
Financial difficulties	Provencher (2010) [29], Welzel (2011) [41], Jephcott (2004) [44]
Stoma-related problems	Welzel (2011) [41]

3.6. Factors influencing QoL scores

Welzel et al. [41] addressed patient and disease-related factors related to QoL and found that fatigue was the only variable to have a significant impact on QoL. Toxicities including late complications and anal dysfunction have also been identified as important factors [34,37,38]. Other studies have uncovered associations between QoL and patient-related factors such as age; while Allal and colleagues [37] found that older patients had lower physical subscale scores, Das et al. [38] identified an opposite trend with lower QoL scores in patients under 51

years old. Das et al. also found that patients with a history of depression or anxiety or other cancers had a tendency to score lower on the physical subscale of the FACT-C. Patients who attained a more advanced level of education reported higher QoL scores in one study [34].

Assessment of the impact of treatment-related variables on QoL is limited given the small number of studies offering treatment comparisons, however Tournier-Rangeard and colleagues [36] found no short-term impact of treatment schedule on the evolution of QoL scores from baseline to 2 months after treatment. The findings of other cross-sectional studies support this observation [39,37].

4. Discussion

This review has found relatively few studies reporting QoL issues of patients undergoing radiochemotherapy for anal cancer with formal QoL assessment largely absent from RCTs. Of the 307 studies reviewed, only 11 (4%) studies included QoL as an outcome assessment and these were predominantly small scale questionnaire-based cross-sectional case reviews. There is no QoL questionnaire specific to anal cancer, which might explain the paucity of QoL research in this field. There is an abundance of reports of toxicities associated with anal cancer and its treatments, often measured with objective indices. The impact of these toxicities on QoL is acknowledged as an important outcome guiding decisions regarding treatment choices [38,34]. Indeed, achieving a good quality of life alongside loco-regional control and the avoidance of a permanent stoma are identified within clinical practice guidelines as the primary aim of anal cancer treatment [11].

Consideration of QoL issues involves subjective evaluations and researchers use patient reported outcome measures to quantify this qualitative information. However, some studies claiming to demonstrate a QoL impact of anal cancer treatment have done so with inappropriate QoL measures, for example, one comparison of QoL following radiochemotherapy and surgery was based on data extracted from medical records [50] which will give a very incomplete assessment. Generic cancer QoL measures such as the EORTC QLQ-C30 are designed to capture issues relevant to all cancer types but are insensitive to unique disease-related features. Cancer site-specific tools thus complement these generic measures. In the absence of an anal cancer specific QoL measure, colorectal cancer specific QoL tools such as the EORTC QLQ-CR38/29 and FACT-C have been used. The studies included in this review all provided formal QoL assessments (although they were obtained with inappropriate

instruments) and they had favourable quality assessment scores using the Efficace checklist [24]. They offer a useful insight into the QoL concerns of anal cancer patients.

The literature on toxicities provides numerous examples of complications associated with anal cancer and its treatments yet these are not necessarily translated into poor overall QoL evaluations. Several reports of anal cancer patients show similar QoL scores to population norms [37,29,40,43,41,34]. Allal et al. [37] also identified disparities between objective and subjective parameters in relation to anorectal function and satisfaction. It has been proposed that over time patients adapt to their changing health status and change their personal reference values regarding QoL [18]. Vordermark and colleagues [40] speculate that satisfaction with the apparent cure of malignant disease may also account for elevated QoL scores amongst anal cancer patients. However, there is evidence to suggest that patients with poorer health status, including more severe late complications and poorer anal function, report lower QoL scores [37,34,40,41]. In addition, bowel and sexual function issues were flagged as particularly significant QoL concerns for anal cancer patients in a number of studies [37,42,38,44,29,41].

The colorectal cancer specific measures used in the studies reviewed were designed to include all relevant and specific issues relating to colorectal cancer. Although there is some overlap in the symptom and toxicity profiles of colorectal and anal cancer, there are several important differences. Thus, certain issues affecting anal cancer are inadequately covered by the generic or the colorectal instruments. Our review highlighted skin reactions such as radiation dermatitis and desquamation as a very common toxicity. Associated pain or soreness caused by skin reactions might be captured by the CR29 items measuring sore skin around the anal area or stoma and the FACT-C measuring pain or the general side effects of treatment, but these do not provide an adequate assessment of the more wide ranging impact of this issue for example on walking, sitting or inability to sleep due to pain. Sexual dysfunction was identified in a number of studies as an important QoL concern and although this was under-reported in the toxicity literature, in the QoL studies patients were given the opportunity to rate the impact of sexual difficulties. The CR29 asks about interest in sex, impotence and dyspareunia while satisfaction with sex life is measured by the FACT-C. Issues relating to sexual dysfunction might however extend beyond those assessed using these measures, for example to include the impact of vaginal symptoms such as dryness and stenosis which were identified as having a negative impact on QoL by a third of female patients in Fakhrian et al.'s

study [34]. In the QoL literature, bowel function issues such as diarrhoea and incontinence were also prevalent and again the CR29 and FACT-C might be regarded as inadequate to assess the full effect on QoL of such distressing symptoms.

One of the main limitations of this review is that the QoL concerns presented in this paper are confined to the content of questions asked of patients. A number of significant issues such as radiation induced skin problems are likely to be under-reported. None of the studies reviewed were qualitative in design or provided patients with an opportunity to rate aspects of their disease or treatment not covered by the questionnaires. The studies reviewed were mostly cross-sectional and included only small numbers of patients, probably as a result of the rarity of anal cancer. Caution is therefore required before making generalisations about the QoL concerns of this patient group. The issue of non-responders and missing data, in particular with respect to the personal and potentially embarrassing issues of sexual dysfunction presents a significant challenge. There is limited information about non-responders thus generalisations from data collected from a small subset of patients who may be more motivated and successfully treated are likely to be unreliable.

This review is also limited in terms of its synthesis of data. The heterogeneous nature of the studies reviewed, for example whether QoL was the primary outcome, the measures used and follow up assessment times, resulted in data being presented in different formats; comparisons between studies were difficult and we were not in a position to present prevalence figures for individual QoL issues. In addition, the absence of baseline QoL data in all but one study [36] makes it difficult to assess the impact of treatment on QoL.

To our knowledge, this review represents the first attempt to systematically review studies where QoL has been formally assessed in anal cancer patients. Despite the limitations of these studies, they can be applauded for their high standard of method reporting and for using validated QoL measures. The review has highlighted the wide ranging and long lasting QoL issues (bowel function, including diarrhoea, and sexual function) facing anal cancer patients treated with radiochemotherapy. We have also identified a need for a site-specific instrument for anal cancer, to allow all specific and relevant QoL concerns to be assessed. It is particularly important to include such an instrument in the design of randomised clinical trials, to ensure complete and prospective assessment of the impact of treatment on QoL. Documentation of late effects and QoL assessment is recommended within the anal cancer clinical practice

guidelines [11]. The results of this review are informative to clinicians in their design of future trials and can support their consultations with patients about the potential impact of treatment on quality of life thus allowing patients to make informed treatment decisions in light of their own preferences and values and attitudes to risk. The issues identified from this review will be considered in the development of a new anal cancer module to supplement the EORTC QLQ-C30 which will be sensitive to the acute and long-term issues facing patients treated with radiochemotherapy.

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Conflict of Interests

The authors declare no conflicts of interest or competing financial interests. The authors have full control of the material presented and give permission to *Supportive Care in Cancer* to review the material if requested.

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