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REVIEW ARTICLE

A systematic review of the impact of contemporary treatment modalities for cervical cancer on women's self-reported health-related quality of life

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Abstract

Purpose Given the high survival rate of cervical cancer patients, understanding women's health-related quality of life (HRQL) during and after treatment is of major clinical importance. We conducted a systematic review to synthesize all available evidence about the effects of each contemporary treatment modality for cervical cancer on all dimensions of women's HRQL, including symptoms, functioning, and global HRQL.

Methods We searched four electronic databases from January 2000 to September 2019, cross-referenced and searched by author name for studies of patients treated for cervical cancer that reported patient-reported outcomes (PROs) before treatment and with at least one post-treatment measurement. Two independent reviewers applied inclusion and quality criteria and extracted findings. Studies were categorized by treatment to determine specific treatment effects on PROs. Results were narratively summarized.

Results We found twenty-nine papers reporting 23 studies. After treatments with curative intent for early or locally advanced disease, lymphedema, diarrhea, menopausal symptoms, tight and shorter vagina, pain during intercourse, and sexual worries remained long-term problems; however, sexual activity improved over time. HRQL and psychological distress were impacted during treatment with also worsening of global HRQL but improved 3–6 months after treatment. In patients with metastatic or recurrent disease, pain improved during palliative treatment or remained stable, with no differences in global HRQL found over time.

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Conclusion Whereas most symptoms worsen during treatment and improve in the first 3 months after completing treatment, symptoms like lymphedema, menopausal symptoms, and sexual worries develop gradually and persist after curative treatment. These findings can be used to inform clinical practice and facilitate communication and shared decision-making. More research is needed in very early cervical cancer and the impact of fertility sparing therapy on PROs.

Keywords Cervical cancer · Surgery · Radiotherapy · Chemotherapy · Patient-reported outcomes · Quality of life

Introduction

Cervical cancer is the fourth most frequently diagnosed cancer in women worldwide, with 570,000 new cases in 2018 [1]. It has a high survival rate in developed countries, with the USA reporting a 5-year survival rate of 66% across stages, and 92% in localized disease [2]. Micro-invasive disease can be surgically treated with simple hysterectomy, cervical conisation, or simple trachelectomy, with the latter two preserving fertility. Early disease is commonly treated with radical hysterectomy (RH). If risk factors on the pathology specimen are present, adjuvant treatment with radiotherapy (RT) +/− chemotherapy (CT) is offered. For locally advanced disease, chemoradiotherapy (CRT) followed by brachytherapy (BT) is standard treatment. For women diagnosed with metastatic disease, CT +/− RT is offered to palliate symptoms [3–6]. Treatment for cervical cancer is often tailored to the individual, taking into account factors such as tumor stage, performance status, comorbidity, personal preferences, frailty, and age [7].

Evidence across pooled treatments for cervical cancer indicates that women may experience a range of disease and treatment-related symptoms and side effects including incontinence, rectal bleeding, diarrhea, and decreased libido [4], which can negatively impact women's overall health-related quality of life (HRQL). HRQL is widely accepted as "a multidimensional construct encompassing perceptions of both positive and negative aspects of dimensions, such as physical, emotional, social, and cognitive functions, as well as the negative aspects of somatic discomfort and other symptoms produced by a disease or its treatment" [8, 9]. Key aspects of this definition indicate that HRQL is a subjective phenomenon, multi-dimensional, and best assessed from patient-reports. Therefore, HRQL is commonly assessed using patient-reported outcomes (PROs), that is, "any report of the status of a patient's health condition that comes directly from the patients, without interpretation of the patient's response by a clinician or anyone else" [9, 10]. PROs can be divided into proximal effects, i.e., direct effects of the disease and side effects of treatment; distal effects, i.e., consequent impacts on core functioning domains (e.g., physical, social, emotional); and in turn, global HRQL. Given the high survival rate, better understanding of women's HRQL during and after treatment is of major clinical importance, since it could facilitate shared decision-making and assist in delivering timely, tailored supportive care interventions to address HRQL issues.

The aim of this systematic review was to synthesize all available evidence about the effects of each contemporary treatment modality for any stage cervical cancer on all dimensions of women's HRQL, including symptoms, functioning, and global HRQL, before treatment and during short- and long-term follow-up.

Methods

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [11]. The following electronic databases were searched using the OVID web gateway: MEDLINE, Embase, PsycINFO, and CINAHL from January 2000 to September 2019, as earlier publications would not reflect current treatments. The search strategy is outlined in supplementary 1. Non-English publications and conference papers were excluded. A manual search of the references to the identified literature from the four databases, including relevant systematic reviews, was conducted. Authors of included studies who had published > 2 papers in the field were searched to identify further research not located through other sources.

Study selection and eligibility criteria

Titles and abstracts were reviewed against three preliminary screening criteria:

1. Study sample was women diagnosed with and treated for cervical cancer; and
2. Study included PROs as a primary or secondary endpoint; and
3. Quantitative study designs that included PROs assessed at baseline before treatment and at least one follow-up assessment during or post-treatment. Relevant review papers were also obtained.

If all three criteria were met or relevance was ambiguous, full texts were obtained and reviewed; the following inclusion criteria were applied:

1. Study sample was clearly defined as women diagnosed with and treated for cervical cancer or mixed samples if

results for women with cervical cancer were reported separately; and
2. The sample of patients was ≥ 30; and
3. PROs were collected using a standardized and validated instrument; and
4. 65% of study patients reported baseline PROs; and
5. If different treatment modalities were used, results had to be reported per treatment modality

Two researchers independently assessed titles, abstracts, and full texts against the eligibility criteria. Disagreements were resolved in team discussions.

Quality assessment

Study quality and quality of PRO reporting were assessed by two reviewers independently using the Standard Quality Assessment Criteria for Evaluating Primary Research Papers—QualSyst and the CONSORT-PRO [12, 13]. Quality assessment was cross-checked for consistency. Each quality criterion was assessed as being met and scored as fully, partially, or not met. If unsure, the item was resolved with a third reviewer. Total quality scores were calculated as a percentage of the total possible score.

Data extraction and analysis

Data from the included studies were extracted into a predefined data extraction table. Data extraction was undertaken by two reviewers independently and was cross-checked for consistency. Discrepancies were checked by a third reviewer. We defined two time periods:

1. Immediately after treatment (0–3 months post-treatment)
2. Post-treatment long-term effects (> 3 months–5 years)

Included studies were classified according to pre-specified treatment groups (supplementary 2). These treatment groups were based on international guidelines and discussions with the research team. Results for studies with treatment subgroup analysis were included in two treatment categories.

Results

The search identified 4983 papers of which 29 papers met eligibility criteria, reporting on 23 individual studies (Fig. 1). All study designs, methods, and PROs results are summarized in Table 1. Thirteen papers (48%) reported on a patient cohort comparing different treatments [14–26]. Ten papers (31%) reported on a patient cohort undergoing a single treatment [27–36]; five of these reported on the EMBRACE study cohort [29, 30, 33, 35, 36]. Only six papers (21%) were randomized controlled trials, all of which evaluated systemic therapy for advanced disease [37–42]. All included studies were conducted before the update of the Féderation Internationale de Gynécologie et d'Obstétrique (FIGO) staging system in 2018 [5, 6].

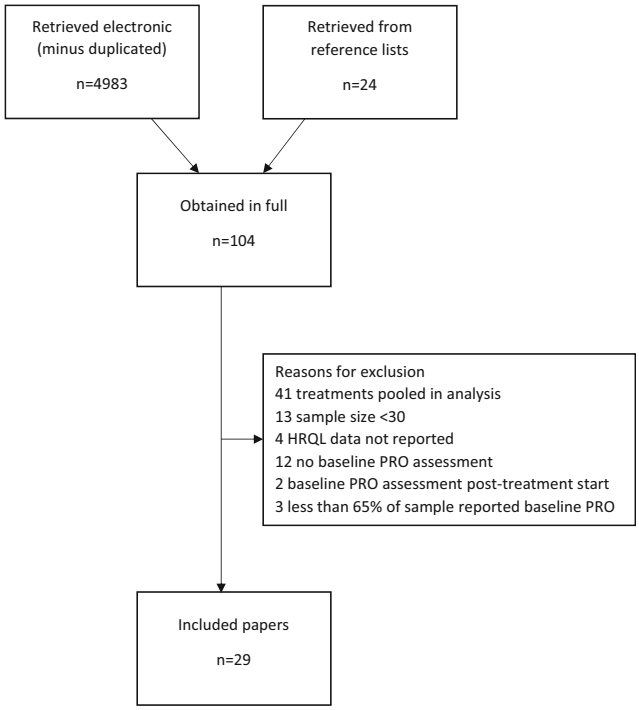

Fig. 1 Flowchart of included studies

Study quality

Individual study quality scores ranged from 50 to 91% (Fig. 2a). Only two studies met all quality criteria at least partially [37, 40]. The proportions of the included papers meeting each quality criterion are listed in Fig. 2b. Overall, 93% (27/29 papers) reported relevant PRO domains, and 52% (15/29 papers) reported all PRO domains measured. Only 24% (7/29 papers) adjusted for multiple testing, and 21% (6/29) reported approaches for handling missing data.

Results across studies by treatment category

A number of PROs were assessed using multi-scale PRO measures (Table 1). All summarized changes in PRO scores from baseline to follow-up are statistically significant. Clinically relevant differences are indicated if reported in the studies.

Radical surgery with or without adjuvant therapy

Early disease, i.e., FIGO stage IB1, IB2, or IIA1, is commonly treated with RH +/− adjuvant therapy. Ten studies reported

Table 1 Summary of characteristics of included studies

Author (year), country	Aim	Design, sample size, treatment/comparison groups	Reported PRO domains (measure), PRO assessment time-points	PRO attrition at assessment time-points; reasons for noncompliance	PRO key findings
Radical surgery with or without adjuvant therapy					
Barnas (2012), Poland	Assess longitudinal HRQL after tx	Prospective cohort, 100 pts with FIGO stage IA2-IIA, surgery (type not specified). No comparison group	QLQ-C30/CX24*,◊ T1 before tx T2 3m after tx T3 6m after tx	T1 $n = 100$ T2 $n = 100$ T3 $n = 100$	Global health status, emotional and cognitive function improved after tx. Role and social function improved after 3 m. Fatigue, nausea/vomiting and diarrhea improved at 6m after tx
Bogani (2014), Italy	Evaluate if implementation of nerve-sparing laparoscopic RH impacts on sexual function	Prospective cohort, 40 sexually active pts with FIGO stage IB and IIA (< 4 cm) receiving conventional laparoscopic RH ($n = 20$) vs nerve-sparing laparoscopic RH ($n = 20$)	FSFI• T1 before tx T2 7–9m after tx	T1 $n = 40$ T2 $n = 40$	Both operation techniques impaired sexual function, but after nerve sparing resection better scores were reported, especially more lubrication and satisfaction
Carter (2010), USA	Assess emotional, sexual and HRQL after radical trachelectomy and RH	Prospective cohort, 71 pts with FIGO stage IA1 with LVSI, IA2-IB2 receiving radical trachelectomy ($n = 43$) vs RH ($n = 28$)	Well-being scores FACT-Cx×, FSFI•; depression (total score CES-D); thoughts/behavior (total score IES) T1 before tx T2 3m after tx T3 6m after tx T4 12m after tx T5 18m after tx T6 24m after tx	T1 $n = 71$ T2 $n = 43$ T3 $n = 45$ T4 $n = 42$ T5 $n = 38$ T6 $n = 40$ Additional tx, surgery aborted due to extended disease, decline of surgery, severe psychiatric issues, recurrence, lost to follow-up, refusal	Sexual functioning improved at 12 months after treatment in both groups. No differences between groups
Conic (2012), Serbia	Compare severity and risk factors for anxiety in cervical cancer pts	Prospective cohort, 30 pts with FIGO stage IB/IIA receiving surgery + CRT (cisplatin 40 mg/m^2) vs 30 pts with FIGO stage IIB/IIIB receiving CRT (cisplatin 40 mg/m^2) vs 30 healthy patients	Anxiety (HAM-A) T1 before tx T2 3m after T1 T3 6m after T1	T1 $n = 90$ (includes healthy pts) T2 $n = 60$ T3 $n = 60$	More anxiety in surgery group than after CRT. Both groups reported more anxiety than controls. Intensity of anxiety gradually decreased. Most important risk factors for anxiety were irregular menstrual bleeding and pain
Ding (2013), China	Determine longitudinal HRQL after tx and the impact of coherence/social support	Prospective cohort, 187 pts with FIGO stage I or II receiving radical hysterectomy +/− BSO +/− LN resection vs 33 pts with stage 0	Well-being scores FACT-Cx× and cervical cancer specific subscale (FACT-Cx); coherence (total score sense of coherence scale 13) T1 before tx T2 3m after T1 T3 6m after T1 T4 9m after T1	T1 $n = 187$ T2 $n = 123$ T3 $n = 112$ T4 $n = 106$ Refusal, death, lost at follow-up	Overall HRQL improved over time, but social/family well-being decreased
Ferrandina (2012), Italy	Evaluate HRQL issues and emotional distress after tx	Prospective cohort, 105 pts with FIGO stage IB-IIA < 4 cm receiving RH + LN dissection vs 122 pts with IB3, IIB-IVA receiving CRT (39.6–50.3 Gy with concurrent cisplatin) followed by RH after 5–6 weeks	QLQ-CX24 ◊ and global HRQL (QLQ-C30); anxiety and depression (HADS) T1 before tx T2 post CRT T3 3m after RH T4 6m after RH T5 12m after RH	T1 $n = 227$ T2 $n = 115$ (CRT only) T3 $n = 115$ T4 $n = 110$ T5 $n = 188$ Refusal, recurrence, lost at follow-up	Global HRQL improved over time in both groups, increase of lymphedema in both groups (more in advanced disease). Menopausal symptoms increased and sexual activity and anxiety scores improved in both groups

Table 1 (continued)

Author (year), country	Aim	Design, sample size, treatment/comparison groups	Reported PRO domains (measure), PRO assessment time-points	PRO attrition at assessment time-points; reasons for noncompliance	PRO key findings
Mantegna (2013), Italy As Ferrandina 2012	Assess longitudinal emotional distress and HRQL	Prospective cohort, 105 pts with FIGO stage IB-IIA < 4 cm receiving RH + LN dissection vs 122 pts with IB3, IIB-IVA receiving CRT (39.6–50.3 Gy with concurrent cisplatin) followed by RH after 5–6 weeks	Global HRQL (QLQ-C30); symptoms experience, body image, lymphedema, menopausal symptoms, sexual activity (QLQ-CX24); anxiety and depression (HADS) T1 before tx T2 post CRT T3 3m after RH T4 6m after RH T5 12m after RH T6 24m after RH	T1 $n = 227$ T2 $n = 115$ (CRT only) T3 $n = 115$ T4 $n = 110$ T5 $n = 190$ T6 $n = 169$ Refusal, recurrence, lost at follow-up	Towards 3m anxiety level reduced in both groups, but after 2y more anxiety after CRT. HRQL increased compared with baseline in both groups, but body image deteriorated after CRT. In both groups lymphedema and menopausal symptoms worsened and remained 2 years after RH but sexual activity improved over time
Fleming (2016), USA	Assess longitudinal HRQL after tx	Prospective cohort, 39 pts with FIGO stage IA1-IB1 receiving radical trachelectomy. No comparison group	FSFI•, well-being scores FACT-Cx×, SF-13 ; distress and total symptom severity (MDASI); satisfaction with decision (SWD) T1 before tx T2 6w after surgery T3 6m after T1 T4 1y after T1 T5 2y after T1 T6 3y after T1 T7 4y after T1	T1 $n = 32$ T2-T7 not reported Conversion to RH, no baseline or postoperative questionnaires completed	Symptoms worsened at 6w but returned towards baseline at 6m for FSFI and MDASI This was also the case for functional and physical well-being, SF-12 bodily pain, physical functioning, role physical, role emotional and social functioning No difference in SWD was found over time
He (2017), China	Compare laparoscopic RH and open RH regarding complications, sexual function and survival outcomes	Retrospective cohort, 1863 pts with FIGO stage IA2-IIA2 receiving laparoscopic RH ($n = 1071$) vs open RH ($n = 792$)	FSFI•; urinary incontinence (ICIQ-LUTS) T1 before tx T2 12m after tx Part of included patients reported baseline PRO, subgroup analysis was performed	T1 $n = 771$ T2 $n = 771$ Death, lost to follow-up, asexual patients	No difference in sexual function and urinary incontinence between groups Less urinary incontinence and sexual symptoms after nerve sparing laparoscopic RH compared with open RH
Jiang (2016), China	Determine whether vaginal extension following laparoscopic RH improves sexual function	Prospective cohort, 216 pts with FIGO stage IA1-IIA2 receiving laparoscopic RH with vaginal extension ($n = 115$) vs laparoscopic RH alone ($n = 101$)	FSFI• T1 before RH T2 1y after RH	T1 $n = 216$ T2 $n = 198$ Death, metastasis, divorce, not resuming sexual activity, loss to follow-up	In both groups FSFI scores declined, but after vaginal extension sexual functioning was less deteriorated Postoperative vaginal length and higher baseline FSFI scores were positively associated with a higher FSFI score
Pieterse (2013), The Netherlands	Evaluate self-reported morbidity of nerve sparing RH + LN resection vs RH + LN resection	Prospective cohort, 229 pts with FIGO stage IA-IIB, and one pts IIB receiving nerve-sparing RH + LN resection ($n = 123$) vs RH + LN resection ($n = 106$)	Diarrhea, constipation, urge incontinence for urine, lymphedema, numbness labia or thigh, sexual activity, narrow/short	T1 $n = 229$ T2 $n = 191$ T3 $n = 174$ Death, recurrence	More bowel, bladder and sexual symptoms up to 2y in both groups. More numbness of labia and/or thigh after conventional RH. RT increased diarrhea, lymphedema and sexual symptoms

Table 1 (continued)

Author (year), country	Aim	Design, sample size, treatment/comparison groups	Reported PRO domains (measure), PRO assessment time-points	PRO attrition at assessment time-points; reasons for noncompliance	PRO key findings
			vagina, pain during intercourse, dry vagina, sexual interest, satisfaction sexual life, lubrication, frequency sexual contact and orgasm (Dutch Gynaecologic Leiden Questionnaire) T1 before tx (recall before symptoms) T2 1y after RH T3 2y after RH		
Ultraradical surgery					
Hawighorst (2004), Germany	Determine impact of tx for cervical cancer on HRQL to assess tx-related needs for quality improvement	Prospective cohort, 129 pts with advanced disease receiving pelvic exenteration +/− RT or CT vs Wertheim's procedure +/− RT or CT	Physical, medical interaction, psychosocial, sexual, marital and global HRQL (CARES-SF); attractiveness or self-confidence and sexual uncertainty (Body image by Strauss and Appelt) T1. before surgery *if adjuvant therapy is applied:* T2 before 2nd CT T3 Before 5th CT T4 once during RT *for all patients* T5 4m after surgery T6 12m after surgery	T1 $n = 129$ T2 NR T3 NR T4 NR T5 $n = 81$ T6 $n = 64$ Death, overwhelmed by disease, refusal, logistic issues	After surgery sexual problems were largest restriction for HRQL, also decreased body image, attractiveness and self-confidence scores. Worries about family and fear of recurrence persisted over time
Neoadjuvant therapy followed by surgery					
Liu (2019), China	Assess changes of HRQL over time	Prospective cohort, pts with FIGO stage IB2-IIIB, receiving 40–50 Gy in 20–25 fractions with concurrent cisplatin 40 mg/m^2 ($n = 197$) vs RT without CT (78), in both groups followed by RH	QLQ-C30/CX24*,◊ T1 before tx T2 6m after tx	T1 $n = 275$ T2 $n = 275$	Physical and role functioning improved at 6m compared with baseline in both groups and fatigue improved. Lymphedema worsened at 6m compared with baseline in both groups. Lymphedema only deteriorated after CRT + RH and sexual worry increased only after RT + RH
Chemoradiation or radiotherapy					
Du Toit (2015), South Africa	Determine impact on HRQL of RT and CRT	Prospective cohort, 219 pts with FIGO stage IB2 to IVA (with and without HIV) receiving CRT, 46–50 Gy in 23–25 fractions with concurrent cisplatin 40 mg/m^2 and BT at 20–26 Gy in 4–5 fractions ($n = 73$) vs RT ($n = 102$) vs surgery ($n = 44$)	QLQ-C30/CX24*,◊ T1 before tx T2 after completion of initial tx T3 3m after tx	T1 $n = 219$ T2 $n = 134$ T3 $n = 96$ Reasons for noncompliance were not reported	CRT resulted in a decrease of pain, fatigue, appetite loss, nausea and vomiting and an increase of social functioning. Pre tx scores of these were higher in the RT group. No significant difference in change in HRQL was reported until 3m after tx. Global HRQL was significant better at T2 and T3

Table 1 (continued)

Author (year), country	Aim	Design, sample size, treatment/comparison groups	Reported PRO domains (measure), PRO assessment time-points	PRO attrition at assessment time-points; reasons for noncompliance	PRO key findings
Fokdal (2018), Denmark	Assess late urinary morbidity	Prospective EMBRACE cohort, 1176 pts with FIGO stage IB-IVA and IVB with para-aortic metastatic nodes below L1–L2 only receiving CRT 45–50 Gy in fractions of 1.8 Gy with concurrent cisplatin 40 mg/m^2 followed by image-guided BT (30–50 Gy). No comparison group	Urine frequency, leaking of urine, pain/burning feel when passing urine, difficulty emptying bladder (QLQ-CX24) T1 before tx T2 3m after T1 T3 6m after T1 T4 9m after T1 T5 1y after T1 T6 1.5y after T1 T7 2y after T1 T8 2.5y after T1 T9 3y after T1 T10 4y after T1 T11 5y after T1	Pts with T1 and at least one additional HRQL follow-up were included in the analysis.	"Quite a bit" or "very much" urinary frequency was reported by 14.0%–20.9% of the pts (not statistically different from baseline). "Quite a bit" or "very much" leaking of urine was reported by 11.5% pts at 5 year, it steadily increased during follow-up
Jensen (2018), Denmark	Evaluate late bowel morbidity	Prospective EMBRACE cohort, 1176 pts with FIGO stage IB-IVA and IVB with para-aortic metastatic nodes below L1–L2 only receiving CRT 45–50 Gy in fractions of 1.8 Gy with concurrent cisplatin 40 mg/m^2 followed by image-guided BT (30–50 Gy). No comparison group	Diarrhea, constipation (QLQ-C30), abdominal cramps, difficulty controlling bowel (QLQ-CX24) T1 before tx T2 3m after T1 T3 6m after T1 T4 9m after T1 T5 1y after T1 T6 1.5y after T1 T7 2y after T1 T8 2.5y after T1 T9 3y after T1 T10 4y after T1 T11 5y after T1	Pts with T1 and at least one additional HRQL follow-up were included in the analysis.	Diarrhea significantly increased at 3m compared with baseline. Difficulty controlling bowel increased significantly at 3–5y after tx compared with baseline. Constipation and abdominal cramps declined significantly at 3m compared with baseline, with a further decline of abdominal cramps until 3–5y after tx compared with baseline
Najjari Jamal (2018), Austria	Assess manifestation pattern of lower limb edema and to identify risk factors	Prospective EMBRACE cohort, 1176 pts with FIGO stage IB-IVA and IVB with para-aortic metastatic nodes below L1–L2 only receiving CRT 45–50 Gy in fractions of 1.8 Gy with concurrent cisplatin 40 mg/m^2 followed by image-guided BT (30–50 Gy). No comparison group	Lymphedema (QLQ-CX24) T1 before tx T2 3m after T1 T3 6m after T1 T4 9m after T1 T5 1y after T1 T6 1.5y after T1 T7 2y after T1 T8 2.5y after T1 T9 3y after T1 T10 4y after T1 T11 5y after T1	Pts with T1 and at least one additional HRQL follow-up were included in the analysis.	16% reported any degree of lower limb edema at baseline, 25% at 3 months post-treatment, and 34% at 5 years post-treatment (statistical significance not reported)
Kirchheiner (2016), Austria	Determine longitudinal QoL and compare with general population	Prospective EMBRACE cohort, 744 pts with FIGO stage IB-IVA and IVB with para-aortic metastatic nodes below L1–L2 only receiving CRT 45–50 Gy in fractions of 1.8 Gy with concurrent cisplatin 40 mg/m^2 followed by image-guided BT (30–50 Gy) vs age-matched norm population	QLQ-C30/CX24*,◊; vaginal dryness and pain during intercourse (QLQ-CX24) T1 before tx T2 3m after T1 T3 6m after T1 T4 9m after T1 T5 1y after T1 T6 1.5y after T1 T7 2y after T1 T8 2.5y after T1	Pts with T1 and at least one additional HRQL follow-up were included in the analysis.	General HRQL, emotional, social and role functioning were reduced at baseline, but increased 6 months after tx. Tumor-related symptoms were increased at baseline but decreased after tx. Diarrhea, menopausal symptoms, neuropathy and sexual dysfunction remained over time. Dyspnea and lymphedema developed after tx

Table 1 (continued)

Author (year), country	Aim	Design, sample size, treatment/comparison groups	Reported PRO domains (measure), PRO assessment time-points	PRO attrition at assessment time-points; reasons for noncompliance	PRO key findings
			T9 3y after T1 T10 4y after T1		
Smet (2019), Austria	Assess manifestation of fatigue, insomnia and hot flashes after treatment	Prospective EMBRACE cohort, 1176 pts with FIGO stage IB-IVA and IVB with para-aortic metastatic nodes below L1–L2 only receiving CRT 45–50 Gy in fractions of 1.8 Gy with concurrent cisplatin 40 mg/m^2 followed by image-guided BT (30–50 Gy). No comparison group	Trouble sleeping, tiredness, weakness need to rest (QLQ-C30); sweats (QLQ-CX24) T1 before tx T2 3m after T1 T3 6m after T1 T4 9m after T1 T5 1y after T1 T6 1.5y after T1 T7 2y after T1 T8 2.5y after T1 T9 3y after T1 T10 4y after T1 T11 5y after T1	Pts with T1 and at least one additional HRQL follow-up were included in the analysis.	"Quite a bit" or "very much" weakness was reported by 21% at baseline, 13% at 3y, 19% at 5y. For tiredness, 25%, 19% and 23%, respectively and for need to rest 21%, 18% and 24%, respectively. Hot flushes increased from 12% at baseline to 28% at 3m and remained increased at 3y (20%) and 5y (19%) (statistical significance not reported).
Heijkoop (2017), Netherlands	Determine HRQL during the acute phase of radiation treatment	Prospective cohort, 138 pts with FIGO stage 1B1-IVB, treated with RT alone ($n = 12$), CRT ($n = 74$), RT with concurrent hyperthermia ($n = 26$), neoadjuvant CT followed by RT with concurrent hyperthermia ($n = 26$) vs age-matched norm population	QLQ-C30/CX24*, T1 before tx T2 week 1 of tx T3 week 2 of tx T4 week 3 of tx T5 week 4 of tx T6 week 5 of tx T7 1 week after tx T8 4 weeks after tx T9 3m after tx T10 6m after tx T11 12m after tx	Pts with T1 and at least one additional HRQL follow-up were included in the analysis.	Most symptoms had a clinically relevant moderate-to-large increase with a maximum at the end of treatment, or 1 week after treatment. Returning towards baseline at 3 months after tx. Bowel cramps and diarrhea increased in the first 3 weeks with a plateau at the 5th week of treatment
Kirchheiner (2014), Austria	Investigate the potential traumatization of treatment with brachytherapy	Prospective cohort, 50 pts with FIGO stage IB-IVA treated with CRT in 25 fractions of 1.8 Gy with weekly cisplatin followed by high-dose rate MRI-guided BT in 4 fractions of 7 Gy	Post-traumatic stress disorder and acute stress disorder (Impact of Event Scale-Revision); Pain and stress (visual analog scale); symptom experience and body image (QLQ-CX24); global HRQL, fatigue, physical functioning, emotional functioning, cognitive functioning, social functioning (QLQ-C30); anxiety and depression (HADS-D) T1 before tx T2 at end of CRT T3 1 week after BT T4 3m after BT	T1 $n = 50$ T2 $n = 50$ T3 $n = 50$ T4 $n = 49$ Death	Symptoms of post-traumatic stress syndrome were found in 30% of patients at T3, and in 41% at T4. Median stress level of BT was 8 (maximum score 10) and was significantly higher compared with undergoing RT, laparoscopic lymph node staging, or CT
Kirchheiner (2015), Austria	Evaluate HRQL before, during and after tx regarding changes over time	Prospective cohort, 50 pts with FIGO stage IB-IVA receiving CRT 45 Gy in fractions of 1.8 Gy with weekly cisplatin	QLQ-C30/CX24^ T1 before tx T2. after CRT, but before BT	Not reported, Persistent disease, peritoneal carcinosis, death	Global health status, physical and role functioning decreased during tx, whereas diarrhea, urinary frequency and nausea

Table 1 (continued)

Author (year), country	Aim	Design, sample size, treatment/comparison groups	Reported PRO domains (measure), PRO assessment time-points	PRO attrition at assessment time-points; reasons for noncompliance	PRO key findings
	and to compare with general population	40 mg/m^2 followed by image-guided BT (4 fractions with planning aim of at least 85 Gy) vs age-matched norm population	T3 1 week after BT T4 3m after BT		increased, but all returned towards baseline levels after tx. More fatigue reported after tx and pts reported hot flashes, sexual worries and limb edema
Ljuca (2011), Bosnia and Herzegovina	Evaluate vaginal and sexual function before and after tx	Prospective cohort, 35 patients with FIBO IIB receiving CRT 45 Gy in 25 fractions with concurrent cisplatin 40 mg/m^2 followed by BT 20–24 Gy in 4–6 fractions. No comparison group	Sexual function, vaginal function, pain during intercourse (QLQ-CX24) T1 before tx (recall before symptoms) T2 12m after tx	T1 $n = 35$ T2 $n = 35$	Vaginal problems and pain during intercourse decreased and after tx vaginal function improved but sexual functioning remained stable over time
Systemic therapy for advanced disease					
Cella (2010), USA	Compare HRQL after 4 cisplatin containing doublet CTs	RCT, 434 patients with stage IVB, recurrent or persistent disease receiving paclitaxel 135 mg/m^2 + cisplatin 50 mg/m^2 ($n = 103$) vs vinorelbine 30 mg/m^2 + cisplatin 50 mg/m^2 ($n = 108$) vs gemcitabine 1000 mg/m^2 + cisplatin 50 mg/m^2 ($n = 112$) vs topotecan 0.75 mg/m^2 + cisplatin 50 mg/m^2 ($n = 111$)	Trial outcome index (FACT-Cx); pain (BPI); neurotoxicity (FACT/GOG-Ntx subscale, BPI) T1 before tx T2 before cycle 2 T3 before cycle 5 T4 9m after cycle 1	T1 $n = 434$ T2 $n = 354$ T3 $n = 248$ T4 $n = 128$ Death, lost to follow-up, refusal, insufficient answer, administrative error, illness or toxicity	No difference in symptoms, functioning and global QoL between treatments at before CT cycle 2 and 5
Long (2006), USA	Compare survival, response rate, toxicities and HRQL after 3 cisplatin containing doublet CTs	RCT, 186 patients with stage IVB, recurrent or persistent disease receiving cisplatin 50 mg/m^2 ($n = 60$) vs cisplatin 50 mg/m^2 + topotecan 0.75 mg/m^2 ($n = 63$) vs cisplatin 70 mg/m^2 + methotrexate 30 mg/m^2 + vinblastine 3 mg/m^2 + doxorubicin 30 mg/m^2 ($n = 63$)	Global HRQL, cervix subscale (FACT-Cx); neurotoxicity (FACT/GOG-Nt-x); pain (BPI) T1 before tx T2 before cycle 3 T3 at week 13 T4 9m after T1	T1 $n = 180$ T2 $n = 145$ T3 $n = 99$ T4 $n = 47$ Reasons for noncompliance not reported	At baseline group, 3 pts reported worse HRQL, and more neurotoxicity, these sustained during and after tx After adjusting for baseline scores no associations with tx schedules were found
Moore (2004), USA	To compare the effect of cisplatin +/− paclitaxel on survival, response rate and HRQL	RCT, 264 patients with stage IVB, recurrent or persistent disease receiving cisplatin 50 mg/m^2 ($n = 134$) vs cisplatin 50 mg/m^2 + paclitaxel 135 mg/m^2 ($n = 130$)	Trial outcome index (FACT-Cx) T1 before tx T2 cycle 2 T3 cycle 3 T4 cycle 4	T1 $n = 247$ T2 $n = 212$ T3 $n = 171$ T4 $n = 134$ Reasons for noncompliance not reported	No difference in HRQL outcomes
McQuellon (2006), USA As Moore (2004), USA	Determine impact of cisplatin +/− paclitaxel on overall HRQL and pain	RCT, 264 patients with stage IVB, recurrent or persistent disease receiving cisplatin 50 mg/m^2 ($n = 134$) vs cisplatin 50 mg/m^2 + paclitaxel 135 mg/m^2 ($n = 130$)	Well-being scores FACT-Cx$^{\times}$ and trial outcome index (FACT-Cx); pain (BPI-SF) T1 before tx T2 before cycle 2 T3 before cycle 3 T4 before cycle 4	T1 $n = 252$ T2 $n = 216$ T3 $n = 177$ T4 $n = 139$ Reasons for noncompliance not reported	No differences in HRQL over time but lower than general population. Pain scores decreased in both groups
Monk (2005), USA As Long (2006), USA	Evaluate impact of treatment of cisplatin +/− topotecan on HRQL	RCT, 293 patients with stage IVB, recurrent or persistent disease receiving cisplatin 50 mg/m^2 ($n = 146$) vs cisplatin 50 mg/m^2 + topotecan 0.75 mg/m^2 ($n = 147$)	Global HRQL (FACT-G, UNI); cervix subscale (FACT-Cx); neurotoxicity (FACT/GOG-Ntx) T1. before tx T2 before cycle 2	T1 $n = 286$ T2 $n = 224$ T3 $n = 146$ T4 $n = 73$ Death, refusal, illness, institution error, lost contact, incomplete	No differences in HRQL expect for more hematologic toxicity in the cisplatin + topotecan arm FACT-G and BPI baseline scores were better with higher age of pts Baseline UNI positively correlated with FACT-G and negatively with BPI

Table 1 (continued)

Author (year), country	Aim	Design, sample size, treatment/comparison groups	Reported PRO domains (measure), PRO assessment time-points	PRO attrition at assessment time-points; reasons for noncompliance	PRO key findings
			T3 before cycle 5 T4 9m after T1	questionnaire, other	
Penson (2015), USA	To compare the impact of 4 different CTs on PRO	RCT,452 patients with stage IVB, recurrent or persistent disease receiving paclitaxel 135 mg/m^2 + cisplatin 50 mg/m^2 (n = 114) vs paclitaxel 135 mg/m^2 + cisplatin 50 mg/m^2 + bevacizumab 15 mg/kg (n = 115) vs paclitaxel 175 mg/m^2 + topotecan 0.75 mg/m^2 (n = 111) vs paclitaxel 175 mg/m^2 + topotecan 0.75 mg/m + bevacizumab 15 mg/kg (n = 112)	Trial outcome index (FACT-Cx); neurotoxicity (FACT/GOG-Ntx); pain (BPI-SF) T1 before tx T2 before cycle 2 T3 before cycle 5 T4 6m after cycle 1 T5 9m after cycle 1	T1 n = 436 T2 n = 372 T3 n = 322 T4 n = 245 T5 n = 193 Death, insufficient answer, illness or toxicities, pts refusal, administrative error, lost to follow-up, other	No statistical differences in HRQL and pain after CT +/− bevacizumab Less neurotoxicity in patients treated with CT + bevacizumab

BDI, Beck Depression Inventory; *BPI*, Brief Pain Inventory; *BPI-SF*, Brief Pain Inventory Short Form; *BSO*, bilateral salpingo-oophorectomy; *BT*, radiation brachytherapy; *CARES-SF*, cancer rehabilitation evaluation system short format; *CRT*, chemoradiation; *CT*, chemotherapy; *DSFI*, Derogatis Sexual Functioning Inventory; *FACT-CX*, functional assessment of cancer therapy-cervix; *FACT-G*, Functional assessment of cancer therapy-General; *FACT/GOG-NTX subscale*, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group neurotoxicity scale; *FSFI*, Female Sexual Function Index; *HADS*, Hospital Anxiety and Depression Scale; *HAM-A*, Hamilton Anxiety Scale; *HRQL*, health-related quality of life; *ICIQ-LUTS*, international consultation on incontinence questionnaire- female urinary tract symptoms; *LN*, lymph node; *LVSI*, lymphovascular space involvement; *MDASI*, MD Anderson Symptom Inventory; *m*, month; *PRO*, patient-reported outcome; *pts*, patients; *QLQ-C30*, global quality of life measurement of the European Organization For Research and Treatment of Cancer; *QLQ-CX24*, module for cervical cancer functioning and symptoms scales of the European Organization For Research and Treatment of Cancer; *RCT*, randomized controlled trial; *RH*, radical hysterectomy; *RT*, radiotherapy; *SF-12*, General Health-Related QOL; *SWD*, Satisfaction with Decision scale; *tx*, treatment; *UNI*, UNISCALE; *w*, weeks; *y*, year

*All scales of EORTC QLQ-C30 reported, these are the following: global health status, physical functioning, role functioning, emotional role functioning, cognitive role functioning, social functioning, fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties

◊ All scales of EORTC QLQ-CX24 reported, these are the following: symptoms experience, body image, sexual/vaginal functioning, lymphedema, peripheral neuropathy, menopausal symptoms, sexual worry, sexual activity, sexual enjoyment

Multiple single items and scales of QLQ-CX24 reported, these are the following: symptom experience, bowel cramps, fecal leakage, rectal bleeding, urinary frequency, dysuria, urinary leakage, difficulty voiding, pain lower back, irritated/sore vagina, vaginal discharge, abnormal blood loss, body image, attractiveness, less female due to disease, discontented, sexual/vaginal symptoms, vaginal dryness, short vagina, tight vagina, pain during intercourse, lymphedema, tingling/numbness, menopausal symptoms, sexual worry, sexual activity, sexual enjoyment

^Multiple single items and scales of QLQ-C30 and QLQ-CX24 reported, these are the following: fatigue, diarrhea, urinary frequency, nausea, appetite loss, bowel control, sexual worries, hot flashes, insomnia, irritation vagina, discharge vagina, abdominal cramps, vomiting urinary pain/burning, leakage urine, blood in stools, difficulties emptying bladder, sexual activity, vaginal bleeding, lymph edema, constipation

▪ All scales of Female Sexual Function Index reported, these are the following: desire, arousal, lubrication, orgasm, satisfaction, pain, overall score

× All well-being scores and total score of FACT-Cx are reported, these are the following: physical well-being, social/family well-being, emotional well-being, functional well-being, total FACT-G score

All scales of SF-13 reported, these are the following: physical function, role physical function, role emotional function, social function, bodily pain, mental health, vitality, general health

PROs before and following these treatment modalities (Table 1). PROs that changed over time are summarized in Fig. 3

In a prospective cohort of 187 patients treated with RH +/− bilateral salpingo-oophorectomy (BSO) +/− lymph node (LN) resection, the FACT-Cx was used to measure HRQL. Functional and physical well-being decreased at 3 months and social/family well-being at 9 months after diagnosis compared with baseline. Functional and physical well-being improved at 9 months compared with baseline [17]. In another prospective cohort of 71 patients treated with a radical trachelectomy or RH, no difference was found in overall HRQL (measured with FACT-G) between groups from baseline to 24 months after surgery. In general, well-being scores improved from baseline to 24 months after surgery, except for social/family well-being. No differences in sexual dysfunction, measured with the Female Sexual Functioning Index (FSFI), were found between groups at 24 months [15]. In

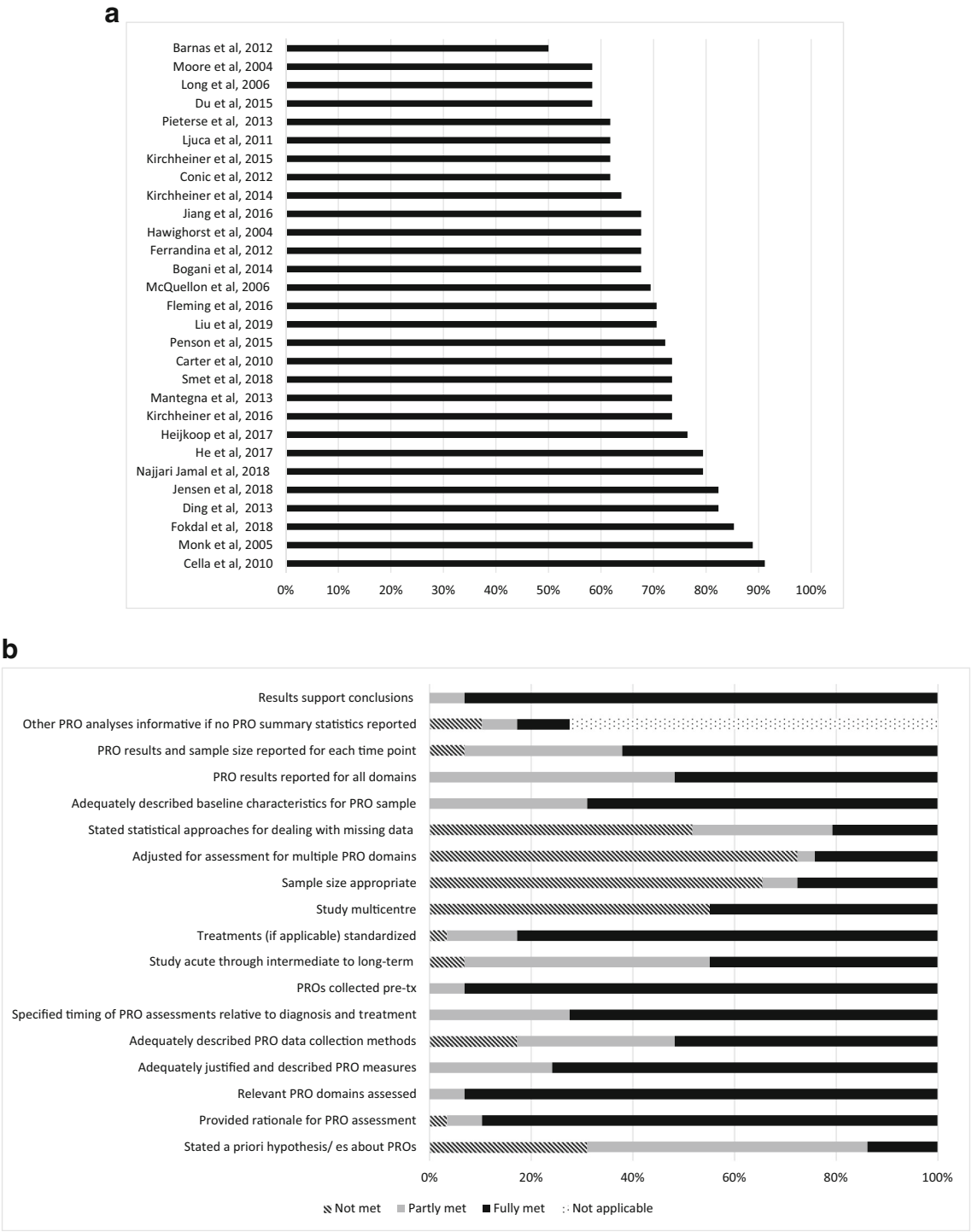

Fig. 2 **a** Quality assessment score (%) for 29 included studies, ranked by score. **b** Proportion of the 29 included papers meeting each quality criterion. Abbreviation: PRO, patient reported outcomes; tx, treatment

another prospective cohort of 39 patients treated with a radical trachelectomy, PROs were assessed with the FACT-Cx, SF-12, MDASI, and FSFI. Physical and functional well-being; social, emotional, and sexual function; and role physical scores decreased at 1 month post-surgery compared with baseline but improved by 6 months [28].

In a study of 215 patients treated with laparoscopic RH, sexual function was worse at 12 months post-treatment compared with baseline (measured with FSFI, clinical relevance not reported), more so for those treated without vaginal extension than those treated with vaginal extension [22]. In a prospective cohort of 40 patients, better lubrication and sexual

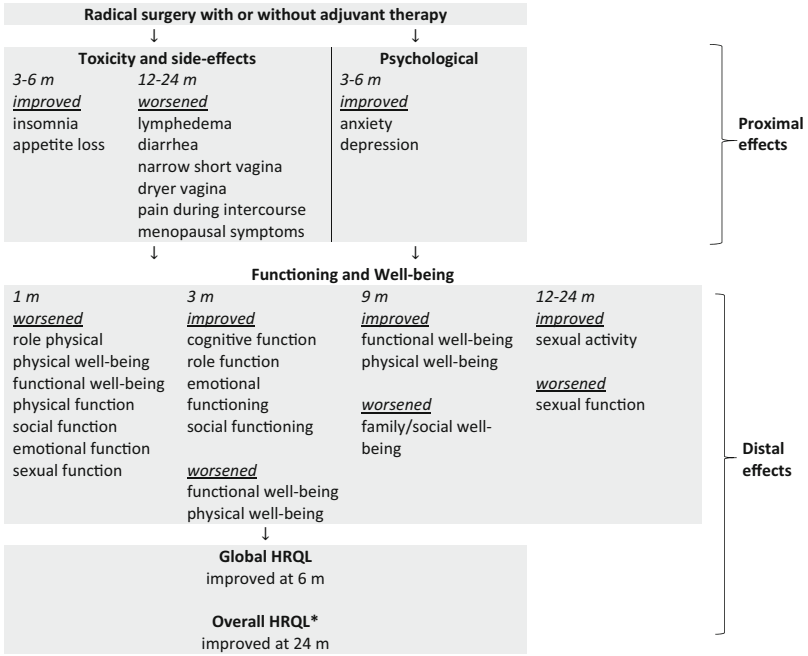

Fig. 3 Statistically significant change in PROs from baseline to follow-up assessment time-points after treatment with radical surgery with or without adjuvant therapy across 10 studies. Proximal effects, direct effects of the disease and side effects of treatment; Distal effects, consequent impacts on core functioning domains (e.g. physical, social, emotional), and in turn, global or overall HRQL. *Overall HRQL (i.e. different from global HRQL), since it is measured using the FACT-G total score
Abbreviation: m, months

satisfaction were reported at 8 months post-treatment after nerve-sparing laparoscopic RH compared with conventional laparoscopic RH; however, all patients reported more sexual symptoms at 8 months post-treatment compared with baseline [14]. In another cohort, including 1863 patients receiving laparoscopic RH or open RH, sexual dysfunction and pelvic floor dysfunction at 12 months post-treatment did not differ significantly from baseline (54.7% reported sexual dysfunction at 12 months after laparoscopic RH vs 57.1% after open RH) [26]. Subgroup analysis revealed that women who received nerve-sparing laparoscopic RH reported less sexual dysfunction and urinary incontinence than those who received open RH at 12 months post-treatment (47.1% vs 56.1% for sexual dysfunction, 28.4% vs 34.7% for urinary incontinence, respectively) [26].

In a cohort of 229 patients treated with nerve-sparing RH + LN resection or RH + LN resection, diarrhea, narrower short vagina, dry vagina with little or no lubrication during intercourse, and pain during intercourse were worse at 12 and 24 months post-treatment compared with baseline (assessed with Dutch Gynecologic Leiden Questionnaire); however, sexual activity increased from baseline (58%) to 24 months (75%). Those who also had RT reported more diarrhea, lymphedema, narrower vagina, and less sexual activity compared with non-irradiated patients at 12 months [25].

In a study of 100 patients treated with any surgery, patients reported less insomnia and appetite loss at 3 and 6 months post-treatment compared with baseline measured with the EORTC QLQ-C30 and QLQ-CX24. Diarrhea improved at 3 months post-treatment but worsened at 6 months after treatment compared with baseline (clinical relevance not reported). Cognitive, emotional, and social function improved at 3 months post-treatment compared with baseline and remained stable at 6 months post-treatment. Role function and global HRQL improved at 6 months post-treatment compared with baseline (clinical relevance not reported) [27]. One study compared 105 patients with early disease treated with RH + LN resection to 122 patients with locally advanced disease receiving chemoradiation (CRT) + RH [19, 24]. For patients with early disease, anxiety (measured with Hospital Anxiety and Depression Scale (HADS)) decreased at 3 months post-treatment compared with baseline. Mean depression scores (HADS) remained below clinical thresholds from baseline to 12 months post-treatment [19]. Lymphedema was worse at 24 months post-treatment compared with baseline (clinically relevant). Menopausal symptoms worsened at 3 months post-treatment compared with baseline and persisted at 2 years (clinically relevant). Despite this, women still reported improved sexual activity and HRQL at 24 months post-treatment compared with baseline (clinically relevant) [24].

One prospective cohort study comparing 30 patients with early disease receiving surgery + CRT and 30 patients with locally advanced disease receiving CRT to healthy controls found decreased anxiety scores in patients with early disease at 3 and 6 months compared with baseline. Yet, their anxiety scores were still higher than those of healthy controls at 6 months post-treatment [16].

Neoadjuvant therapy followed by surgery

Internationally, this treatment regime is not commonly used. Three papers assessed PROs with the EORTC QLQ-C30 and QLQ-CX24 in patients with locally advanced disease (Fig. 4). One study compared 105 early disease patients treated with

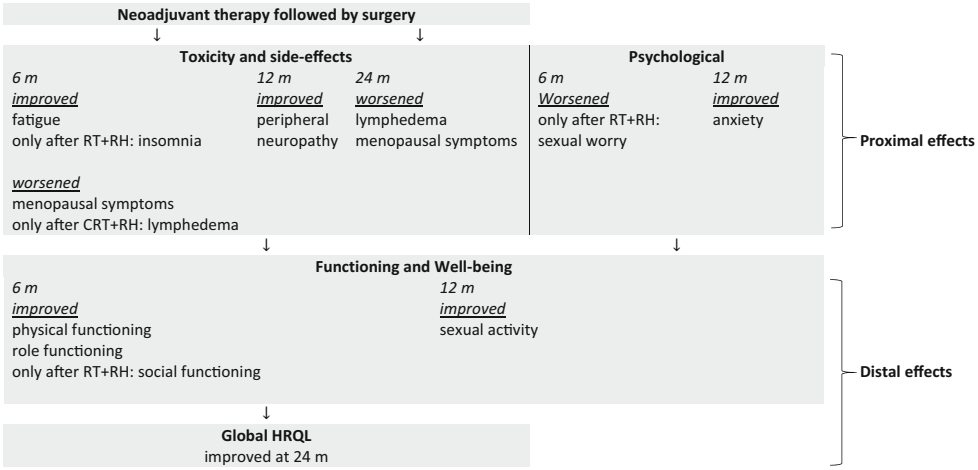

Fig. 4 Clinically relevant change in PROs from baseline to follow-up assessment time-points after treatment with neoadjuvant therapy followed by surgery across three studies. Proximal effects, direct effects of the disease and side effects of treatment; Distal effects, consequent impacts on core functioning domains (e.g. physical, social, emotional), and in turn, global or overall HRQL. Abbreviation: m, months

RH + LN resection with 122 locally advanced disease patients receiving CRT + RH [19, 24]. .A difference larger than 5% was considered clinically relevant. After treatment with CRT + RH, all patients reported worsened lymphedema and menopausal symptoms, but improved sexual activity and global HRQL at 24 months post-treatment compared with baseline [24] and a decrease in peripheral neuropathy at 12 months post-treatment compared with baseline (clinically relevant) [19]. Anxiety reduced by 24 months post-treatment compared with baseline (clinically relevant). However, a proportion of these patients (15.6%) still reported clinically elevated anxiety at 24 months post-treatment (HADS score > 11 points). Over time, no differences in depression scores were found at 24 months post-treatment compared with baseline; in fact, depression mean scores were consistently low throughout the duration of the study. Body image was worse at 24 months post-treatment compared with baseline [24].

Another prospective study with patients receiving CRT or RT followed by RH reported clinically relevant differences where at least a 10-point change in means scores was observed. Physical and role function improved at 6 months compared with baseline after CRT + RH and RT + RH, while social function improved after RT + RH. At 6 months, fatigue improved in both groups while insomnia improved only after RT + RH (all clinically relevant). Additionally, menopausal symptoms worsened in both groups at 6 months compared with baseline. Worsening of lymphedema after 6 months compared with baseline was only reported after CRT + RH. No differences were found in global HRQL or sexual function over time; however, sexual worry was clinically worse after RT + RH at 6 months compared with baseline [23].

Chemoradiation or radiotherapy

Chemoradiation is the preferred treatment for locally advanced disease, i.e., FIGO stage IB-IVa and IVb with paraaortic metastatic nodes below L1–L2 only. Eleven papers reported PROs measured at baseline and at post-treatment follow-up time-points. All studies used the EORTC QLQ-C30 and QLQ-CX24. Outcomes that changed from baseline to follow-up are summarized in Fig. 5.

Two studies reported EORTC QLQ-C30 scores during treatment, and in both, clinical relevance was interpreted using the EORTC criteria for clinically small, medium, and large mean changes over time [21, 32, 43]. .One study of 138 patients treated with RT alone versus CRT versus RT with concurrent hyperthermia or neoadjuvant CT followed by RT with concurrent hyperthermia, compared with age-matched population norms, found that most symptoms worsened (clinically moderate-to-large increase), with a maximum at the end of treatment, or 1 week after treatment. This returned towards baseline at 3 months after treatment. Bowel cramps and diarrhea increased in the first 3 weeks with a plateau at the 5th week of treatment. In the 5th week of treatment, global HRQL, role, and social and physical functioning decreased compared with baseline (small-to-moderate clinically relevant effects) but returned to baseline levels by 3 months post-treatment. Cognitive functioning decreased in the 5th week but improved by 3 months post-treatment, then decreased again at 12 months post-treatment (both decreases were small clinically relevant effects) [21]. Other changed symptoms (listed in Fig. 5) had a clinically moderate-to-large increase with a maximum at the end of treatment, or 1 week after treatment, returning to baseline levels by 3 months. In a study with 50 patients treated by CRT followed by BT, diarrhea, urinary frequency, nausea, and physical and role function worsened during treatment compared with baseline but returned to baseline levels by 3 months post-treatment (all clinically relevant). Cognitive, social, and emotional function remained stable, while lymphedema, hot flushes, and sexual worries increased during and at 3 months post-treatment compared with baseline (all clinically relevant). Global HRQL improved at 3 months post-treatment compared with baseline (not clinical relevant) but was lower than population norms [32].

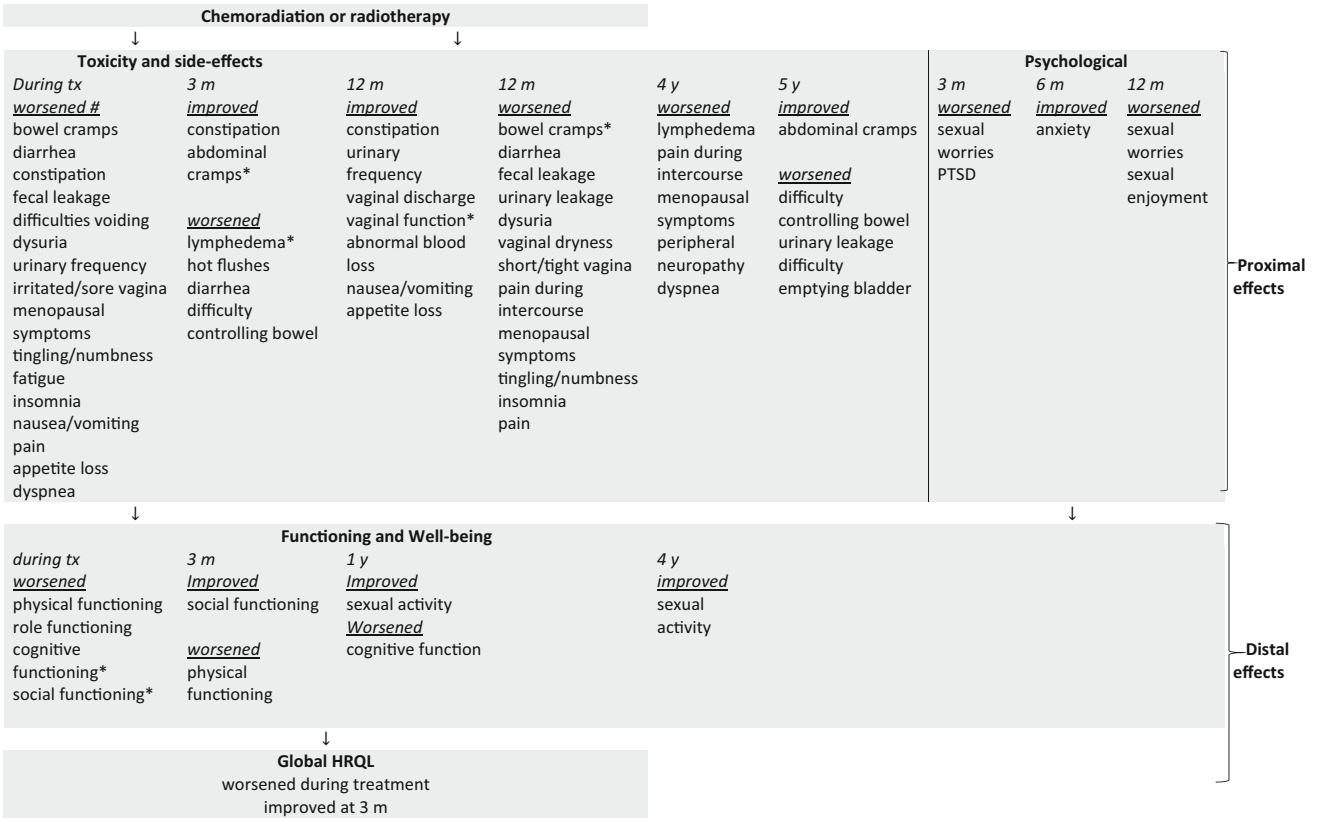

Fig. 5 Statistically significant change in PROs from baseline to follow-up assessment time-points after treatment with chemoradiation or radiotherapy across studies. Abbreviation: m, months; y, years; tx, treatment; PTSD, post-traumatic stress syndrome symptoms * Conflicting PRO results reported by studies (e.g. one found an improvement while another found a decrease in the same PRO) # most symptoms improved again within 3 months after treatment

Five papers reported on the EMBRACE cohort (Table 1), which assessed HRQL with the EORTC QLQ-C30 and QLQ-CX24 in 1416 patients treated with CRT followed by image-guided BT (30–50 Gy) [29, 30, 33, 35, 36]. Diarrhea and inability to control bowels were worse at 3 months (37% of patients and 26% of patients, respectively) compared with baseline (26% and 11% respectively); controlling bowels was still a problem for 44% of patients at 5 years post-treatment. Constipation and abdominal cramps improved at 3 months (17.4% and 36% respectively) compared with baseline (32% and 39% respectively), with abdominal cramps improving further at 5 years post-treatment (28%) [30]. Lower limb edema was reported by 16% of women at baseline compared with 34% at 5 years post-treatment [35]. At 5 years, patients reported gradual increase in urine leakage and difficulty emptying their bladder (proportion of patients reporting "very much" or "quite a bit" 11.5% and 8.9% respectively) compared with baseline (4.6% and 3.6% respectively) [29]. Hot flushes increased from baseline (12%) to 3 months (28%) and remained above baseline levels at 3 (20%) and 5 years (19%) [36]. Moreover, in 744 patients, less pain and fatigue were reported at 4 years post-treatment compared with baseline, and while statistically higher than the general population, this difference was not clinically relevant. Over time, dyspnea, peripheral neuropathy, and lymphedema gradually worsened and remained higher than baseline levels 4 years post-treatment [33].

Another three studies reported PROs after CRT followed by BT. In 35 patients, vaginal function improved 12 months post-treatment compared with baseline, but sexual function remained stable over time [34]. Four years post-treatment, an increase in sexual activity was reported by 219 patients despite more menopausal symptoms and pain during intercourse. At 3 months post-treatment, physical function decreased while social function increased compared with baseline. More pain, fatigue, appetite loss, nausea, and vomiting were reported by patients treated with CRT at 3 months post-treatment compared with CRT + BT [18]. In a cohort of 50 patients treated with CRT followed by high-dose rate MRI-guided BT, 41% of patients at 3 months after BT reported symptoms of post-traumatic stress syndrome [31].

Moreover, 30 patients treated with CRT reported less anxiety 6 months post-treatment compared with baseline, but still reported higher anxiety scores than healthy controls [16].

Ultraradical surgery

Ultraradical surgery is used as salvage therapy for relapsed disease. Only one study investigated pelvic exenteration compared with a Wertheim's procedure in 129 patients with advanced disease [20]. Four months post-treatment, all patients reported more sexual uncertainty (baseline mean score 1.60, 4-month mean score 2.37, total score range 0–6), attractiveness or self-confidence (11.44 and 10.37, respectively; total score range 0–15), and HRQL compared with baseline (0.70 and 0.75, respectively; mean values > 0.5 indicate problems). More physical and sexual problems were reported after pelvic exenteration compared with patients who underwent the Wertheim's procedure (physical mean value 1.14 and 0.66, and sexual mean value 1.61 vs 0.88, respectively; mean values > 0.5 indicate problem). Twelve months post-treatment, patients with two ostomies reported lower body image and decreased global HRQL compared with patients with one or no ostomy (mean values not provided) [20].

Systemic therapy for advanced disease

Advanced (i.e., FIGO stage IVB), recurrent, or persistent disease is commonly treated with CT. Before receiving CT, patients might have had other treatments which may also affect PROs, making it difficult to isolate the PRO impacts of CT. Six studies reported PROs measured at baseline, i.e., before beginning CT, and at follow-up times. Most regimens included cisplatin and the longest follow-up time was 9 months post-first cycle of CT. All studies used the FACT-Cx (with or without the neurotoxicity subscale) and the Brief Pain Inventory (BPI).

Two papers reported on the same randomized controlled trial including 264 patients receiving cisplatin versus cisplatin + paclitaxel [39, 41]. Pain decreased from baseline to the 4th cycle of CT, with the largest decline in the cisplatin-only arm, but all scores were below the clinical threshold of pain, while emotional well-being improved [39]. No differences in global HRQL were found over time or between treatment groups [41].

Three studies compared cisplatin + topotecan with other CT regimens. No difference in global HRQL between treatments was found [37, 38, 40]. In 434 patients treated with cisplatin and topotecan or paclitaxel or vinorelbine or gemcitabine, neurotoxic symptoms decreased from the start of the 5th CT cycle to 9 months post-CT cycle 1. Patients reported stable pain scores from baseline to 9 months post-CT cycle 1 (ranging from 2.3 to 4.0; total score range 0–10) [37]. In 293 patients treated with cisplatin +/− topotecan, neurotoxicity increased from baseline to 9 months post-baseline, with the highest increase from cycle 5 to 9 months after starting treatment. No differences in cervical cancer PROs (FACT-Cx) were observed from baseline to 9 months post-baseline between the different CT schedules [40]. In a study comparing 186 patients treated with cisplatin +/− topotecan or cisplatin + methotrexate + vinblastine + doxorubicin, no differences were found in cervical cancer PROs (FACT-Cx total score) over time or between treatment arms [38].

In a study of 452 patients treated with paclitaxel + cisplatin +/− bevacizumab or paclitaxel + topotecan +/− bevacizumab, self-reported neurotoxicity was higher at 9 months post-first CT cycle compared with baseline. However, less neurotoxic symptoms were reported after CT with bevacizumab (OR 0.58; 98.75% CI 0.17–0.98) compared with CT without bevacizumab. No differences in pain scores or global HRQL were found over time or between treatments [42].

Discussion

Twenty-nine papers were found reporting 23 studies that assessed PROs before and after treatment for cervical cancer. Studies were categorized per treatment to gain insights into differential treatment effects. Persistent long-term problems after treatments with curative intent for early or locally advanced disease included lymphedema, diarrhea, menopausal symptoms, tight and shorter vagina, and pain during intercourse. In general, this resulted in more sexual worries, but despite these symptoms and worries, sexual activity increased one or more years post-treatment. Across these curative treatments, global HRQL and core domains of HRQL (functioning and well-being) and psychological distress were impacted during treatment but improved by 3 to 6 months after treatment. After salvage therapy for relapsed disease (ultraradical surgery), patients were more sexually uncertain and had less self-confidence/perceived attractiveness and worse HRQL 4 months post-treatment compared with baseline. Among patients with advanced disease, PROs were measured after several CT regimes, most involving cisplatin. In general, pain improved during treatment or remained stable, likely representing the palliative effect of CT but this was not generally accompanied by improvements in global HRQL.

In order to interpret whether a statistically significant change in a PRO represents an impact on the patient, information about clinically meaningful differences is needed. Few studies included in this review provided information on whether statistically significant differences were clinically relevant, and none of the studies reported effect sizes. Another aid to interpreting the clinical impact of diagnosis and treatment on PROs is to compare patients' PRO results with those of an age- and sex-matched population, which was done in five studies [16, 17, 21, 32, 33], .However, the difference still needs to be above the minimally important difference to be interpreted as clinically relevant.

In order to determine differential treatment effects on PROs, studies with pooled treatment groups were excluded.

However, even within one treatment category, heterogeneity existed. For instance, among studies examining RH +/− adjuvant therapy, different adjuvant therapies were given, which is likely to have impacted on PROs differently. Similarly, different CT regimes were given to those with advanced disease, so results should be interpreted with caution. Moreover, although the size and location of the radiation field have an influence on PROs during and after treatment, these details are often not reported.

A limitation of this review is that it only included studies published in English, and most of the studies were conducted in Europe or the USA. Therefore, results may not be generalizable to patients in other continents due to differences in contextual health care factors. Furthermore, PROs may also be influenced by socio-economic status [44]. Further, increasing attrition rate over time and whether or not treatment is successful can lead to bias in PROs.

This is the first systematic review, utilizing robust methods, comparing PROs between treatment groups, during and after contemporary treatments for cervical cancer. Previous reviews reporting HRQL following treatment for cervical cancer share a number of limitations: they (1) focus on a limited range of treatment modalities (e.g., variations of RH, ovarian transposition) [45–47]; (2) investigate a specific time frame (e.g., only long-term treatment side effects) [48, 49]; (3) assess only few dimensions of HRQL [50]; and (4) include study designs that obscure differential treatment effects (i.e., results pooled across different treatment modalities) or the effect of treatment over time (e.g., limited to cross-sectional, retrospective designs) [47–52], and none of the reviews compared PROs between contemporary treatments.

The results of this review have important clinical implications. Better understanding of the impact of specific treatments for cervical cancer on HRQL of patients may facilitate patient-clinician communications about concerning issues, better prepare patients for treatment effects, facilitate shared decision-making, and assist clinicians to deliver timely, tailored supportive care interventions to address these issues.

Our review highlights the impact of treatments on core aspects of HRQL, such as social and sexual functioning, psychological well-being, and global HRQL. Treatment causes many symptoms, and while some improve within the first 3 months, other issues like lymphedema, menopausal symptoms, and sexual worries develop gradually after treatment and persist for years. Little is known about the quality of life impact of treatment for very early-stage cervical cancer on PROs, and very limited information is published about fertility sparing therapy. Future research should address these gaps.

Authors' contributions Wiltink, L.M: led data extraction, analysis, and manuscript drafting and revision

King, M: conception and design, data interpretation, and manuscript revision and approval

Müller, F: data extraction, analysis, and manuscript revision and approval

Sousa, M.S.: data extraction, analysis, and manuscript revision and approval

Tang, M: data extraction, analysis, and manuscript revision and approval

Pendlebury, A: data extraction, analysis, and manuscript revision and approval

Pittman, J: data extraction, analysis, and manuscript revision and approval

Roberts, N: data extraction, analysis, and manuscript revision and approval

Mileshkin, L: conceptualization, methodology, data interpretation, and manuscript revision and approval

Mercieca-Bebber, R: data extraction, analysis, and manuscript revision and approval

Tait, M.-A: data extraction, analysis, and manuscript revision and approval

Campbell, R: data extraction, analysis, and manuscript revision and approval

Rutherford, C: conceptualization, methodology, data interpretation, writing original draft, writing—review, editing and approval, and supervision

Compliance with ethical standards

Conflict of interest MT reports travel support from Roche, outside the submitted work. RMB reports UCB project funding, outside the submitted work. The other authors have no conflicts of interest to disclose.

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