

Assessing patient-reported quality of life outcomes in vulva cancer patients – a systematic literature review

Abstract

Objectives

Vulva cancer (VC) treatment carries a high risk of severe late effects that may have a negative impact on Quality of Life (QoL). Patient-reported outcome measures (PROMs) are increasingly used when evaluating disease- and treatment-specific effects. However, the adequacy of measures used to assess sequelae and QoL in VC remain unclear. The aim of the present study was to evaluate disease- and treatment- related effects as measured by PROMs in VC patients and to identify available VC- specific PROMs.

Methods/Materials

A systematic literature search from 1990 to 2016 was performed. The inclusion criterion was report of disease- and treatment-related effects in VC patients using PROMs in the assessment. Methodological and reporting quality was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. This systematic review was performed as part of Phase one of the development of a European Organisation for Research and Treatment of Cancer QoL questionnaire for VC patients.

Results

The search revealed 2299 relevant hits, with 11 papers extracted including a total of 535 women with VC; no randomized controlled trials were identified. The selected studies exhibited great heterogeneity in terms of PROMs use. Twenty-one different instruments assessed QoL. Most of the questionnaires were generic. Different issues (sexuality, lymphedema, body image, urinary and bowel function, vulva-specific symptoms) were reported as potentially important but the results were not systematically collected. Only one VC-specific questionnaire was identified but did not allow assessment and reporting on scale level.

Conclusions

Vulva cancer treatment is associated with considerable morbidity deteriorating QoL. To date there is no validated PROM available that provides adequate coverage of VC-related issues. The study confirms the need for a VC-specific QoL instrument with sensitive scales that allows broad cross-cultural application for use in clinical trials.

Keywords

Vulva Cancer; Quality of Life; Questionnaire; Late effects

Highlights

- Vulva cancer treatment is associated with considerable morbidity
- Data on PROMs after treatment of vulva cancer are scarce
- There is a need for PROMs that cover vulva cancer-related morbidity

Introduction

The surgical treatment of vulvar cancer (VC) has changed dramatically in the last few decades towards a less radical approach. The standard treatment for small tumors (< 4 cm) is wide local excision (WLE) combined with sentinel lymph node biopsy (SLNB) and vulvectomy with inguinal lymph node dissection (ILND) for larger tumors or sentinel node (SN) metastases [1-3]. In the case of metastatic lymph nodes in the groin, adjuvant radiation therapy (RT) improves survival [4]. Primary or neoadjuvant chemo radiation (CRT) is considered in locally advanced unresectable tumors involving the urethra or anus [5-7]. Despite the less radical surgery to the vulva and groin, multimodality treatment is mutilating and associated with a high risk of short- and long-term consequences that may interfere with the quality of life (QoL) [8-14]. Several aspects of treatment options are being investigated and issues related to radicality of surgery and radiotherapy are still unresolved. The patient perspective is important when evaluating treatment effects. Patient-reported outcome measures (PROMs) complements clinical data with the patient's perspective and there is an increasing demand for systematic implementation of PROMs in daily clinical practice and clinical trials [15]. It has therefore become important to develop PROMs that allow broad cross-cultural application.

The aim of the present study was to evaluate disease- and treatment- related effects as measured by PROMs in VC patients. Further, to identify available VC-specific PROMs with the overall purpose of assessing the need for developing a new questionnaire module which specifically focuses on the consequences of VC treatment. This systematic review was performed as part of the first of four phases in the development of a new questionnaire module for QoL assessment in VC patients, alongside the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) [16].

Material and Methods

The present systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [17]. The population included women undergoing surgery and/or CRT for primary or recurrent VC. The primary outcome was VC-specific PROMs, which were not covered by generic questionnaires. Furthermore, studies were excluded if they included fewer than 20 patients or involved patients with vulvar intraepithelial lesions (VIN) or non-vulvar gynecological cancer patients *only*, unless results for a VC subgroup were reported separately. We also excluded studies evaluating late effects after "*en bloc*" vulvectomy since this procedure has been replaced by individualized surgery. Finally, papers reporting on acute or late effects as rated by health care professionals, surgical guidelines, case reports, letters to the editor, or reviews were excluded.

Literature Search

The search was conducted by one author (LPF) in collaboration with an information specialist at Copenhagen University Library. The PubMed, Embase, the Cochrane Library, CINAHL and psychINFO was searched for articles reported in English and published since 1990 using the following search string: ("Vulvar Neoplasms") OR ((Vulva*) AND (Neoplasm* OR Cancer* OR Tumor* OR Tumour* OR Malign* OR Carcinom*)) AND (("Sexual Dysfunction"]) OR ("Quality of Life") OR "Complications" OR "Morbidity" OR "Lymphedema" OR "Body Image" OR "Proctitis" OR "Urology" OR "Groin"). In PubMed, all search terms were coined as MESH terms and as Title/ abstract ensuring the capture of articles that had not yet been indexed. No constraints related to publication type were applied. The primary search was performed on April 1st 2011 as the initial step in developing an EORTC QoL questionnaire for VC. The search was updated on February 5th 2016 for the present systematic review.

Study selection and data collection

The titles of all studies were reviewed by two authors (LPF, PTJ). If both authors agreed, studies were included/excluded. Disagreements were resolved by consensus. Reference lists of identified articles were reviewed. Subsequently, all potentially included papers were further screened by abstract by both authors. The study selection process is shown in Figure 1.

Results

Literature search and study selection

Eleven original studies were selected through a step-wise exclusion (Figure 1) from the 2299 studies initially identified in the search. No randomized controlled trials were identified. The characteristics of the included studies are shown in Table 1. The studies comprised 535 cases of VC. The patients' age ranged from 24 to 98 years. Four of the studies included patients who had recurrent disease. In general, all studies were small, with fewer than 100 patients included. The methodological quality of the studies is summarized in Table 2.

Questionnaires used

In the included studies, 21 different questionnaires were used to assess QoL (Table 2). Seven studies used cancer-specific generic questionnaires: EORTC QLQ- C30, The Functional Assessment of Cancer Therapy —

General (FACT- G) and the Utility-Based Questionnaire Cancer (UBQ-C)) [18-20]. One non- cancer specific generic QoL instrument, the Medical Outcomes Study Short Form SF Health survey – (SF-36 and SF-12), was used in three studies (Table 2) [21]. All of the included generic questionnaires have been validated and used in different patient populations and will not be further commented upon.

In seven of the studies, non-vulva-specific questionnaires were used to assess disease- and treatment-related outcomes in VC patients: the EORTC QLQ Cervical Cancer Module (CX24), the Female Sexual Function Index (FSFI), the Electronic Pelvic Floor Assessment Questionnaire (ePAC-PF), the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) and the Body Image Scale (BIS) (Table 3) [22-26]. One VC-specific QoL questionnaire was identified [27]. The Functional Assessment of Cancer Therapy Vulva (FACT-V) consists of 15 single items assessing different aspects of patients' concerns [28].

Vulva cancer-specific effects and QoL issues

Vulva-specific symptoms

Vulva-specific symptoms were assessed in two studies [27, 29] by FACT-V (Table 2 and 3). In the study by Oonk *et al.* no differences in vulva-specific symptoms (discharge/blood loss, odor, itching and pain/numbness) were identified between patients treated with SLNB compared to ILND [29]. The majority of patients (94%) included in this study received WLE. They reported on subscale level for the vulva symptoms [29] although no scale structure was given in the paper on validation of the FACT-V [27]. In the study by Janda *et al.*, patients treated for recurrent disease (eight of 97 patients) had a significantly lower FACT-V summary score ($p= 0.03$), indicating a worse QoL and a higher level of symptoms compared to patients with primary disease [27]. However, all symptoms were summarized in one scale score [27]. When assessing patients longitudinally (20 patients) within the same study, symptoms related to the vulva (discharge/bleeding, odor, itching/burning) improved at two months post-surgery as compared to baseline [27].

Sexual function (SXF)

Different aspects of SXF were evaluated in all the included studies by either self-designed non-validated questionnaires [30-33], the FSFI [34-36]; the sexual function scale, or by sexual single items of the EORTC QLQ- CX24 and the general sex life domain of the e-PAQ-PF [37, 38] (Table 2 and 3). Two studies used the FACT-V questionnaire (Table 2 and 3), but for 15 items of very different issues only summary scores were given; no scores on SXF or vaginal problems were presented [27, 29] .

Information on sexual activity (yes or no) was given in eight studies and varied between 8 and 61% with baseline data available in three studies [29-35, 37]. Only half of the sexually active women regained sexual activity within six months after surgery [30, 31]. Gunther *et al.* found decreased sexual activity in women treated with vulvectomy compared to women treated with WLE (16% vs. 43%) [32], whereas three other studies assessing changes in sexual activity over time and across surgical methods were not able to detect differences regardless of the questionnaire used (FACT-V, FSFI, EORTC QLQ- CX24) (Table 2-3) [29, 34, 37]. Two studies identified significantly decreased desire and arousal [30], and more problems with dyspareunia and ability to achieve orgasm in VC patients compared to healthy control women [31], using self-designed non-validated questionnaires (Table 2). Significant deterioration of general SXF over time before and after the treatment in VC patients was reported in two studies, assessed by self-designed non-validated questionnaire and the general sex life domain of the e-PAQ-PF (Table 2-3) [30, 39]. Furthermore, in one study adjuvant inguinal RT was negatively associated with the ability to achieve orgasm ($p= 0.01$) [34]. Factors associated with post-treatment sexual dysfunction included ILND [36], older age [30, 34-36] poor performance status, a history of depression and preoperative psychosexual difficulties [30].

Body image

Body image (BI) was assessed in five studies [27, 29, 30, 34, 37] by four questionnaires (FACT-V, EORTC QLQ CX-24, BIS and a self-designed questionnaire) (Table 2 and 3). In the study by Green *et al.*, women after vulvectomy were questioned on BI disturbances prior to surgery and three months post-treatment using a self-designed questionnaire (five items on BI) [30]. A significant worsening in BI after surgery compared to baseline was reported ($p= 0.004$) [30]. In the study by Novackova *et al.*, women had a significantly worse BI after vulvectomy and ILND as compared to women who had WLE and SLNB ($p=0.033$) at 12 months follow-up as measured by the BI sum-score of the EORTC QLQ CX24 [37]. In contrast, two studies, using the FACT-V and BIS questionnaire, did not find any difference in BI between patients treated with ILND or SLNB [29, 34].

Lymphedema

Lower limb lymphedema (LLL) was assessed in six studies [27, 29, 32, 33, 35, 37] by self-designed non-validated questionnaires [32, 33]; single item in the FACT-V [27, 29]; and Miller's Clinical Evaluation of Lymphedema and the lymphedema scale of the EORTC QLQ- CX24 [34] (Table 2 and 3).

Overall, a high incidence of LLL after ILND as compared to a healthy control group was reported (in two studies 68- 73% vs. 11%) ($p< 0.001$) [33, 35]. Additionally, leg pain and cellulitis were experienced by 53% and 23% of the patients, respectively [33]. In line with these findings, Oonk *et al.* reported that patients who

underwent ILND had more discomfort in the groin, vulva and legs ($p= 0.03$), resulting in a greater need to wear stockings ($p=0.003$) as compared to the SLNB group [29]. Oonk et al. used the FACT-V questionnaire supplemented with additional non-validated items [29]. Novackova *et al.* observed that LLL after ILND persisted with no signs of improvement at six and 12 months follow-up ($p= 0.046$ and $p= 0.028$) [37]. Moreover, LLL was significantly negatively associated with most of the EORTC QLQ- C30 domains (physical, cognitive, emotional and social function, fatigue, pain, sleep, and financial impact) ($p< 0.05$) indicating worse QoL [33, 35, 37] in addition to lower BI ($p= 0.003$) [37] and worse SXF [33].

Urinary function

Urinary function was assessed in five studies [27, 29, 35, 37, 38] by four questionnaires (FACT-V- to items and EORTC QLQ CX-24, ePAC-PF and ICIQ-SF- four items each on urinary function) (Table 2 and 3). The FACT-V and the EORTC CX-24 included urinary items in a common summary score. Novackova *et al.* did not find any difference in Symptom Experience Scale score between patients treated by extensive versus less extensive surgery using the EORTC CX24. Furthermore, no difference was observed at six and 12 months follow-up as compared to the base line level [37]. In line with this, de Melo Ferreira *et al.* did not find any difference in urinary incontinence between VC patients (28 patients) treated with vulvectomy and ILND and healthy controls [35].

Bowel function

Assessment of bowel function was included in six studies [27, 29, 32, 35, 37, 38] and four questionnaires (EORTC QLQ C30, EORTC QLQ- CX 24, FACT-V, and ePAQ-PF) were used (Table 2 and 3). In the study by Gunther *et al.*, diarrhea was more commonly reported in patients treated with vulvectomy compared to patients treated with WLE [32]. In the study by Novackova *et al.* patients who received adjuvant RT to the groin in addition to ILND (13 patients) had a higher score on the Symptom Experience Scale from the EORTC CX-24, indicating more symptoms ($p= 0.05$) at six and 12 months as compared to patients who were not given adjuvant RT (11 patients) [37]. It should be noted that reporting on scale level for the Symptom Experience Scale does not provide any knowledge regarding the origin of symptoms (urinary, bowel, pain or vulva/vaginal), and individual symptom scores were not reported [37].

Discussion

To our knowledge, this systematic review is the first to evaluate available PROMs for use in patients with VC. The review was performed to explore the need for development of a VC-specific PROM. Overall, the

literature review supports the clinical impression that treatment of VC is associated with long-term consequences within several domains of the patient's well-being. However, the conclusions are vague and probably fail to include symptoms and issues of importance for this particular patient group. The reporting of late effects exhibits great heterogeneity between studies, probably reflecting the lack of a PROM with robust and sensitive scales. Thus, the present study supports the necessity of developing a VC-specific PROM to evaluate disease- and treatment-specific domains in VC patients undergoing different treatment modalities.

Despite wide inclusion criteria, only 11 studies were identified as eligible and most of the studies used PROMs that were either generic, non-vulva cancer-specific, or developed for other cancer diagnoses. We identified only one study, which used a VC-specific PROM- FACT-V [27, 28]. The measure has no scale structure but is suggested to be summarized as one sum-score although conceptually very different domains are being assessed and the sensitivity of the measured concepts is therefore doubtful. The psychometric properties have been tested in a comparatively small sample of Australian patients only (20 patients for test-retest analyses and additionally 77 patients for the validity analyses, of whom only eight had received adjuvant radiotherapy) [27, 28]. Conceptual scale problems and the fact that reliability and validity have been assessed in only one country in a very limited population, preclude broad cross-cultural adaptation. For international multi-center studies it would be valuable if a balanced patient sample, representing different cultures and languages is included in the development and validation phases.

Several areas of potential importance to VC patients were identified. Results for SXF and BI seem to be conflicting. However, the inconsistencies may be attributed to the lack of power due to the small study size and the low percentage of sexually active patients. The well-known reluctance among elderly patients in particular to respond to intimate questions, and their minor concern about body image might explain this observation to some point [29, 34, 35, 37]. Furthermore, only half of the included studies reported data on partner status. Finally, the instruments for assessment of SXF in VC patients used in the included studies were generally non-validated, self-designed, or validated in healthy women or cervical cancer patients. None of the questionnaires assessed potential vulvo-vaginal problems such as narrowing of the vaginal entrance or swelling of the genital area that may interfere with SXF after VC treatment. The outcomes of the studies in regard to SXF were predominantly sexual activity (yes or no) and an overall female sexual dysfunction total score, which may not properly reflect vulva cancer patients' SXF. The present review indicates that despite less extensive and more individualized surgery to the vulva and groin, SXF and BI are likely to deteriorate, especially among patients who have had ILND and/or adjuvant RT. These findings need confirmation in high quality longitudinal studies including patient-reported vulva-specific outcomes.

Lower limb lymphedema is a disabling complication affecting women with VC after surgery and adjuvant RT of the groin [40-42]. In the present review the incidence of LLL in two studies was approximately 70%, which was substantially higher than in the results of previous studies reporting LLL rates between 14 and 48% [42]. It is well known that the incidence of LLL is higher when subjectively assessed using PROMs as compared to using data obtained from medical records [43]. The present review suggests that LLL has a significant negative impact on the QoL following treatment of VC and that LLL may be associated with sexual life disruption, lower physical functioning, and decrease in social activities [33, 35]. The focus in most included studies seemed to be assessment of LLL only. However, retrospective studies not involving PROMs have indicated that lymphedema of the groin and the vulva region also appear to be of great importance for the QoL of VC patients [11]. Therefore, lymphedema of the groin and the vulva should be covered in a future comprehensive assessment of lymphedema in VC patients following treatment.

Less attention has been paid to urinary, bowel and vulva symptoms following VC treatment. Though these symptoms were assessed in several included studies, the individual scores on urinary, bowel, and vulva symptoms were not provided, but rather included in the Symptom Experience Scale (EORTC CX-24) or in the Vulvar Cancer-Specific Subscale (FACT-V) [29, 37]. Several studies on gynecological cancer indicate that severe late effects related to both the small and large intestine, bladder, vagina and vulva are prevalent following pelvic RT [13, 33, 44-46]. Due to small sample sizes in the studies included in the review, the impact of CRT on the VC patient's QoL cannot be validly evaluated.

In conclusion, vulva cancer treatment is associated with considerable morbidity and deteriorating QoL. To date there is no validated PROM available that provides adequate coverage of VC-related issues. The study confirms the need for a VC-specific QoL instrument with sensitive scales that allows broad cross-cultural application. Based on the findings of this review the EORTC quality of life group is currently developing such a PROM to supplement the generic QLQ-C30 with disease- and treatment-specific QoL dimensions for use in cancer clinical trials of VC patients.

Conflict of interest statement

None declared

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Legends of Tables and Figures

Figure 1: Flowchart for study selection (PRISMA)

Table 1: Demographic and patient characteristics of the included studies

Table 2: Study characteristics

Table 3: Patient-reported quality of life instruments used to assess vulva-specific symptoms

Reference List

- [1] Covens A., Vella E.T., Kennedy E.B., Reade C.J., Jimenez W., Le T. Sentinel lymph node biopsy in vulvar cancer: Systematic review, meta-analysis and guideline recommendations. *Gynecol Oncol* ;137:351-61;2015
- [2] Levenback C.F., Ali S., Coleman R.L., Gold M.A., Fowler J.M., Judson P.L. et al. Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: a gynecologic oncology group study. *J Clin Oncol* ;30:3786-91;2012
- [3] van der Zee A.G., Oonk M.H., de Hullu J.A., Ansink A.C., Vergote I., Verheijen R.H. et al. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. *J Clin Oncol* ;26:884-9;2008
- [4] Kunos C., Simpkins F., Gibbons H., Tian C., Homesley H. Radiation therapy compared with pelvic node resection for node-positive vulvar cancer: a randomized controlled trial. *Obstet Gynecol* ;114:537-46;2009
- [5] Mak R.H., Halasz L.M., Tanaka C.K., Ancukiewicz M., Schultz D.J., Russell A.H. et al. Outcomes after radiation therapy with concurrent weekly platinum-based chemotherapy or every-3-4-week 5-fluorouracil-containing regimens for squamous cell carcinoma of the vulva. *Gynecol Oncol* ;120:101-7;2011
- [6] Moore D.H., Ali S., Koh W.J., Michael H., Barnes M.N., McCourt C.K. et al. A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: a gynecologic oncology group study. *Gynecol Oncol* ;124:529-33;2012
- [7] Tans L., Ansink A.C., van Rooij P.H., Kleijnen C., Mens J.W. The role of chemo-radiotherapy in the management of locally advanced carcinoma of the vulva: single institutional experience and review of literature. *Am J Clin Oncol* ;34:22-6;2011
- [8] Aerts L., Enzlin P., Vergote I., Verhaeghe J., Poppe W., Amant F. Sexual, psychological, and relational functioning in women after surgical treatment for vulvar malignancy: a literature review. *J Sex Med* ;9:361-71;2012
- [9] Barton D.P. The prevention and management of treatment related morbidity in vulval cancer. *Best Pract Res Clin Obstet Gynaecol* ;17:683-701;2003
- [10] de Hullu J.A., van der Zee A.G. Surgery and radiotherapy in vulvar cancer. *Crit Rev Oncol Hematol* ;60:38-58;2006
- [11] Gaarenstroom K.N., Kenter G.G., Trimbos J.B., Agous I., Amant F., Peters A.A. et al. Postoperative complications after vulvectomy and inguinofemoral lymphadenectomy using separate groin incisions. *Int J Gynecol Cancer* ;13:522-7;2003

- [12] Grigsby P.W., Russell A., Bruner D., Eifel P., Koh W.J., Spanos W. et al. Late injury of cancer therapy on the female reproductive tract. *Int J Radiat Oncol Biol Phys* ;31:1281-99;1995
- [13] Viswanathan A.N., Lee L.J., Eswara J.R., Horowitz N.S., Konstantinopoulos P.A., Mirabeau-Beale K.L. et al. Complications of pelvic radiation in patients treated for gynecologic malignancies. *Cancer* ;120:3870-83;2014
- [14] Woelber L., Kock L., Giesecking F., Petersen C., Trillsch F., Choschzick M. et al. Clinical management of primary vulvar cancer. *Eur J Cancer* ;47:2315-21;2011
- [15] Wintner L.M., Sztankay M., Aaronson N., Bottomley A., Giesinger J.M., Groenvold M. et al. The use of EORTC measures in daily clinical practice-A synopsis of a newly developed manual. *Eur J Cancer* ;68:73-81;2016
- [16] EORTC Quality of Life Group. Guideline for Developing Questionnaire Modules. <http://groups.eortc.be/qol/>. 2011. Type: Online Source
- [17] Liberati A., Altman D.G., Tetzlaff J., Mulrow C., Gotzsche P.C., Ioannidis J.P. et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* ;151:W65-W94;2009
- [18] Aaronson N.K., Ahmedzai S., Bergman B., Bullinger M., Cull A., Duez N.J. et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* ;85:365-76;1993
- [19] Cella D.F., Tulsky D.S., Gray G., Sarafian B., Linn E., Bonomi A. et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* ;11:570-9;1993
- [20] Grimison P.S., Simes R.J., Hudson H.M., Stockler M.R. Deriving a patient-based utility index from a cancer-specific quality of life questionnaire. *Value Health* ;12:800-7;2009
- [21] Ware J.E., Jr. SF-36 health survey update. *Spine (Phila Pa 1976)* ;25:3130-9;2000
- [22] Greimel E.R., Kuljanic V.K., Waldenstrom A.C., Duric V.M., Jensen P.T., Singer S. et al. The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life questionnaire cervical cancer module: EORTC QLQ-CX24. *Cancer* ;107:1812-22;2006
- [23] Rosen R., Brown C., Heiman J., Leiblum S., Meston C., Shabsigh R. et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* ;26:191-208;2000
- [24] Jones G.L., Radley S.C., Lumb J., Jha S. Electronic pelvic floor symptoms assessment: tests of data quality of ePAQ-PF. *Int Urogynecol J Pelvic Floor Dysfunct* ;19:1337-47;2008
- [25] Hopwood P., Fletcher I., Lee A., Al G.S. A body image scale for use with cancer patients. *Eur J Cancer* ;37:189-97;2001
- [26] Avery K., Donovan J., Peters T.J., Shaw C., Gotoh M., Abrams P. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. *Neurourol Urodyn* ;23:322-30;2004
- [27] Janda M., Obermair A., Cella D., Perrin L.C., Nicklin J.L., Ward B.G. et al. The functional assessment of cancer-vulvar: reliability and validity. *Gynecol Oncol* ;97:568-75;2005

- [28] Janda M., Obermair A., Cella D., Crandon A.J., Trimmel M. Vulvar cancer patients' quality of life: a qualitative assessment. *Int J Gynecol Cancer* ;14:875-81;2004
- [29] Oonk M.H., van Os M.A., de Bock G.H., de Hullu J.A., Ansink A.C., van der Zee A.G. A comparison of quality of life between vulvar cancer patients after sentinel lymph node procedure only and inguinofemoral lymphadenectomy. *Gynecol Oncol* ;113:301-5;2009
- [30] Green M.S., Naumann R.W., Elliot M., Hall J.B., Higgins R.V., Grigsby J.H. Sexual dysfunction following vulvectomy. *Gynecol Oncol* ;77:73-7;2000
- [31] Aerts L., Enzlin P., Verhaeghe J., Vergote I., Amant F. Psychologic, relational, and sexual functioning in women after surgical treatment of vulvar malignancy: a prospective controlled study. *Int J Gynecol Cancer* ;24:372-80;2014
- [32] Gunther V., Malchow B., Schubert M., Andresen L., Jochens A., Jonat W. et al. Impact of radical operative treatment on the quality of life in women with vulvar cancer--a retrospective study. *Eur J Surg Oncol* ;40:875-82;2014
- [33] Farrell R., Gebiski V., Hacker N.F. Quality of life after complete lymphadenectomy for vulvar cancer: do women prefer sentinel lymph node biopsy? *Int J Gynecol Cancer* ;24:813-9;2014
- [34] Hazewinkel M.H., Laan E.T., Sprangers M.A., Fons G., Burger M.P., Roovers J.P. Long-term sexual function in survivors of vulvar cancer: a cross-sectional study. *Gynecol Oncol* ;126:87-92;2012
- [35] de Melo Ferreira A.P., de Figueiredo E.M., Lima R.A., Candido E.B., de Castro Monteiro M.V., de Figueiredo Franco T.M. et al. Quality of life in women with vulvar cancer submitted to surgical treatment: a comparative study. *Eur J Obstet Gynecol Reprod Biol* ;165:91-5;2012
- [36] Forner D.M., Dakhil R., Lampe B. Quality of life and sexual function after surgery in early stage vulvar cancer. *Eur J Surg Oncol* ;41:40-5;2015
- [37] Novackova M., Halaska M.J., Robova H., Mala I., Pluta M., Chmel R. et al. A prospective study in the evaluation of quality of life after vulvar cancer surgery. *Int J Gynecol Cancer* ;25:166-73;2015
- [38] Jones G.L., Jacques R.M., Thompson J., Wood H.J., Hughes J., Ledger W. et al. The impact of surgery for vulval cancer upon health-related quality of life and pelvic floor outcomes during the first year of treatment: a longitudinal, mixed methods study. *Psychooncology* ;2015
- [39] Jones G.L., Ledger W., Bonnett T.J., Radley S., Parkinson N., Kennedy S.H. The impact of treatment for gynecological cancer on health-related quality of life (HRQoL): a systematic review. *Am J Obstet Gynecol* ;194:26-42;2006
- [40] Beesley V., Janda M., Eakin E., Obermair A., Battistutta D. Lymphedema after gynecological cancer treatment : prevalence, correlates, and supportive care needs. *Cancer* ;109:2607-14;2007
- [41] Ryan M., Stainton M.C., Slaytor E.K., Jacconelli C., Watts S., Mackenzie P. Aetiology and prevalence of lower limb lymphoedema following treatment for gynaecological cancer. *Aust N Z J Obstet Gynaecol* ;43:148-51;2003
- [42] Wills A., Obermair A. A review of complications associated with the surgical treatment of vulvar cancer. *Gynecol Oncol* ;131:467-79;2013

- [43] Beesley V.L., Rowlands I.J., Hayes S.C., Janda M., O'Rourke P., Marquart L. et al. Incidence, risk factors and estimates of a woman's risk of developing secondary lower limb lymphedema and lymphedema-specific supportive care needs in women treated for endometrial cancer. *Gynecol Oncol* ;136:87-93;2015
- [44] Abbott-Anderson K., Kwekkeboom K.L. A systematic review of sexual concerns reported by gynecological cancer survivors. *Gynecol Oncol* ;124:477-89;2012
- [45] Mirabeau-Beale K.L., Viswanathan A.N. Quality of life (QOL) in women treated for gynecologic malignancies with radiation therapy: a literature review of patient-reported outcomes. *Gynecol Oncol* ;134:403-9;2014
- [46] Barraclough L.H., Routledge J.A., Farnell D.J., Burns M.P., Swindell R., Livsey J.E. et al. Prospective analysis of patient-reported late toxicity following pelvic radiotherapy for gynaecological cancer. *Radiother Oncol* ;103:327-32;2012