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REVIEW

# The Impact of Chronic Pelvic Pain and Bowel Morbidity on Quality of Life in Cervical Cancer Patients Treated With Radio (Chemo) Therapy. A Systematic Literature Review

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**Introduction:** Radiotherapy, administered with or without chemotherapy is the gold standard treatment for cervical cancer with both curative and palliative intent. However, the treatments often result in adverse events, mainly chronic pelvic pain and bowel morbidity, which can negatively impact quality of life.

**Aim:** To systematically appraise peer reviewed evidence regarding chronic pelvic pain and bowel morbidity and their impact on quality-of-life of cervical cancer patients treated with radiotherapy with or without chemoradiation therapy.

**Design:** A systematic review of original peer-reviewed research evidence.

**Data Collection Methods and Tools:** A systematic search conducted between April and May 2021, and updated in September 2024, using PubMed, Hinari, CINAHL and Google Scholar, for peer reviewed papers published between 2008 and 2019. Data were extracted using a structured checklist designed to capture key elements about the methods and findings of the research.

**Results:** There were 245 articles retrieved with 29 meeting the inclusion criteria. 11 studies were conducted in Europe, eight in Asia, one in North America, three in Africa, while six were multinational/multicontinental. 13 of the papers were longitudinal, 10 cross-sectional, three literature reviews, one open randomised controlled trial, and two retrospective studies of prospectively collected data. Studies reported disruptions in nearly all domains of quality-of-life, including global, physical, emotional/psychological, financial, sexual, social, role functioning as a result of being treated with radiotherapy or radio-chemotherapy.

**Conclusion:** Chronic pelvic pain and bowel morbidity are common adverse events experienced by cervical cancer patients receiving, or who have received, pelvic radiotherapy or radio-chemotherapy. Symptoms occur to varying degrees and exert a negative toll on the quality-of-life of women. Clinicians should be more aware and prioritise thorough assessment and management of symptoms before, during and after treatment. There is limited population-based and longitudinal research about the topic, and on chronic pelvic pain in general, which limits generalisability. Longitudinal studies with more extended periods of follow-up are needed.

**Keywords:** chronic pelvic pain, bowel morbidity, cervical cancer, quality of life, radio (chemo) therapy

## Introduction

Globally, cervical cancer (CC) remains a major public health problem.[1,2] For example, in the year 2022, an estimated 660,000 new cases and 350,000 deaths due to CC were recorded.[1] Notably, over 80% of the global burden of CC is disproportionately concentrated in low- and middle-income countries (LMICs)[1–6] which have only 5% of the global cancer resources.[7] That is to say, the global burden of CC reflects significant global health inequities including but not limited to limited access to vaccination, screening, and treatment services.[8]

CC is a prime cause of cancer-related mortality and morbidity in Uganda and is associated with significant disruptions in the quality of life (QoL) of the women effected.[4,9] CC accounts for about 4100 incident cases and 2300 deaths annually in Uganda.[1,10]

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Exacerbating the problem is that the majority (over 80%) of CC cases in Uganda are diagnosed in late advanced stage when a cure is no longer possible.[11]

Globally, radiotherapy (RT), usually with concurrent chemotherapy (CT), is currently the radical standard choice of treatment for CC for both curative and palliation intent.[12] Similarly, RT/CT is currently the gold standard treatment for CC in Uganda, given with or without surgery for both curative and palliation intent. It has been shown that CT (usually Cisplatin-based agent) acts as a radio-sensitizer to optimize local response of the cancerous cells to RT and/or or vice versa.[13,14] However, Bjelic-Radisic et al[3] reported that CT increases the risk of additional toxicities, including Chronic Pelvic Pain (CPP) and bowel morbidities that cause significantly diminished QoL among cervical cancer survivors (CCS).

However, pelvic irradiation with or without CT has been shown to be associated with both acute- and long-term toxicities that cause both acute and chronic pelvic pain and bowel morbidities. Acute-related toxicities include mucositis and diarrhoea. Long-term treatment-related toxicities include bowel morbidities such as impaired anorectal function, chronic diarrhoea or proctitis, pelvic and insufficiency fractures,[15–18] and pelvic pain.[19] However, there exist wide variations in the prevalence rates of these toxicities.

The American College of Obstetricians and Gynaecologists (ACOG)[20] Practice Bulletin No. 5 defines CPP as non-cyclic persistent pain lasting for six or more months, that localizes to the anatomic pelvis, anterior abdominal wall at or below the umbilicus, the lumbosacral back, or the buttocks and is of sufficient severity to cause functional disability or lead to medical care. Vistad et al[21] define CPP as pain that persists longer than the time of natural healing, located in hips, groins, lower back, radiating pain, pain at rest or activity and/or pain influencing daily activities. It encompasses insufficiency fractures, chronic radiation enteritis (CRE), proctitis, cystitis, lumbosacral plexopathies, chronic radiation myelopathy, lymphoedema pain, burning perineum syndrome, and osteoradionecrosis. To note, CRE is inflammation of the intestines following RT and is associated with disabling symptoms like nausea, vomiting, appetite loss, diarrhoea or constipation (bowel obstruction), abdominal cramps, bleeding tendencies and sometimes anaemia. These profoundly compromise the QoL of the patient and their family.

CPP has been shown to have negative implications on domains of QoL of a patient including cognitive, behavioural, sexual and emotional consequences as well as causing morbidities, including of the lower urinary tract, bowel, pelvic floor and sexual or gynaecological functioning.[22,23] In Uganda, no published empirical study examining the burden of CPP and chronic bowel morbidity among CC patients treated with chemoradiation can be traced. The extent to which the topic has been studied on the regional and global landscape is also not well understood. This review could identify the extent to which the topic has been studied and identify important evidence gaps and inform future studies.

## Aim of the Review

To systematically-:

1. Appraise available evidence about chronic pelvic pain and bowel morbidity in cervical cancer patients treated with radiotherapy with or without chemotherapy.
2. Examine the impact on quality-of-life chronic pelvic pain and bowel morbidity on QoL of cervical cancer patients treated with radiotherapy with or without chemotherapy.

# Methods

## Design

This was a systematic review of published peer reviewed research evidence.

### Ethical Considerations

This was a review of secondary data. This meant that the study did not require ethical review and approval from an Institutional Review Board (IRB). To note, all the papers included in this review had an ethics statement stating that they had obtained ethical approval from a recognised IRB. The review was conducted and reported in accordance with the PRISMA guidelines.[24]

## Search Strategy

The review was conducted between April 2021 and May 2021 and was updated in September 2024. The authors performed a systematic search in trusted online databases for peer reviewed subject- and content-specific literature. Four databases, Hinari "Research4Life", Google Scholar, CINAHL and PubMed were searched for eligible articles. A uniform search strategy was applied to each of the databases using the search terms, "Prevalence" OR "Severity" AND "radiotherapy-induced chronic pelvic pain" OR "Bowel morbidity" OR "bowel dysfunction" AND "quality of life" AND "cervical cancer" AND "English articles" AND "full text articles" AND "peer reviewed" AND "Published 2008 to 2024". The search was filtered for articles which were peer-reviewed, in English, full and open access articles published between 2008 and 2024. A supplementary parallel Google search was performed to retrieve eligible papers, yielding an additional seven papers. The retrieved papers were first screened on title and abstract and then full-text for eligibility for inclusion in the review. Results of the search are summarised in Figure 1.

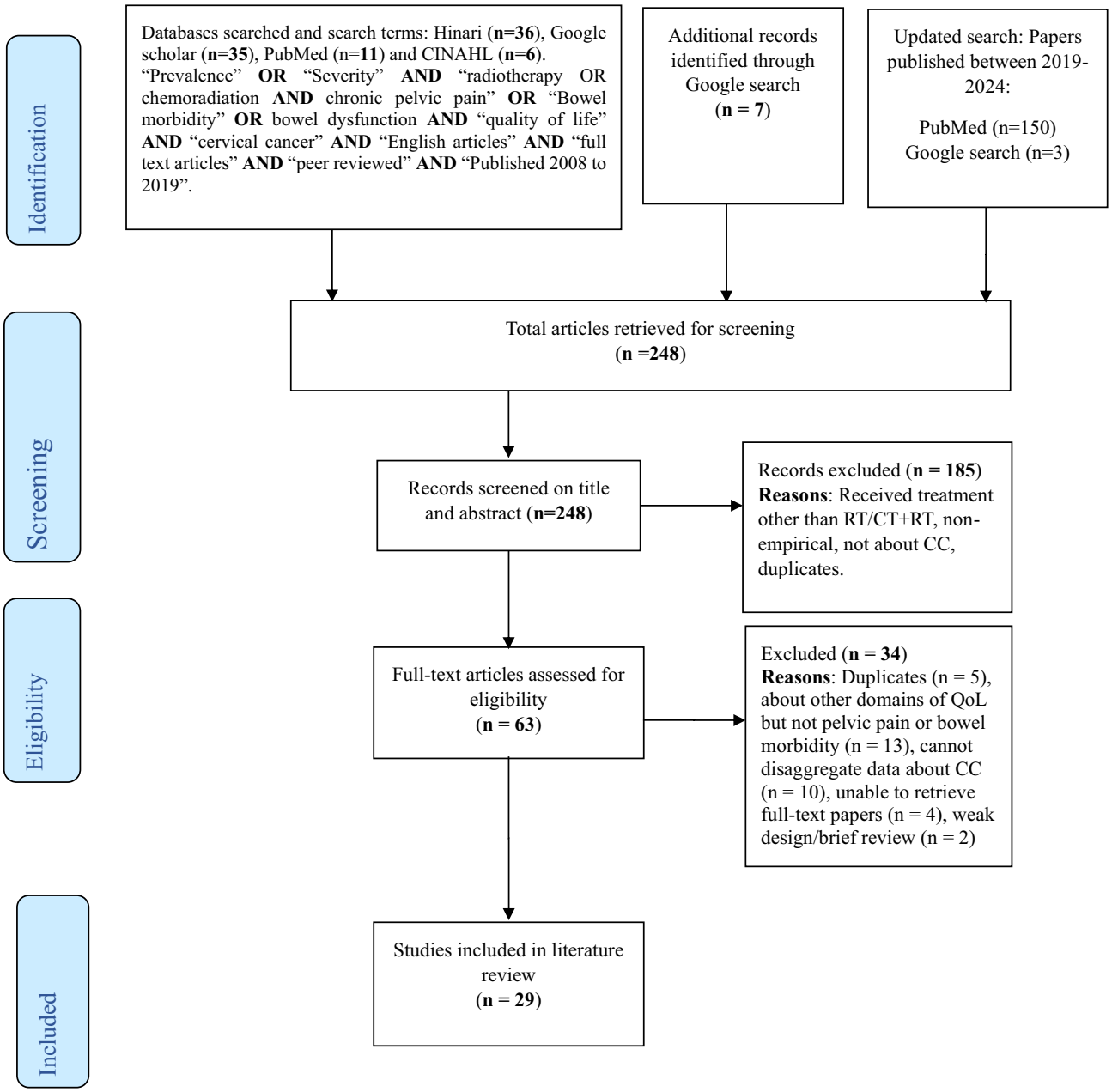


**Figure 1** Flow diagram showing search strategy underpinning the review. Adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. Creative Commons.[24]

**Abbreviations**: CC, Cervical Cancer; CINAHL, Cumulative Index to Nursing and Allied Health Literature; CT, Chemotherapy; QoL, Quality of Life; RT, Radiotherapy.


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## Assessment of Methodological Quality of the Studies

The articles were each subjected to a thorough methodological critique for quality using appropriate validated Critical Appraisal Skills Programme (CASP) checklists. The articles were all found to be of good quality. The papers were initially independently assessed by GN followed by PE. Decision on the papers eligible for inclusion and exclusion and their quality scores was reached through consensus. To note, GN had identified 31 eligible papers for inclusion but two were deemed ineligible for inclusion following assessment of the papers by PE. The two ineligible papers examined different types of gynaecological and pelvic cancers including cancer of the cervix, vagina, prostate, endometrium/uterus, rectum and bladder but findings were not disaggregated by diagnosis and gender.

To note, the 11-item CASP checklist for descriptive/cross-sectional studies and the 10-item CASP checklist for systematic/literature/records reviews were used to assess the selected articles. The questions are designed to be answered with "Yes", "Can't tell" or "No". Each "Yes" response was scored as 1 point. A response of "Can't tell" or "No" was scored as zero (0) points. The

**Table 1** CASP[25] Scoring for Qualitative and Quantitative Studies (n = 26)

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Bjelic-Radisic et al (2012)[3] | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y |
| Chopra et al (2021)[26] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Dahiya et al (2016)[27] | Y | Y | Y | N | Y | N | C | Y | Y | Y | Y |
| Di Donna et al (2023)[28] | Y | Y | Y | N | Y | N | Y | Y | Y | C | Y |
| Donovan et al (2014)[29] | Y | Y | Y | Y | Y | N | Y | Y | N | Y | Y |
| du Toit & Kidd (2015)[30] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Greimel et al (2009)[31] | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y |
| Heijkoop et al (2017)[32] | Y | Y | Y | N | C | Y | Y | Y | Y | Y | Y |
| Hsu et al (2009)[33] | Y | Y | Y | N | Y | N | Y | Y | Y | Y | Y |
| Jensen et al (2018)[34] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Kirchheiner et al (2015)[35] | Y | Y | Y | Y | C | N | C | Y | Y | Y | Y |
| Krikeli et al (2011)[36] | Y | Y | Y | N | Y | N | Y | Y | Y | Y | Y |
| Kuku et al (2013)[37] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Le Borgne et al (2013)[38] | Y | Y | Y | Y | N | N | Y | Y | Y | Y | Y |
| Mikkelsen, Sorensen & Dieperink. (2017)[18] | Y | Y | Y | C | Y | N | Y | Y | Y | Y | Y |
| Pasek et al (2012)[6] | Y | Y | Y | Y | Y | Y | C | Y | Y | Y | Y |
| Rahman et al (2017)[39] | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y |
| Sabulei & Maree (2019)[5] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Spampinato et al (2023)[40] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Sumdaengrit et al (2010)[13] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Vistad et al (2011)[21] | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y |
| Vittrup et al (2023)[41] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Yang et al (2020)[42] | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y |
| Yoshida et al (2011)[12] | Y | Y | Y | Y | Y | N | C | Y | N | Y | Y |
| Zayyan et al (2018)[7] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Zhou et al (2016)[43] | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | Y |

1. Did the study address a clearly focused research issue/question?
2. Did the authors use an appropriate method/design to answer the research question?
3. Were the subjects recruited in an acceptable/appropriate way?
4. Were the measures accurately measured to reduce bias?
5. Were the data collected in a way that addresses the research questions?
6. Did the study have enough participants to minimise the play of chance?
7. How are the results presented and what is the main result?
8. Was the data analysis sufficiently rigorous?
9. Is there a clear statement of the findings?
10. Can the results be applied to the local population?
11. How valuable is the research?

**Abbreviations**: N: No, Y: Yes, C: Cannot tell.

total possible maximum score for each question item in the CASP checklist was 11. The range of scores (0–11) were then assigned a rating of the article as very good (score ≥9–11), good (score 7–8), average (score 5–6) and then weak (score less than 5). All the studies (articles) selected for review had a score ≥8 and so were of good or very good quality (Table 1–4).

**Table 2** Systematic/Literature Review Quality Assessment Using Critical Appraisal Skills Programme (CASP) checklist[44]

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Jensen and Froeding (2015)[45] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Mirabeau-Bede and Viswanathan (2014)[15] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Wenzel et al (2022)[46] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |

1. Was there a clear statement of the aims of the research?
2. Is a qualitative methodology appropriate?
3. Was the research design appropriate to address the aims of the research
4. Was the recruitment strategy appropriate to the aims of the research?
5. Was the data collected in a way that addressed the research issue?
6. Has the relationship between researcher and participants been adequately considered?
7. Have ethical issues been taken into consideration?
8. Was the data analysis sufficiently rigorous?
9. Is there a clear statement of findings?
10. How valuable is the research?

**Abbreviations**: N: No, Y: Yes, C: Cannot tell.

**Table 3** Summary of CASP Checklist Methodological Quality Scores of Descriptive Studies (n=26)

| | Yes | No | Cannot tell |
|---|---|---|---|
| 1. Did the study address a clearly focused research issue/question? | 26 | 0 | 0 |
| 2. Did the authors use an appropriate method/design to answer the research question? | 26 | 0 | 0 |
| 3. Were the subjects recruited in an acceptable/appropriate way? | 26 | 0 | 0 |
| 4. Were the measures accurately measured to reduce bias? | 19 | 6 | 1 |
| 5. Were the data collected in a way that addresses the research questions? | 23 | 1 | 2 |
| 6. Did the study have enough participants to minimise the play of chance? | 13 | 13 | 0 |
| 7. How are the results presented and what is the main result? | 21 | 1 | 4 |
| 8. Was the data analysis sufficiently rigorous? | 26 | 0 | 0 |
| 9. Is there a clear statement of the findings? | 24 | 2 | 0 |
| 10. Can the results be applied to the local population? | 25 | 0 | 1 |
| 11. How valuable is the research? | 26 | 0 | 0 |

**Table 4** Summary of CASP Checklist Methodological Quality Scores of Systematic/Literature Reviews (n=3)

| | Yes | No | Cannot tell |
|---|---|---|---|
| 1. Was there a clear statement of the aims of the research? | 3 | 0 | 0 |
| 2. Is a qualitative methodology appropriate? | 3 | 0 | 0 |
| 3. Was the research design appropriate to address the aims of the research | 3 | 0 | 0 |
| 4. Was the recruitment strategy appropriate to the aims of the research? | 3 | 0 | 0 |
| 5. Was the data collected in a way that addressed the research issue? | 3 | 0 | 0 |
| 6. Has the relationship between researcher and participants been adequately considered? | 3 | 0 | 0 |
| 7. Have ethical issues been taken into consideration? | 3 | 0 | 0 |
| 8. Was the data analysis sufficiently rigorous? | 3 | 0 | 0 |
| 9. Is there a clear statement of findings? | 3 | 0 | 0 |
| 10. How valuable is the research? | 3 | 0 | 0 |

**Abbreviations**: N: No, Y: Yes, C: Cannot tell.

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**Table 5** Methodological Characteristics of Studies Included in the Review

| Author & Year | Country | Aim | Tools | Design | Sample Size (n) | Diagnosis | Treatment modality | Limitations | Main Findings |
|---|---|---|---|---|---|---|---|---|---|
| Bjelic-Radisic et al (2012)[3] | Multi-continent (14 countries) including Taiwan, UK, Austria, Denmark, Croatia, Sweden, Germany. | To investigate the effect on different QoL domains during and after treatment for CC according to menopausal status, treatment status and treatment modality | EORTC QLQ-C30/CX24 | Multi-continent cross-sectional study | 346 | CC | - Surgery<br>- CT<br>- RT-CT<br>- Brachytherapy<br>- EBRT<br>- hyperthermia | - Cross-sectional study with no control group<br>- Selection bias, ie may have included women with more problems / women with more symptoms may have been more likely to participate | Active treatment had the strongest negative impact on QoL domains: physical, role, emotional, cognitive, social functioning, global health, fatigue, nausea and vomiting, pain, appetite loss, constipation, symptom experience and sexual enjoyment. Irradiation alone ± other therapy was associated most with diarrhoea. Age had the most negative impact on sexual activity and strongest positive effect on sexual worry. |
| Chopra et al (2021)[26] | India | To investigate if postoperative image-guided IMRT (IG-IMRT) gives a lower incidence of late GI toxicity than three-dimensional conformal radiation therapy (3D-CRT) | Common Toxicity Criteria for Adverse Events v 3.0 and estimated using time-to-event, intention to-treat analysis. | An open-label, parallel group, Phase III randomised controlled trial conducted between 2011 and 2019. | 300 | CC | - IG-IMRT<br>- 3D-CRT | - Investigators and participants not blinded which could lead to ascertainment bias | On long-term follow-up, IG-IMRT led to better functional scores and lower symptom scores and a significant increase in the global health score (p=0.01). IG-IMRT treated women had improved physical functioning (p=0.042), role functioning (p=0.024), and emotional functioning (p=0.02). During follow up women treated with IG-IMRT had less fatigue (p=0.004), appetite loss (p=0.008), diarrhoea (p=0.048), and bowel symptoms (p=0.002). Notably, QoL scores did not differ significantly when time by treatment arm interaction was performed.<br>The proportion of women with grade ≥ 2 any late toxicity was lower in the IG-IMRT group. Numerically, a lower proportion of women in the IG-IMRT arm reported moderate to severe diarrhoea (1.6% v 3.8%), abdominal cramps (1.7% v 9.1%), and difficulty in controlling bowel function (5.1% v 14.9%) at 36 months. |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Dahiya et al (2016)[27] | India | To assess QoL before, and after CT+RT in CC patients | EORTC QLQ-C30<br>EORTC QLQ-CX24 | Longitudinal study | 67 | CC patients2B-4B | - CT+RT | | At six months survival was 92.53%, mean global health score 59.52 (pre-treatment 50.15 (p< 0.00007)). Post-treatment physical, cognitive and emotional functioning improved (p<0.05) as did fatigue, pain, insomnia and appetite loss. Diarrhoea increased after treatment. Mean symptoms score post treatment 20.0 compared to the pre-treatment 30.0 (p<0.00001). |
| Di Donna et al (2023)[28] | Italy | To analyse urinary, bowel, and sexual dysfunctions in women with advanced CC who underwent CT, RT, RS, or a combination of these. | Researcher-developed non-validated questionnaire | Multicentre retrospective study of prospectively collected data. | 90 (from five oncological referral centres). | CC patients, stage 1B-4A, who treated between November 2010 and September 2019 | - CT<br>- RT<br>-*RS*<br>- combination | - Small sample size<br>- Did not use standardised scales<br>- The retrospective nature of the study could have data quality limitations | Significant reduction in evacuations (p< 0.01) and sensation of incomplete bowel emptying (p=0.04). A reduced number of evacuations (<3 times a week) was more common in women who underwent upfront surgery (UPS) compared with neoadjuvant (NA) RT/CT (50% v 97.1%; p<0.01), UPS & NACT (50% v 88.2; p<0.01), and UPS & exclusive radio–chemotherapy (ERT/CT) (50% v 96.4%; p<0.01). The sensation of incomplete bowel emptying, NACT & UPS (58.8% v 20%; p=0.047), NACT & ERT/CT (58.8% v 17.9%; p <0.01), and NACT & NART/CT (58.8% v 25.7; p=0.02). |
| Donovan et al (2014)[29] | USA | To estimate the prevalence of bladder and bowel symptoms in CC & endometrial cancer survivors. | - Medical records review<br>- Self-report<br>- Behavioural<br>- Risk Factor Surveillance Survey<br>- Charlson Comorbidity Index | Cross-sectional design with non-cancer controls. | 104 | - CC<br>- Ca endometrium | - Surgery<br>- CT<br>- RT | - Assessed limited number of symptoms<br>- Did not assess bowel symptoms in controls<br>- Limited racial diversity<br>- Cross-sectional design limited in examining symptom burden at baseline and overtime | Survivors reported a higher prevalence of bladder symptoms than controls. Prevalence of bowel symptoms in survivors higher than reported in literature. Greater symptom severity associated with younger age, lower income, less education, higher BMI & history of smoking. More severe symptoms associated with RH & pelvic irradiation. |

(*Continued*)



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**Table 5** (Continued).

| Author & Year | Country | Aim | Tools | Design | Sample Size (n) | Diagnosis | Treatment modality | Limitations | Main Findings |
|---|---|---|---|---|---|---|---|---|---|
| du Toit & Kidd (2015)[30] | South Africa | To compare the QoL for women treated with RT or CT +RT | EORTC-QLQ-C30/CX24 | Prospective study | 219 | Advanced CC | - RT,<br>- CT+RT | - Three months follow-up limits conclusions on long-term QoL | CT+RT improvement in the pain ($p<0.05$), fatigue ($p <0.05$), appetite loss ($p<0.01$), and nausea and vomiting ($P < 0.05$). Pretreatment QoL scores significantly higher in RT group, implying a poorer QoL status at initiation. Post hoc analysis - global health domain improved ($p<0.03$) by CT+RT. |
| Greimel et al (2009)[31] | Austria | To investigate long term QoL & sexual functioning after CC treatment | - EORTC QLQ-C30/CX24<br>- Sexual Activity Questionnaire. | Longitudinal prospective study. | 121 | CC | −63 Surgery<br>- 38 Surgery/ CT<br>- 20 Surgery/ RT | - No baseline information regarding QoL & sexual functioning<br>- Potential QoL differences cannot be excluded<br>- More women with early stages received only surgery, women with advanced cancer received adjuvant CT, or RT: potential for confounding | Women in the Surgery/RT group had significantly worse QoL outcomes (physical, role, cognitive, and social functioning) compared with women in the Surgery or Surgery/CT groups. Level of symptoms higher in irradiated women eg nausea/ vomiting, pain, appetite loss, frequent urination ($p=0.019$), urine leakage urine ($p<0.015$), and the feeling of a tight vagina ($p<0.018$). Women in the surgery/RT group reported lower sexual activity rate compared with women in the surgery or surgery/CT groups ($p<0.05$). No differences concerning sexual pleasure and discomfort among the three treatment groups ($p>0.05$). |
| Heijkoop et al (2017)[32] | Netherlands | To evaluate dynamics of patient-reported QoL & symptoms in the acute phase of EBRT for LACC | EORTC QLQ-C30/CX24 | Longitudinal prospective census | 138 | CC | - RT (EBRT) | - Sub-groups were small and heterogeneous | Most symptoms peaked at the end of treatment, or first week after treatment, returning to baseline at three-months. While most symptoms gradually increased, diarrhoea and bowel cramps markedly increased within the first three weeks to plateau at the fifth week of treatment. Global health and functioning domains temporarily decreased and returned to baseline three-months after treatment, except cognitive functioning.<br>A profound impact on QoL occurred during RT, temporarily affecting functioning. Maximum impairment was reached at end of EBRT. |


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| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Hsu et al (2009)[33] | Taiwan | To compare long-term complications and QoL of women with stage IB & IIB uterine CC treated by surgery or RT | EORTC QLQ-C30/CX24 | Retrospective cross-sectional survey | 202 | CC | - Surgery<br>- RT | - Cannot elicit sequential effects<br>- May under-estimate frequency and sequelae<br>- Clinician-treated modalities were uncontrolled<br>- Non-random sampling may cause sampling errors | Constipation ($p<0.001$), flushing ($p<0.001$), dysuria ($p<0.001$), urinary incontinence ($p<0.01$), dyspareunia ($p<0.05$) and vaginal dryness ($p<0.05$) were higher in the surgery treated group. Diarrhoea ($p<0.001$), bloody stools ($p<0.001$) and abdominal pain ($p<0.01$) were higher in the RT group. Factor analysis revealed pelvic neural dysfunction was significantly higher in surgery group and intestinal dysfunction higher in RT group. |
| Jensen et al (2018)[34] | Multinational: Austria, UK, Netherlands | To describe late bowel morbidity prospectively assessed in the multi-institutional EMBRACE study on MRI-guided adaptive brachytherapy in LACC. | CTCAE V.30<br>EORTC QLQ-C30/CX24 | Longitudinal multinational prospective study, consecutive sampling | 1176 | CC | - RT-CT<br>-<br>Brachytherapy<br>- RT | - Follow-up too short to examine long-term effects of CT+RT on participants' QoL | At 3/5 years, incidence of bowel morbidity grade 3–4 was 5.0%/5.9%, including stenosis/stricture/fistula (2.0%/2.6%). Grade 1–2 morbidity prevalence of 28–33% during follow-up. Diarrhoea & flatulence significantly increased after three months and stayed elevated. Incontinence gradually worsened. PRO diarrhoea increased from 26% to 37% at baseline to three months and remained elevated. Difficulty in controlling bowels increased from 11% at baseline to 26% at three months. Constipation & abdominal cramps improved post treatment. |
| Jensen and Froeding (2015)[45] | Global | To summarize the latest knowledge on pelvic RT & sexual function in women | Mixed | Review of retrospective cross-sectional and prospective longitudinal studies | 46 | Cancer<br>- Anal<br>- Rectal<br>- Bladder<br>- Vulva<br>- CC<br>- Endometrial | - Surgery<br>- RT<br>- CT | - Only very limited data available on modern radiotherapy modalities | Pelvic irradiation, independent of modality, increases the risk significantly for FSD compared to data from age-matched healthy control women and data on women treated by surgery only. Pelvic RT has a persistent deteriorating effect on vaginal mucosa impacting negatively on sexual functioning. |

(*Continued*)


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**Table 5** (Continued).

| Author & Year | Country | Aim | Tools | Design | Sample Size (n) | Diagnosis | Treatment modality | Limitations | Main Findings |
|---|---|---|---|---|---|---|---|---|---|
| Kirchheiner et al (2015)[35] | Multinational: Austria, Netherlands and Greece | To evaluate health-related QoL (HR-QoL) and patient-reported symptoms (PRS) before, during and early after treatment for LACC | EORTC QLQ-C30/CX24 | Mono-institutional longitudinal prospective study | 50 | CC | - EBRT<br>- CT<br>- IGBAT | - Small sample size limits generalisability<br>- Results refer to a mono-institutional experience<br>- Observation time after treatment was short to examine long-term effects. | GHS & physical and role functioning declined during treatment ($p<0.001$), returning to near baseline after three months. Compared to reference population, GHS & emotional and role functioning remained impaired. The most frequent PRS during treatment were fatigue (78%), diarrhoea (68%), urinary frequency (60%) and nausea (54%). These decreased three months post-treatment but fatigue remained high (50%) and hot flushes (44%), sexual worries (38%) and limb oedema (22%) was observed. |
| Krikeli et al (2011)[36] | Greece | To compare the impact of RT and CT+RT on the QOL of 1-year survivors with CC. | - EORTC QLQ-C30/CX24<br>- Questionnaire of post-traumatic psychological disorder<br>- Greek symptom control questionnaire | Cross-sectional survey employing consecutive sampling and retrospective data collection methods | 105 | CC | - RT,<br>- RT+CT | - Response bias could affect results<br>- Selection bias could impact generalisability<br>- Retrospective data collection cannot exclude difference at start of study | Other than differences in descriptive characteristics (age, parity, contraceptive use) and early toxicity in some organs, no difference was observed in the main (physical, sexual, emotional) aspects of QoL between the groups. Treatment type had no effect on total QoL. Addition of CT to RT had no significant impact on QoL. |
| Kuku et al (2013)[37] | UK | To evaluate predictors of severity and chronicity in women with radiation-induced bowel injury after treatment for CC & endometrial cancers | Records review of oncology and RT database | Retrospective cross-sectional study | 541 | - CC (219)<br>- Endometrial (322) | - CT<br>- RT<br>- Surgery | - Single researcher data collection (potential systematic error)<br>- Clinician-reported retrospective study so potential for under-reporting/no documentation of symptoms deemed less serious<br>- No baseline data identifying women's bowel function | Univariate analysis showed increasing age, smoking, extended field radiation, CC treatment and need for surgical intervention as significant predictors for severity of ongoing disease at last follow-up. Multivariate analysis showed age, CC & symptom combinations (bloating, flatulence, urgency, rectal bleeding and per-rectal mucus) were significant predictors of disease severity. 19% women in CC group had radiation-induced bowel injury requiring surgical intervention versus 6.7% in endometrial cancer group. |

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|---|---|---|---|---|---|---|---|---|---|
| Le Borgne et al (2013)[38] | France | To assess long term QoL in CC survivors (CCS) 5, 10 and 15 years after diagnosis | - SF-36<br>- EORTC-QLQ-C30/CX24<br>- MFI-Fatigue questionnaire<br>- STAI | Population based cross-sectional study, stratified sampling | 173-localised CCS<br>- 594 controls.<br>42% treated with surgery alone and 58% with a combination of treatment | CC | - Surgery<br>- Brachytherapy<br>- RT<br>- RT Surgery±CT | - Did not assess QoL of women treated with CT-RT<br>- Cross-sectional design precludes assessment of QoL over time | Compared to controls, CCSs expressed globally similar good QoL, except impaired psycho-emotional domains in 15-year survivors ($p<0.01$). 15-year CCSs reported significantly more lymphoedema than 5-year ($p<0.0009$) and 10-year CCSs ($p<0.002$). QoL of CCSs who received RT was more affected in terms of symptom burden, ie sexual dysfunction ($p<0.002$), voiding and abdominal symptoms ($p<0.01$) and lymphoedema ($p<0.01$). |
| Mikkelsen, Sorensen & Dieperink (2017)[18] | Denmark | To describe late adverse effects, health-related QoL, and self-efficacy in a representative CC population in order to describe rehabilitation needs | - EORTC QLQ- EORTC QLQ C30 +CX24<br>- Self-efficacy questionnaire | Cross-sectional retrospective study | 85 | CC | RT+CT, Surgery | - Small sample size;<br>- No information about cause of death<br>- Non-response bias if non-participants differed from participants<br>- Retrospective data (self-reported) information could limit generalisability | Women under 45 years had significantly more menopausal symptoms and lower body image scores. Prevalence of participants with menopausal symptoms decreased with time. Symptom experience was significantly higher in women with locally advanced disease and self-efficacy significantly lower. Women who had surgery had more lymphoedema and women who received chemotherapy had a lower QoL. |
| Mirabeau-Bede & Viswanathan (2014)[15] | USA | To summarize the literature on QoL for women treated with definitive radiation for gynaecological cancers | - QoL-CS<br>- LENT-SOMA<br>- CTVAE V.4<br>- SAQ-59<br>- FSFI<br>- FACIT<br>- EORTIC QLQ-C30/CX24 | Literature review of PROs | _____ | Endometrial cancer<br>- CC<br>- Ca vulva | RT | Review of studies that have used multiple, different survey instruments, potentially introducing variations in findings. | All women described a degree of compromise in physical and social functioning and sexual dysfunction. Bowel concerns were predominant in endometrial cancer, while body image was more concerning for women with CC. |

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**Table 5** (Continued).

| Author & Year | Country | Aim | Tools | Design | Sample Size (n) | Diagnosis | Treatment modality | Limitations | Main Findings |
|---|---|---|---|---|---|---|---|---|---|
| Pasek et al (2012)[6] | Poland | To evaluate the QoL in hospitalised women with CC treated by RT | EORTC QLQ-C30/CX24 | Longitudinal prospective study. | 205 | CC | RT | - About a quarter of enrolled women did not participate in the third survey | Physical functioning was the worst before RT & improved throughout later stages. Emotional functioning scored highest before RT & was significantly lowest at stage two. Role functioning was statistically highest immediately after treatment and lowest prior to RT. Financial problems significantly negatively impacted on QoL throughout consecutive stages of the study. Overall, QoL was poorest immediately after the end of RT. |
| Rahman et al (2017)[39] | India | To assess the QOL in women treated for CC | EORTC QLQ-C30/CX24 | Prospective longitudinal study | 90 | CC | - Surgery<br>- CT+RT | - Follow-up too short to report late side effects and evaluate long-term QoL<br>- Small sample size, limits generalisation<br>- Unable to evaluate QoL differences between treatments | Statistically significant improvement in physical, emotional function, pain, fatigue and vaginal symptoms. No improvement in social, cognitive or role functioning, body image, sexual activity or sexual enjoyment. Vaginal & sexual function significantly worsened. Younger women, earlier stage and well-differentiated CC & a higher level of education had superior QoL. |
| Sabulei & Maree (2019)[5] | South Africa | To describe the QoL of women treated for CC during (M0), and at 6 months and 12 months after completing treatment (M6 & M12 respectively) | - Structured interviews<br>- EORTC QLQ-C30/CX24 | Cross-sectional design, convenience sampling | 153 | CC | - EBRT<br>- Brachytherapy with or without CT | - Cross-sectional design does not allow for the investigation of changes over time<br>- Respondents could have provided socially acceptable answers and not reflect what is true for them | GHSs improved significantly in contrast to functional scores post treatment. Pain was prevalent with mean scores 38.2, 31.4 and 24.8 at M0, M6 & M12 respectively and failed to significantly improve over time. In gastrointestinal symptoms, nausea and vomiting had the lowest overall mean score (10.2), while diarrhoea had the highest (22.7). A post hoc analysis showed a statistically significant difference between M0 & M12 ($p<0.000$) and M6 & M12 ($p<0.007$) in terms of diarrhoea, nausea and vomiting which improved post treatment. CC & its treatment had a negative influence on the QoL in all domains. |

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| Spampinato et al (2023)[40] | Multi-continent: (Europe, Asia, and North America) | To quantify the association of persistent morbidity with different aspects of quality of life (QoL) in LACC survivors | PRS and QoL prospectively scored using EORTC-C30/ CX24 at baseline and follow-ups. Physician-assessed symptoms were reported using CTCAEv.3 | Longitudinal outcome study. | 741 | CC, FIGO stage IB-IVA & IVB | - EBRT, concomitant CT & IGABT | - Univariate analysis precludes intercorrelations between symptoms and QoL<br>- The model was adjusted only for a few confounders | Women reported persistent symptoms, with incidences from 21.8% (difficulties in controlling bowels) to 64.9% (tiredness). The numbers of women experiencing worsening beyond baseline varied depending on the symptoms.<br>Pain was mainly associated with persistent fatigue, lower back pain, neuropathy and abdominal cramps (19–22%).<br>Rectum/bowel symptoms (diarrhoea, tenesmus, urgency) had the largest impact on QoL. |
| Sumdaengrit et al (2010)[13] | Thailand | To describe symptom experience and self-care among Thai women with CC before, during and one month post treatment for CC | - Demographic, Disease and Treatment Questionnaire<br>- Modified Memorial Symptom Assessment Scale (MMSAS);<br>- Modified Self Care Diary (MSCD) | Prospective, longitudinal study; Convenience sampling | 190 | CC | - RT+ Brachytherapy<br>- RT+CT | - Self-report data assumes women were truthful in responses.<br>- Convenience sample at one hospital, results have limited generalisability | Pre-treatment vaginal discharge was the commonest, and difficulty swallowing the most distressing symptom. Both pre- and post-treatment, mood changes was the symptom requiring the most self-care. During treatment, fatigue was the most prevalent, while diarrhoea and rectal irritation were the most distressing symptoms. Post treatment, skin changes were the most prevalent symptom, while problems with sexual interest/ activity were the most intense and nervousness the most bothersome. Sleeping difficulty was present during all periods. Changes in symptom experience increased significantly during and decreased post-treatment, while self-care effectiveness decreased during and increased post-treatment. |

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**Table 5** (Continued).

| Author & Year | Country | Aim | Tools | Design | Sample Size (n) | Diagnosis | Treatment modality | Limitations | Main Findings |
|---|---|---|---|---|---|---|---|---|---|
| Vistad et al (2011)[21] | Norway | To describe chronic pelvic pain after RT in survivors of LACC | Questionnaire | Cross-sectional study | 91 | CC | RT (EBRT) and ICRT | - Use of ad hoc items to assess for chronic pelvic pain<br>- No biopsies or radiographic investigations to detect pathological differences<br>- Unable to identify case finding screening tools<br>- Small sample size | Lower back and hip pain more prevalent ($p<0.001$) in CCSs than general female population. 38% of the CCSs had CPP and a significantly lower QoL, more anxiety and depression and a higher prevalence of bladder and bowel problems than those without CPP. Multivariate regression showed the use of analgesics and bowel and bladder problems to be significantly associated with CPP. |
| Vittrup et al (2023)[41] | Multi-continent **Europe** (Austria, Spain, Norway, Finland, UK, Netherlands, Hungary, France, Belgium, Denmark, Slovenia), **Asia** (India) **North America** (Canada, Iowa) | To evaluate overall severe late morbidity (grade ≥3) in patients with LACC treated with CRT & magnetic resonance IGBAT within the prospective EMBRACE-I study, and to compare the results with published literature after standard radiograph-based brachytherapy. | Conversion of Common Terminology Criteria for Adverse Events version 3.0 morbidity into Radiation Therapy Oncology Group & European Organization for Research & Treatment of Cancer morbidity scale (RTOG/EORTC). | Prospective observational multi-institutional study | 251 | CC | EBRT with concomitant CT & IGABT | - The observational design, and the study did not record management of morbidity, hence it is not possible to determine whether a symptom resolved spontaneously or due to a successful medical intervention, n<br>- The heterogeneity in study design (retrospective/ prospective),<br>- Morbidity grading scales, summary statistics, and practice for aggregating endpoints might be potential sources of bias | GIT adverse events were prevalent, (grade 3 (n=83), grade 4 (n=34)). Anorectal morbidity included bleeding, stenosis, fistula, incontinence and proctitis, while sigmoid and colon/small bowel morbidity included bleeding, stenosis, and fistula. These were confirmed causes of 13 deaths.<br>Baseline morbidity and smoking were risk factors for most events, while increasing age was a risk factor for incontinence and bleeding. Treatment-related risk factors included higher EBRT dose, larger lymph node boosts and extended elective fields. Doses to bowel, rectum, and ICRU recto-vaginal point were risk factors for multiple adverse events. |
| Wenzel et al (2022)[46] | Multinational/multi-continent | To update available information on oncological outcome, adverse events, QOL & sexual functioning, after primary (chemo) radiotherapy (PRT) and RH & adjuvant (chemo) radiotherapy (RHRT) for intraoperatively discovered lymph node metastasis in CC. | Review of published evidence | Review | 623 | CC, FIGO 1A-4B | EBRT+BT<br>EBRT+BT+CT<br>RH | - Heterogeneity of the retrospective studies potential for selection bias.<br>- PRT was administered more often in those of older age, with higher disease-stage and with comorbid disease.<br>- Surgical & (chemo) radiotherapeutic treatment protocols were not standardised across studies<br>- Limited sample sizes, particularly in the PRT groups of the studies limit generalisability | - Symptom experience was higher after PRT.<br>- Overall bowel dysfunction, defecation urgency and loose stool after PRT & RHRT commonly associated with severe distress.<br>- Severe defecation symptoms post PRT increased body image disturbance.<br>- Defecation distress was higher following PRT<br>- Social functioning was worse post PRT. |

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| Yang et al (2020)[42] | China | To examine the outcomes QoL of young patients undergoing adjuvant RT versus NRT following surgery. | - FSFI.<br>- The EORTC QLQ-C30 questionnaire. | Retrospective cohort study of prospectively-collected data | 97 patients≤35 years of age divided into RT & NRT groups. | CC | EBRT with IMRT | - Clinician treatment modalities were uncontrolled<br>- Non-random sampling<br>- Retrospective design may underestimate severity and frequency of toxicities | Women who had received adjuvant RT had a higher incidence of diarrhoea (p=0.018), bloody stool (p=0.007), lower extremities oedema (p=0.033), and vaginal dryness (p=0.000). The most prevalent long-term radiation toxicities included proctitis, cystitis, osteitis.<br>The NRT group scored higher on the GHS scale (72.10± 14.78 v 64.30± 16.35, p=0.044), in functional scales, including physical function (71.30± 18.90 v 61.80± 19.28, p=0.043) and emotional function (68.12± 16.98 v 59.12± 16.15, p=0.023). Diarrhoea (72.46±23.89 v 52.70 ±33.11, p=0.009) and financial difficulties (85.51±16.89 v 62.16 ±34.16, p=0.002) were also significantly different. |
| Yoshida et al (2011)[12] | Japan | To examine the preliminary survival outcomes and treatment-related toxicity for elderly pts with CC treated with RT | - Medical records review<br>- CTCAE V.4.0 | Longitudinal | 40 pts aged ≥75 years | CC | RT or Surgery +adjuvant RT | - The authors did not acknowledge any limitations. | Five women experienced grade 3 acute toxicity, two grade 3 late toxicity. Conclusion was RRT for elderly women with CC is generally effective and safe, but severe toxicity may occur with aggressive treatment. |
| Zayyan et al (2018)[7] | Nigeria | To determine the QoL in advanced CC | EORTC QLQ-C30 | Cross-sectional descriptive study | 378 | CC | - CT,<br>- RT,<br>CT-RT | - No multivariate analysis was not performed to examine predictors of QoL between groups receiving different treatments | Participants on RT had better (p<0.05) physical health than those on CT or CT-RT. |
| Zhou et al (2016)[43] | China | To investigate the QoL of CC survivors | FACT-CX,<br>FACIT-SP,<br>FSFI | Prospective longitudinal study | 140 | CC I, II or III | Surgery, CT, RT | - Possible some women whose QOL was seriously affected by treatment may have declined participation | Prevalence of sexual dysfunction was 78%. QoL & sexual function of CCSs were lower than general population. Treatment-related complications and sexual dysfunction significantly affected women's QoL. Having health insurance was associated with higher QoL. Sexual function was adversely affected by RT & RH. |

**Abbreviations**: BMI, Body Mass Index; Ca, Cancer; CC, Cervical cancer; CCSs, Cervical Cancer Survivors; CRT, Chemo-Radiation Therapy; CT, Chemotherapy; CTCAE, Common Terminology Criteria for Adverse Events; EBRT, External Beam Radiotherapy; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; ERT/CT, Exclusive Radio–Chemotherapy; FACIT-SP, Functional Assessment of Chronic Illness Therapy – Spiritual well-being; FACT-CX, Functional Assessment of Cancer Therapy – Cervix Cancer; FIGO, International Federation of Gynaecology and Obstetrics; FSD, Female Sexual Dysfunction; FSFI, Female Sexual Function Index; GHS, Global Health Status; GIT, Gastrointestinal Tract; HADS, Hospital Anxiety and Depression Scale; ICRT, Intracavitary Radiation Therapy; ICRU, International Commission on Radiation Units; IGBAT, Image-guided Brachytherapy; IMRT, intensity-modulated radiation therapy; LACC, Locally advanced cervical cancer; LENT-SOMA scale, Late Effects Normal Tissues-Subjective, Objective, Management, Analytic scale; MFI, Multidimensional Fatigue Inventory; MSCD, Modified Self Care Diary; MMSAS, Modified Memorial Symptom Assessment Scale; NACT, Neoadjuvant Chemotherapy; NART/CT, Neoadjuvant Radio–Chemotherapy; NRT, Non-Radiotherapy; PRO, Patient-Reported Outcome; PRS, Patient Reported Symptoms; PRT, Primary Chemo (Radiotherapy); RH, Radical Hysterectomy; RHRT, Radical Hysterectomy and adjuvant (Chemo)radiotherapy; RRT, Radical Radiotherapy; RS, Radical Surgery; RT, Radiotherapy; SAQ, Sexual Activity Questionnaire; STA1, State-Trait Anxiety Inventory; UPS, Upfront Surgery; 3D-CRT, Three-Dimensional Conformal Radiation Therapy.

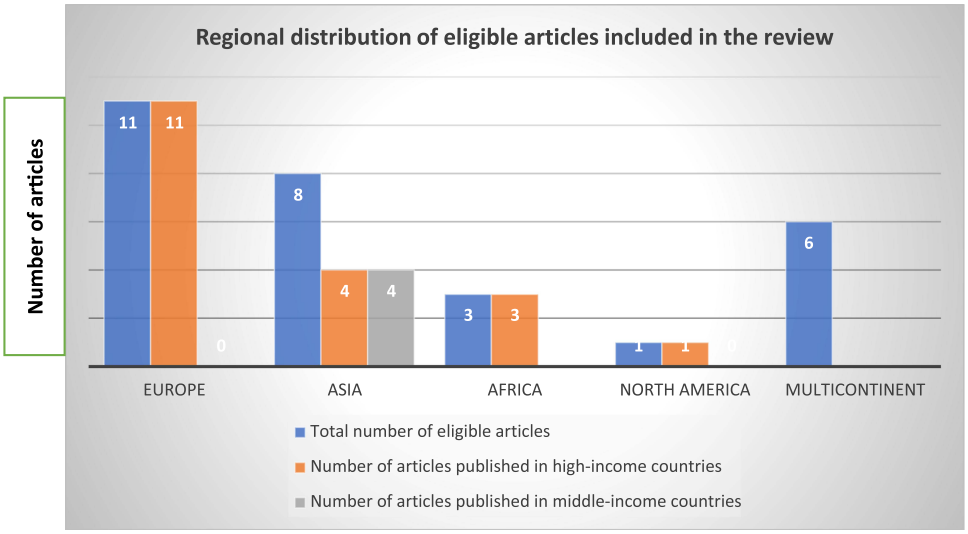


**Figure 2** Regional distribution of articles included in the review.

# Results

## Characteristics of the Articles Reviewed

The regional distribution of the studies used in the review (n = 29) is shown in Table 5. To note, the studies were conducted in four continents with most being undertaken in high-resourced countries. For example, eleven (n = 11) studies were conducted in Europe,[6,18,21,28,31,32,34–38] eight (n = 8) in Asia,[12,13,26,27,33,39,42,43] one (n = 1) in North America,[29] three (n = 3) in Africa,[5,7,30] and six (n = 6) were multi-continental; including three conducted in Europe, Asia and North America[3,40,41] and three (n = 3) reviews of global literature.[15,45,46] To note, all the three studies done in Africa were from high-income or middle-income countries, ie South Africa (n = 2)[5,30] and Nigeria (n = 1).[7]

Figure 2 shows regional distribution of eligible articles included in the review.

Regarding study design, thirteen (n = 13) studies were longitudinal,[6,12,13,27,30–32,34,35,39–41,43] ten (n = 10) were cross-sectional,[3,5,7,18,21,29,33,36–38,] one (n = 1) randomised controlled trial,[26] three (n = 3) were reviews[15,45,46] and two (n = 2) retrospective studies of prospectively collected data[28,42] (Table 4).

# Discussion

This review aimed to systematically appraise literature about the burden of bowel morbidity and CPP and their effects on QoL in patients treated with RT or RT/CT. Findings suggest that bowel morbidity and CPP are common symptoms in RT or RT/CT-treated CC patients and profoundly compromise QoL. The review further reveals there is scant published research evidence about these two common issues in LMICs. For example, of the 29 papers reviewed, only three were from Africa, while no paper was identified in South America. This highlights a huge evidence gap on the topic. Again, very few of the studies reviewed studied CPP, which is shown to be a common complaint in patients receiving, or who have received, pelvic irradiation.

## CPP and Its Effects on QoL of CC Patients

QoL has been defined as a person's self-reported perception of physical, psychosocial and sexual well-being.[36] It is thought that the toxicity of treatment in women receiving RT or RT/CT could be due to RT as some authors report they did not find any significant differences between RT/CT and RT treated groups.[36] However, conflicting findings also exist. For example, Bjelic-Radisic et al[3] reported that CT increases treatment related toxicities when concurrently administered with RT. Nonetheless, RT/CT is now the most widely used modality of CC treatment for both early-stage disease for curative intent and for palliation of CC symptoms. In fact, it is estimated that 52% of cancer patients will require RT for optimal treatment while a further 23% need re-treatment.[45] It is likely that these figures are an underestimate of the number needing retreatment for example because of relapse.

Pain is a common symptom experienced by CC patients. Its aetiology has been cited in many studies as linked to the CC itself and its invasive treatments. Numerous studies report the prevalence of pain among CCSs ranges between 40% and 70%.[7,31,37] This finding is corroborated by a study conducted in South Africa by Ntinga and Maree.[47] Sadly, CPP is often underreported and under described,[21] and inevitably poorly treated as seen in a number of other studies.[19,48,49]

Vistad et al[21] in their study of CPP after RT in survivors of locally advanced CC found 38% of the women they studied in Norway met the criteria for CPP and CPP had a significant link to bladder and bowel morbidity. These findings are corroborated by Donovan et al[29] in the US, who found 36% of CCSs reported pelvic pain. However, wide variations in the prevalence of pelvic pain are observed in the literature. For example, Le Borgne et al[38] in their study in France, found prevalence rates of lower back pain and peripheral neuropathies were lower at 14.6% and 17.2% respectively. It is unclear as to why these wide variations exist.

CPP has been shown to have a negative impact on women's QoL. CT/RT usually causes chemotherapy-induced peripheral neuropathy (CIPN) which causes nerve pain, sensory discomfort like numbness, fatigue and psychological problems (anxiety, worry and depression) all of which could exacerbate poor QoL among patients and even their family. For example, Vistad et al[21] found participants who had CPP significantly had a lower QoL, higher levels of anxiety and depression, and more severe bladder and bowel morbidity compared to their counterparts without CPP. Furthermore, Tian et al[17] found poor sleep quality was prevalent in 52.63% and 64.47% of CC patients before and after RT respectively while Sumdaengrit et al[13] found emotional changes, difficulty sleeping, worrying and feeling irritable were frequently reported by CC participants.

Furthermore, research suggests that CPP and bowel morbidities post RT could negatively affect rehabilitation, increase suffering and negatively influence QoL. In fact, several other negative symptoms including anxiety, depression, fatigue, insomnia, sexual and sexuality problems, social problems, and extended lost work days have been reported by studies done among CCSs after RT/CT. Insomnia has been reported to be a common symptom in CC patients receiving RT or RT/CT in many studies.[5,6,47,50] These findings underscore the crucial role of CPP in the pathophysiology and exacerbation of physical, emotional and psychological morbidity among RT-treated CC patients. The prevalence of insomnia, however, varies quite widely across studies. Insomnia was the most commonly reported symptom in a South African study by Ntinga and Maree,[47] followed by pain and fatigue. Goker et al[50] found fatigue was most prevalent followed by pain and insomnia. Pasek et al[6] reported insomnia was the commonest followed by fatigue and diarrhoea. Whereas Sabulei and Maree[5] found insomnia, pain and fatigue showed a downward trend from baseline throughout treatment, research elsewhere found contrary findings ie these symptoms registered an upward trend.

Everhov et al[16] in the US, found that disabled CCSs have significantly more depression than working patients, and the prevalence of delayed return to work was at 71% among those treated with RT. These finding support those of Vistad et al[21] who found CPP is associated with higher overall mental and somatic morbidity. Earlier studies found that significant psychological impairment; eg, feelings of guilt, self-blame, fear of recurrence, and anxiety and sexual functioning impairment were related to CC treatment, including RT.[51–53]

While it is likely that CPP and bowel morbidity have a close link in the aetiology of insomnia and fatigue, the studies reviewed lack data about to what extent CPP and bowel morbidity account for the aetiology of fatigue and insomnia and their overall effect on QoL. This underlines a need for future longitudinal studies to examine these predictor variables to have a better evidence-supported understanding of the salient cause-effect relationships that exist.

In their population-based study of 243 gynaecological cancer survivors who had received pelvic irradiation, Kollberg et al[19] found dyspareunia (painful intercourse) affected 67% of the study participants. 55%, 40%, and 36% reported superficial pain, deep pain and both types of dyspareunia respectively. Previous studies have linked dyspareunia to a shortened vagina following pelvic irradiation.[52,54,55] These findings reveal disruptions on the sexuality and sexual functioning, an essential QoL domain. Jensen et al[54] in their longitudinal study assessing sexual functioning following primary or postoperative RT for 118 CC patients found sexual dysfunction persisted up to two years after RT treatment with 50% reporting severe disabling distress. Numerous large sample studies report similar findings.[31,48,51,56–60]

Swelling of the feet (lymphoedema pain) is another symptom that negatively impacts women's QoL during or following RT or RT/CT.[32,47] Other longitudinal studies report worsening of lymphoedema from start of treatment and onwards,[61,62] except Bjelic-Radisic et al[3] who reported that lymphoedema improved during follow-up. Le Borgne et al[38]

found voiding (bowel) problems and lymphoedema were more prevalent among long-term CCSs (5–15 years) unlike other symptoms which improved over time during treatment. Findings are corroborated by another study conducted in China.[49] This calls for clinical settings to be more aware of these issues and make practical efforts to identify and address these issues in order to improve the QoL of patients.

## Bowel Morbidity and Its Effects on the QoL of Patients

Bowel morbidity in patients receiving or who have received RT or RT/CT manifesting as incontinence, diarrhoea, tenesmus, constipation, rectal dysfunction, chronic radiation enteritis-(CRE), bloating, flatulence, urgency, rectal bleeding and per-rectal mucus is a great concern and predictor of poor QoL among CCSs receiving RT singly and/or in combination with CT. Bowel morbidity was reported in 20 of the 29 studies in this review[3,5,13,18,21,26–30,32–35,37,38,40–42,46] as well as in numerous studies elsewhere[63–67] while CRE is reported, as occurring in 19–20% of patients.[37] In contrast, a cross-sectional study of 105 Greek women found treatment type (RT or RT/CT) had no effect on total QoL.[36]

Dahiya et al[27] in their longitudinal study assessing the QoL of 67 Indian women before and after RT/CT in CC found the mean global health score after six months of treatment was 59.52, which was significantly higher than the pre-treatment score of 50.15 ($P< 0.00007$). Similarly, physical, cognitive and emotional functioning improved significantly ($P<0.05$) after treatment. Fatigue, pain, insomnia and appetite loss improved whereas episodes of diarrhoea which is common in CRE increased after treatment.

Bowel injury is often due to impaired anorectal function following RT or RT/CT treatment. Hsu et al[33] found diarrhoea, bloody stools, intestinal dysfunction and abdominal pain were significantly higher in the RT-treated group. Kuku et al[37] in their medical records review of 541 women treated with RT with or without CT for CC and endometrial cancer identified 152 women who reported significant new bowel symptoms after pelvic radiation. 19% of participants in the CC group had a radiation-induced bowel injury requiring surgical intervention compared with five (6.7%) in the endometrial cancer group. Bowel morbidity is also reported by Bjelic-Radisic et al[3] who found pelvic irradiation with or without other therapy was more associated with symptoms of diarrhoea. Studies also report that RT-treated patients reported greater intestinal dysfunction or bowel morbidity eg voiding and abdominal symptoms.[33,38,66]

Furthermore, to note, the prevalence of bowel dysfunction varies quite widely in the literature. In their study, Vistad et al[21] reported a prevalence of 19% for defecation urgency and 60% of their study subjects (CCSs) previously treated with RT had bowel problems. Le Borgne et al[38] reported a slightly lower prevalence of incontinence of 14.6% compared with Hazewinkel et al[64] who found the prevalence of defecation urgency in women who had completed radiation therapy for CC was 49%.

The effect of RT and/or CT/RT treatment on the overall QoL of women is also widely documented in both cross-sectional and longitudinal studies in the literature. In their longitudinal study of 121 CC patients, Greimel et al[31] reported participants in the surgery/RT group reported significantly worse QoL outcomes (lower scores on physical, role, cognitive, and social functioning) compared with participants in the surgery group or surgery/CT group. The severity of symptoms such as nausea/vomiting, pain, appetite loss, frequent urination ($P < 0.019$), urine leakage ($P < 0.015$), and the feeling of tightness in the vagina ($P < 0.018$) was significantly higher in irradiated participants. Regarding the sexual functioning QoL domain, patients in the surgery/RT group reported a significantly lower sexual activity rate compared with women in the surgery group or those in the surgery/CT group ($P < 0.05$).

In another longitudinal study, Kirchheiner et al[35] found global health status and physical and role functioning showed a highly significant decline during CT/RT treatment ($P < 0.001$) and declined further to near the baseline levels three months after end of treatment. Compared to the reference population (CT group), global health status (GHS) and emotional and role functioning remained impaired in the CT/RT group. Other studies report poor or lower GHS, social, emotional and functional status and higher symptom and financial suffering in patients treated with RT or RT/CT.[7,42,46] The most frequently reported PRS predictors of poor QoL during active treatment were fatigue (78%), diarrhoea (68%), urinary frequency (60%) and nausea (54%). Findings are consistent with those of other studies.[3,5,32,34,37,38] Pasek et al[6] in their longitudinal study found that physical, emotional role and financial functioning were poor during and after RT and profoundly compromised QoL of the participants. Bjelic-Radisic et al[3] found that pelvic irradiation alone or with other therapy (surgery or CT) was associated with most symptoms of diarrhoea. Compromised QoL was also observed in 13

other domains of QoL, namely physical, role, emotional, cognitive, social functioning, global health/QoL, fatigue, nausea and vomiting, pain, appetite loss, constipation, symptom experience and sexual enjoyment. Mikkelsen et al[18] found QoL was lower in participants who received CT/RT.

It can be argued that whereas chemotherapy increases the sensitivity of CC cells to RT, CT/RT combination is associated with a higher symptom burden. Sumdaengrit et al[13] found diarrhoea and rectal irritation were the most distressful symptoms for the participants, while Heijkoop et al[19] found diarrhoea and bowel cramps increased markedly during RT treatment and profoundly impacted the QoL of the participants, particularly reducing their score in the global health and functioning status domains.

Research elsewhere, notably in South Africa, found bowel problems (urgency, diarrhoea, pain, constipation, and appetite loss, nausea and vomiting) negatively impacted QoL.[5] However, contradictory findings also exist. For example, Heijkoop et al[32] found RT-induced bowel morbidity was associated with reduced global health and functioning status while Sabulei and Maree[5] found the GHS of the participants improved significantly compared to the functioning scores, while financial difficulties were common. The differences in the observations could be due to different study designs used in each of the studies, for example, Heijkoop et al[32] used a longitudinal design while Sabulei and Maree[5] used a cross-sectional design. Interestingly, du Toit and Kidd,[30] in their earlier South African longitudinal study found that RT resulted in an improvement in pain and bowel (gastrointestinal) symptoms. It is unclear as to whether patient- and treatment-related differences or limited sample sizes are possible predictors of the observed differences. This suggests a need for large studies of longitudinal designs to examine both short-term and long-term effects.

## Strengths and Limitations of the Review

This study has important strengths worth mentioning. First, the study is informed by rich literature retrieved through a systematic rigorous search performed in trusted databases that publish high quality peer reviewed work. The methodological critique applied to select and appraise eligible articles is also strong, this increases the dependability and credibility of the findings. Secondly, the evidence used in the review was pooled from studies that used different study designs, hence some triangulation of the study findings. Thirdly, based on the findings, this is one of the first systematic reviews to examine, in detail, CPP and bowel morbidity and their impact on QoL of CCSs treated with RT or RT/CT. Hence, the review is novel to some extent.

However, the review has a few limitations to acknowledge. *First*, the literature search was conducted in just four databases. It is likely some papers published and indexed in other databases could have been missed. Hence, findings may not be a true reflection or representative of the available published research on the topic. *Second*, we know that bowel morbidity and CPP may develop later, several months or years following RT treatment, requiring longitudinal studies with longer duration of follow-up to better examine late adverse events. Most of the studies used in this review had a short duration of follow-up and small sample sizes, while some used cross-sectional design and lacked baseline and follow-up data. *Third*, to a large extent, findings in this review are skewed towards high-income countries (HICs), with very few studies conducted in LMICs. In addition, most of the studies had small sample sizes. Moreover, the findings from the studies done in HICs may not be wholly generalised to the situation in LMICs due to potential contextual differences such as dosages and the quality of radiotherapy treatment and sociocultural nuances, all which could influence patients' symptom experience. *Fourth*, the heterogeneity of the data, eg uncontrolled treatment modalities, poses an additional limitation. These make it hard to make a more realistic balanced discussion of the findings and draw generalisable deductions.

# Conclusion

This review found that CPP and bowel morbidity are common symptoms in CCSs treated with RT or RT/CT. The review found there exists a strong relationship between these morbidities and poor QoL among CCSs. Studies reported disruptions in nearly all domains of QoL of an individual, including global, physical, emotional/psychological, financial, sexual, social, and role functioning as a result of being treated with RT or RT/CT for CC. To note, research evidence, particularly from large sample longitudinal studies with extended periods of follow-up is sparse, as are studies from LMICs. There is a need for more longitudinal population-based (large sample size) studies with extended follow-up periods to examine late adverse effects of RT treatment. In addition, studies in which treatment modalities are controlled would give findings that are more accurate.

Research employing qualitative designs is also needed to capture lived experiences of patients treated for CC which may be missed by quantitative design. Interventions for timely and effective assessment and management of CPP and bowel morbidity need to be given a priority as in clinical settings, and as evidenced in the literature, the failure to manage these morbidities profoundly compromises the QoL of patients, and may even worsen the outcome.

## Strengths and Limitations of the Study

This is a worldwide systematically appraised review of original peer-reviewed evidence.

The review integrates mixed methodologies evidence. The heterogeneity of the data makes it difficult to generalise findings across different contexts. Most of the studies lacked baseline data, had small sample sizes and or had short follow-up times and hence had limited ability to examine late adverse events.

# Author Contributions

Both authors made a significant contribution to the work reported ie conception, study design, execution, acquisition of data, analysis and interpretation; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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