Diplomarbeit

Consequences of vulvar diseases and therapy on sexuality and quality of life in women

Eingereicht von **Katrin Filler**

Zur Erlangung des akademischen Grades
Doktorin der gesamten Heilkunde
(Dr.in med.univ.)

an der
Medizinischen Universität Graz

Ausgeführt an der
klinischen Abteilung für Gynäkologie und Geburtshilfe

Unter der Anleitung von
Ass.-Prof.in Priv.-Doz.in Dr.in Gerda Trutnovsky

Graz, 05.07.2018

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 05.07.2018 Katrin Filler eh

Acknowledgements

At this point, I would like to thank the supervisor of my diploma thesis Assoz.-Prof.in Priv.-Doz.in Dr.in med.univ. Gerda Trutnovsky for providing me the topic of my diploma thesis, her patience and her support during the entire process of writing my thesis.

Furthermore, I would like to thank my sister Doctor of Philosophy Student Serina Filler for her advises, support and encouragement during the whole time of my study.

Another thank you must be given out to my mother and father, for always being there for me and the financial support during my entire study time.

Additionally, I would like to thank my friends, who always motivated and encouraged me to achieve my goals.

Table of contents

Abbreviations List

BP ..... *bodily pain*

cGY ..... *centrigray*

DLQI ..... *Dermatology Life Quality Index*

DVIN ..... *differentiated type of vulvar intraepithelial lesion*

EORTC-QLQ30 ..... *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30*

FACT-V ..... *Functional Assessent of Cancer Therapy-Vulvar*

FSDS ..... *Female Sexual Distress Scale*

GH ..... *general health*

HPV ..... *human papillomavirus*

HSIL ..... *high-grade squamous intraepithelial lesion*

IFL ..... *inguinofemoral lymphadenectomy*

LSIL ..... *low-grade squamous intraepithelial lesion*

MCS ..... *Mental Component Scale*

MH ..... *mental health*

PCS ..... *Physical Component Scale*

PF ..... *physical functioning*

RE ..... *role-emotinal*

RP ..... *role-physical*

SAQ ..... *Sexual Activity Questionnaire*

SCC ..... *squamous cell carcinoma*

SF ..... *social functioning*

SF-12 ..... *Short Form-12 Health Survey*

SF-36 ..... *Short Form-36 Health Survey*

UV-1A *Ultraviolet-A1*

UVB ..... *Ultraviolet B*

VIN ..... *Vulvar Intraepithelial Neoplasia*

VLP ..... *Vulvar Lichen Planus*

VLS ..... *Vulvar Lichen Sclerosus*

VLSC ..... *Vulvar Lichen Simplex Chronicus*

VT ..... *vitality*

Table of Figures

Table of tables

Abstract

Introduction: There is evidence that vulvar diseases, like dermatoses (vulvar lichen sclerosus, vulvar lichen planus, vulvar lichen simplex chronicus), vulvar intraepithelial neoplasia and vulvar cancer reveal a strong impact on a women's life. This thesis aims to give an overview on how vulvar disease affect the female sexuality and quality of life.

Methods: A PubMed literature search on questionnaires concerning sexuality and quality of life in women with a vulvar disease was performed. Questionnaires were analysed and the results were compared.

Results: 3 questionnaires on sexuality and 6 questionnaires on quality of life of women with a vulvar disease were included. Their results and their usage for either conservative or surgical treatment were evaluated. A negative impact of vulvar diseases on sexuality and quality of life, yet a varying effect of each disease on different aspects of sexuality and quality of life, was found.

Discussion: Although all questionnaires revealed an impact of vulvar diseases on sexuality and quality of life, an exact comparison was often not possible, due to questionnaires evaluating different aspects of sexuality and quality of life. A valid tool for measuring sexuality, including masturbation, and quality of life in women suffering from a vulvar disease would be necessary for comparison and evaluation of the influence of vulvar diseases.

Zusammenfassung

Einleitung: Vulväre Erkrankungen, wie Dermatosen (vulvärer Lichen Sklerosus, vulvärer Lichen Planus, vulvärer Lichen Simplex Chronicus), vulväre intraepitheliale Neoplasien und Vulvakarzinom besitzen einen starken Einfluss auf das Leben von betroffenen Frauen. In dieser Diplomarbeit soll ein Überblick über das Ausmaß an Auswirkungen von vulvären Erkrankungen auf die weibliche Sexualität und Lebensqualität gegeben werden.

Methoden: Eine PubMed Literaturrecherche, welche Fragebögen zum Thema Sexualität und Lebensqualität bei Frauen mit vulvären Erkrankungen beinhaltete, wurde durchgeführt. Die Fragebögen wurden analysiert und die Ergebnisse verglichen.

Ergebnisse: 3 Fragebögen zum Thema Sexualität und 6 Fragebögen zum Thema Lebensqualität bei Frauen mit vulvären Erkrankungen wurden inkludiert. Deren Ergebnisse und deren Gebrauch für konservative oder chirurgische Therapien wurden beschrieben. Ein negativer Effekt von vulvären Erkrankungen, welcher jedoch in verschiedenen Aspekten von Sexualität und Lebensqualität je nach Art der vulvären Erkrankung variierte, konnte festgestellt werden.

Diskussion: Obwohl alle Fragebögen den Einfluss von vulvären Erkrankungen auf die weibliche Sexualität und Lebensqualität widerspiegelten, war der direkte Vergleich der Fragebögen oft nicht möglich, da die einzelnen Fragebögen unterschiedliche Aspekte von Sexualität und Lebensqualität erforschten. Ein validierter Fragebogen zur Messung der Sexualität, welcher Masturbation einschließt, und Lebensqualität von Frauen, welche an einer vulvären Erkrankung leiden, wäre notwendig, um einen direkten Vergleich zu ermöglichen und den Einfluss von vulvären Erkrankungen auf das Leben einer Frau zu erschließen.

Introduction

This master thesis should give an overview of vulvar diseases and their influence on the sexuality and quality of life in women, to prove the thesis, if quality of life and sexuality in women are affected by the presence of a vulvar disease. Assessment will include the following diseases: Dermatoses (Vulvar Lichen Sclerosus, Vulvar Lichen planus, Lichen simplex chronicus), vulvar intraepithelial neoplasia and vulvar cancer.

The Vulva

The female genitalia can be divided into the internal and external genitalia. The internal genitalia include the vagina, the uterus, the two Fallopian tubes and the ovaries. The Hymen separates the internal from the external genitalia. The external genitalia consist of the vulva, which is build up by the mons pubis, the labia majora, the labia minora, the vestibulum vaginae and the clitoris.

The mons pubis, a fatty tissue, lays on the pubic bone. During puberty, hair growth gets induced, forming a horizontal line, due to lack of testosterone. This line counts as a secondary gender feature of women.

The labia majora, two bulges, build up by a fatty connective tissue, unite above the prepuce clitoridis in the commisura anterior and in front of the frenulum in the commisura posterior. They contain hair follicles, sebaceous and sweat glands. They mainly consist of a keratinized squamous epithelium.

The labia minora consist of a very fatty connective tissue, which is rich in nerves and blood vessels and elastic fibers. The external sides contain sebaceous and sweat glands and is covered by a slightly keratinized squamous epithelium, while the internal sides are covered by an unkeratinized squamous epithelium. In the front, the labia minora join in the frenula clitoridis and merge in the clitoris and join in the prepuce clitoridis. In the back, they merge in the frenulum labiorum pudendi.

The vestibulum vaginae lies between the labia minor, the hymen and the fossa vestibuli vaginae. It includes the ostium urethrae externum, the skene glands and the excretory ducts of the bartholin glands and the glandulae vestibulares minores.

The clitoris consists of two strand of an erectile tissue that connect in the corpus clitoridis. It has a rich nerve supply. The whole vulva changes with age, meaning

that the decrease of female hormons over the years or a performed ovariectomy can induce atrophy of the involved tissue.(6, 7)

Over the years, media and internet have strongly influenced women´s view on their own genital region, especially the vulva. Female genital surgery is becoming increasingly conventional for a variety of reasons. As an example, it is still controversial, whether a labia minora enlargement or hypertrophy is just a variability of the female anatomy or not. It may lead to aesthetic, functional and psychosocial problems, justifying the need for surgical intervention.
The need to have a “normal” vulva, even though “normal” is very subjective, is becoming stronger, mainly caused by a media created image of the “perfect” vulva.(8) In contrast to healthy women being affected by this and are often having a high level of suffering, women with a vulvar disease are frequently in need of medical procedures, like surgery, which can change the appearance of the vulva. Additionally, the disease itself may lead to optical changes of the vulvar architecture, which can lead to sexual dysfunction and a reduction of quality of life.(9) In this master thesis, different studies will be compared and evaluated to determine the impact of vulvar diseases and their respected therapies on women’s sexuality and quality of life.

Dermatoses: Vulvar Lichen Sclerosus (VLS)

Characteristics

VLS, commonly appearing in women and children, especially affects the external genitalia, often resulting in significant vulvar disfiguration.(10)
Although the exact prevalence is not known, it is believed, that it ranges somewhere between 0.1-1.7%.(5) It is mostly diagnosed in postmenopausal women, although the onset in 50% of the women is in a premenopausal stage, reasoning in an approximately 5 year delay of the diagnosis.(11)
Due to its high potential for atrophy and destructive scarring, it causes a loss of the anogenital structure. This destruction

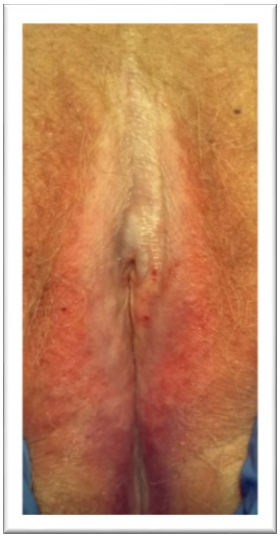

Figure 1 Vulvar Lichen Sclerosus (1)

can lead to a fusion of the labia minora, tightening of the vaginal introitus and a phimosis of the clitoral prepuce.(12, 13) The epithelium can be presented with a thin and wrinkly surface, induced by the atrophy. Furthermore, the epithelium can be hypopigmented, appearing white, as a consequence of hyperkeratosis, sometimes also with erosions and fissures, sclerosis or even dot-like bleedings underneath the epithelium(ecchymosis).(11, 13)

Pathogenesis

Research has shown, that VLS is associated with autoimmune mechanisms, often appearing simultaneously with autoimmune diseases like autoimmune thyroiditis, alopecia areata, vitiligo and pernicious anemia.(14, 15)

Potential risk factors are trauma, induced by scratching of the involved anogenital area, surgery, sexual offence during childhood and friction through tight clothing.

Infections with HPV (human papilloma virus), Hepatitis C, Spirochetes, Epstein-Barr Virus and *Borrelia Burgdorferi* are still playing a controversial role in the development of LS.(11, 15, 16)

Symptoms

The clinical symptoms of VLS are vulvar pain and soreness, itching and burning, dysuria, such as impeded urination and irritation. Moreover dyspareunia, which can lead to an emotional distress such as sexual dysfunction has been described in assosciation with VLS.(11-13) These symptoms typically develop in a later stage of the disease, first, only a slight redness is shown.(11)

Diagnosis

Considering the numerous symptoms and unspecific appearance, the diagnosis of VLS remains difficult. A persisting itch combined with the hypopigmentation of the skin can lead to the diagnosis VLS. A biopsy can be performed on older white alterations, that appear healthy and do not contain ulcerations or fissures. Newly emerged lesions are often unspecific. Normally, the biopsy is taken under local anesthesia. In case of different histological and clinical findings, the process of examination and biopsy must be repeated to provide an accurate diagnosis.(11)

Prognosis

If VLS appears in girls, a spontaneous remission can be expected in 25% of cases. Often, a decreased disease activity during puberty is found. Full remission during puberty, however is not certain. Usually, the activity of VLS increases again during adulthood. All in all, VLS is a chronic disease, which in itself is premalignant and increases the risk of vulvar cancer.(11, 17)

Therapy

The first line therapy of VLS contains topical steroids that should be applied on the affected skin for three months. After those months, the use of topical steroids can still be continued in a non-active phase of VLS.(11, 18) There are some alternatives to steroid therapy. As an example, topical calcineurin inhibitors may be used. They are mainly indicated, if treatment with topical steroids was ineffective or if topical steroids are contraindicated(15). Further, retinoids, photodynamic therapy and also emollients are being used as an alternative treatment to the topical steroids.(15) Research also showed, that in an early stage of the disease, the appliance of avocado and soya bean extract can lead to a relief of the itching and dryness and help to restore the mucosal texture.(19) Surgery is only performed, if there are complications related to LS.(17)

Dermatoses: Vulvar Lichen Planus (VLP)

Characteristics

Vulvar Lichen Planus primarily occurs in women during their 5th and 6th decade in life. In contrast to VLS, the erosive type of VLP does not affect children, which makes it simpler to differentiate from other vulvar diseases. In about 57% of patients, suffering from oral Lichen Planus, vulvar lichen planus occurs concurrently. Also, about 68% of patients suffering from erosive VLP additionally suffer from oral Lichen Planus.(5) There are three different clinical types of VLP, including an

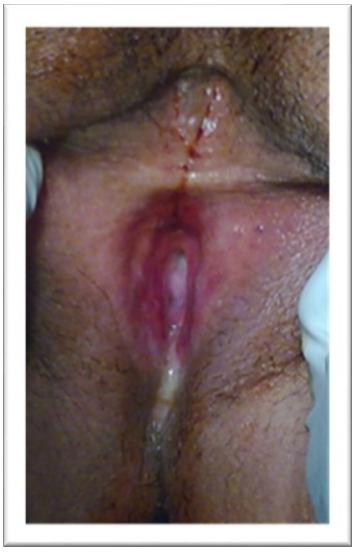

Figure 2 Vulvar Lichen Planus (2)

erosive, a papulosquamous, a and a hypertrophic form. (5)

The prevalent variant is the erosive type, which is complex to treat and often results in scarring. It can appear as a subtype involving the mouth, vaginal and vulvar region and is then declared vulvar-vaginal gingival syndrome. VLP can also lead to a loss of the vulvar architecture.

The papulosquamous type typically appears with papules and/or plaques, often with Wickham striae (a reticulated white hyperkeratosis overlying the lesions). (5, 11, 20)

Hypertrophic VLP displays with bulky plaques, which may resemble malignancy.

The erosive type presents with an eroded mucosal surface, enclosed by a red or purple epithelium, occasionally with Wickham striae.(20)

Pathogenesis

Like VLS, VLP is also associated to autoimmune diseases like thyroid diseases, alopezia areata and celiac disease. Erosive VLP often simultaneously occurs with contact dermatitis, candidiasis and atrophic vaginitis. It is still controversial, if there is a correlation between VLP and HCV (Hepatitis C Virus). While the exact emergence of VLP is still unclear, it is believed, that the disease is mediated by T-cells, leading to a destruction of the stratum basale and keratinocytes, which is specific for VLP. (5)

Symptoms

The main symptom of VLP is pruritus. Additionally, pain, dysuria and dyspareunia can occur, though they are mainly caused by the erosive type of VLP. If the vagina is involved as well, patients often suffer from discharge. Nonetheless, VLP can also be asymptomatic. (5)

Diagnosis

Even though it is often a clinical diagnosis, especially for the non-erosive VLP, plenty cases need a biopsy for a sure declaration of VLP.

The erosive type of VLP needs a biopsy performed on the outline of the lesion to rule out diseases like pemphigus vulgaris, bullous pemphigoid and mucus membrane pemphigoid. A biopsy performed on the hypertrophic type of VLP can

rule out a squamous cell carcinoma, which may have a similar macroscopic appearance.(5)

Prognosis

The effectiveness of treatment generally depends on the type of VLP. While the papulosquamous and the hypertrophic type often respond well, the erosive type is more difficult to treat and can lead to scarring or even a full stenosis of the vulva. (5, 20)

Therapy

Equally to VLS, VLP is generally treated with topical corticosteroids. Second line therapy involves calcineurin inhibitors. If there is a severe clinical picture, including an extensive mucosal involvement, corticosteroids will be given orally. Additionally, Metronidazol and Rituximab can be prescribed. Furthermore, photodynamic therapy can be performed. Surgery is only indicated, if labial adhesions, secondary to VLP, are present.(5)

Dermatoses: Vulvar Lichen Simplex Chronicus (VLSC)

Characteristics

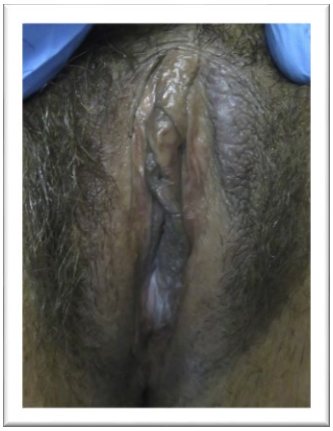

Figure 3 Vulvar Lichen Simplex Chronicus (5)

Vulvar Lichen Simplex Chronicus primarily affects adults, but it can also appear during childhood. The exact prevalence of VLSC is still unknown but is believed to be 0,5% in developed countries.(5, 20) It often arises though, when patients suffer from atopic dermatitis or other dermatological diseases. It frequently occurs simultaneously with psoriasis, LS, candidiasis, neoplasia and tinea cruris.(5, 21)

Patients experience a ceaseless itch, typically followed by massive scratching. The irritation of the skin leads to further itching and scratching, which results in a thickening of the skin.(5) The disease can be triggered by sweat and heat, such as an excess dryness, sometimes caused by skincare products. Also, thyroid disease, uraemia and liver disease can be the

origin of the itch and have to be ruled out. Very rarely, the itch is triggered neuropathically secondary to other conditions such as diabetes, postherpetic neuralgia or compression of the sacral spine. (20, 21) Further, psychological stress, like an obsessive compulsive disorder, anxiety or depression can be the cause of VLSC.(20)

Lichenoid plaques, mostly on the labia majora, can be found during physical examination. Occasionally, those plaques are also found on the labia minora or perianal region. Sometimes excoriations are present. Also, hyper-/hypopigmentation, scaling or erythema can appear.(5)

Pathogenesis

It most commonly appears in patients already suffering from atopic dermatitis, which is then named the primary type of VLSC. Furthermore, it can develop secondary to other dermatological diseases, including yeast or fungal infections, eczema, psoriasis or VLS (secondary VLSC).(5, 20)

Symptoms

The main symptom of VLSC is the intense pruritus. Some patients even suffer from sleep deprivation due to the permanent itch.(5) The permanent scratching can lead to a harm of the skin, often resulting in fissures, which can lead to secondary infection of the area with bacterial or fungal organisms.(14) Dyspareunia can also be a result, due to the permanent manipulation of the vulvar area, caused by the itch-scratch-itch-cycle. The hair in the affected area can be broken, as a result of the permanent rubbing.(20)

Diagnosis

Physical Examination and a good anamnesis are mainly leading to the diagnosis. Nonetheless, a biopsy can help to ensure the diagnosis.(5, 20)

Prognosis

VLSC is a chronic disease. Even when treatment is provided, VLSC has a high recurrence rate. Many patients need ongoing treatment for many years.(5)

Therapy

The probably most important role in the therapy of VLSC is good patient education about the illness itself and its known trigger factors. If possible, with a reduction of triggers, symptoms and also scarring can be prevented.(5) After trigger elimination, the cycle of the permanent itching and scratching needs to be stopped. It can help to give oral antihistamines and/or topical steroids. After one month of therapy, patients should be re-examined, to assess clinical response. If the itch remains, there might be a psychological background needing further investigation Psychological problems can be the root or the effect of VLSC. Saline soaks, lubricants and unperfumed creams should be used to improve the skin barrier function. Surgery is rarely performed and only indicated, if the labia majora is severely affected by lichenification. The resected segments need to undergo histopathological examination, to rule out other causes of the observed clinical picture.(14, 20) Furthermore, calcineurin inhibitors may be used off-label. Silk fabric underwear is also believed to help, such as UVB therapy.(20)

Vulvar Intraepithelial Neoplasia(VIN)

Characteristics

VIN is a chronic condition of vulva, involving the squamous epithelium, where dysplastic changes appear.(20) To classify the variety of VINs, the 2015 ISSVD decided on three main types.

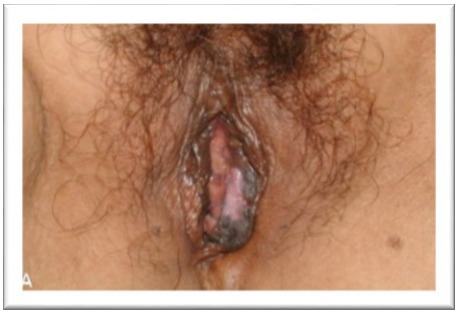

Figure 4 Vulvar Intraepithelial Neoplasia (4)

LSIL - low-grade squamous intraepithelial lesion, HSIL – high-grade squamous intraepithelial lesion, which used to be the VIN usual type and DVIN – differentiated type of vulvar intraepithelial lesion.(22-24) LSIL and HSIL are both associated with chronic HPV infection. The LSIL presents as a flat condyloma. HSIL has a great variability, which includes multifocal erythematous, whitish or even pigmented plaques. The DVIN lesions are hard to differentiate from lesions that already persist, due to VLS. They appear more unifocal than HSIL lesions, are mostly red or grey-white, often with an impaired surface or even ulceration.(20) There is an increase in the

appearing of HSIL that might be caused by the accumulation of HPV infections in the anogenital area and/or the more frequently use of vulvar biopsy, which eases the detection of HSIL. An immuno-compromised state and smoking are risk factors and it has the highest peak between the ages of 35 and 49. In all cases of VIN, 95-98% are LSIL or HSIL.(20, 23) DVIN mainly occurs in elderly women and has a higher malignant potential than HSIL.(20)

Pathogenesis

LSIL and HSIL mainly emerge due to a persisting HPV-infection.(20, 24)

DVIN is associated with chronic inflammatory diseases, such as VLS and VLSC.(22-24) In DVIN, mutations of the p53 gene can lead to a development of a vulvar SCC.(25) Mazellier et al.(23) showed, that the coexistence of HSIL and DVIN is possible and that the most commonly appearing HPV type in VIN is HPV 16.(23) The HPV types HPV 18, HPV 33 and HPV 56 are also often present.(23, 26)

Symptoms

Although VIN can present asymptomatically, it can also lead to itching, burning, irritation, dyspareunia and discomfort, which lead to a great morbidity. Yet, the highest concern is the progression of a VIN to vulvar cancer. (20, 27)

Diagnosis

The diagnosis of VIN is typically made through histopathological examination of vulvar biopsy specimens .(27) If the appearance is multifocal, it is important to biopsy every lesion. Histopathologically, HSIL appears as a disorganized squamous epithelium, harboring a high rate of mitotic figures, such as cytological atypia and a high nuclear/cytoplasmic ratio. DVIN can appear with hyper-,para- or dyskeratosis, hyperplasia, basal cell atypia, an maturation and anastomosis and/or elongation of the rete ridges, prominent nucleoli and atypical mitosis in the basal layer .(20)

Prognosis

Spontaneous regression rarely appears, although it has been reported in some

cases.(20) DVIN only occurs in healthy, immunocompetent women, while the risk of developing vulvar cancer is higher in women with a concurrent immunosuppression. The 2- or 4-valent HPV vaccination might prevent women from developing HPV 16 or HPV 18 related VIN. Furthermore, the newest invention of the 9-valent vaccine could also prevent against HPV33, HPV 31, HPV 58, HPV 52 and HPV 45 related VIN additionally to the HPV 16 and HPV 18 related types of diseases. Women suffering from VLS should be regularly examined to recognize a DVIN in an early stage.(26)

Therapy

Surgery is the main therapy for VIN, even though there is still a high recurrence rate and the whole procedure has a huge negative impact on the female sexuality and quality of life. For HSIL, a surgical cold knife excision, which can include a wide local excision or a vulvectomy, an ablation with a CO2 Laser, a combination of an excision and ablation, a loop electrosurgical procedure, imiquimod cream, cidofovir and 5-fluorouracil can be used as treatment. Further, HSIL can be observed without any treatment, to see, if a spontaneous regression might occur. DVIN is mainly treated with a surgical cold knife excision. (20, 26, 27) Long-term follow-up after a chosen therapy is mandatory, due to the high risk of recurrence. Women with HSIL should also be accurately examined, to rule out the presence of a concurrent HPV related dysplasia in the vaginal, cervical and intra-anal region.(26)

Vulvar Cancer

Characteristics

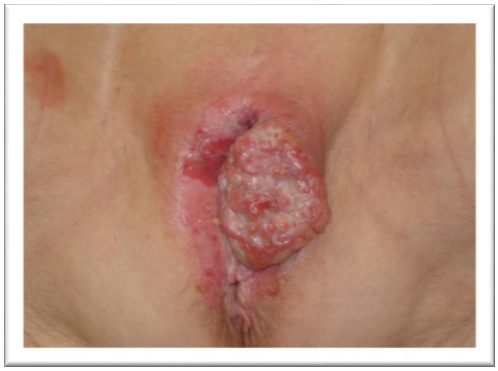

Figure 5 Vulvar Cancer (3)

The yearly incidence of vulvar carcinoma is about 2-3 out of 100.000 women, living in developed countries. Even though it is still a rare disease, the occurrence of vulvar cancer has increased.(28) In 43% of cases, chronic human papiloma virus (HPV) infections cause the development of a vulvar carcinoma. Additionally, smoking, chronic vulvar inflammatory dermatosis, immunosuppression, such as a cervical cancer in one's patient history, are potential risk factors.(29, 30) Further, women with a vulvar (VIN) or cervical (CIN) intraepithelial neoplasia, which still are premalignant lesions, are having a higher risk to develop a vulvar carcinoma. The prevalent vulvar carcinoma is the squamous cell carcinoma (SCC).(30)

Pathogenesis

SCC most commonly develops after chronic infection with HPV or secondary to autoimmune disease, most frequently, VLS. HPV-associated vulvar cancer generally appears in younger women, who have a history of smoking and other risk factors in their patient history. They often appear in an area, where these women already suffer from a bowenoid/classical VIN. Non-HPV-associated vulvar cancer often arises from a DVIN background, which is not well probed yet, but is associated with a p53 mutation. It can appear at all ages, even though it is most commonly appearing in elderly women, who have suffered from VLS over many years, without any treatment.(30, 31)

Symptoms

HPV-associated vulvar SCC mostly appears warty or basaloid, while the non-HPV-associated vulvar cancer is often keratinized.(28) There is no typical affliction for vulvar cancer. Most women suffer from pruritus, pain or soreness over many years, before consulting a doctor. Rarely women suffer from light bleedings and/or

palpable nodules. In an early stage of the disease, carcinomas normally do not cause symptoms.(32)

Diagnosis

The diagnosis of VIN is usually made clinically. An accurate inspection, including a colposcopy and a biopsy from the center of the affected region can determine the diagnosis.(32, 33) Magnetic resonance imaging can help to monitor the progression of the disease.(34)

Prognosis

The role of HPV in the prognosis of a vulvar carcinoma is still controversial. Several different studies demonstrated, that survival rates did not differ, with HPV or non-HPV-associated vulvar SCC. (30) HPV-associated vulvar cancer usually slowly develops with a VIN as a precursor. In an early stage, it can spontaneously regress. The recurrence rate of non-HPV-associated vulvar cancer is 50%, even if a vulvectomy or an excision is performed. It is typical for this kind of vulvar cancer to recur with numerous local and hematogenous metastases.(31)

For both types, the lymph node status plays an important role in the survival as does any additional therapy of these women.(35) The expected metastatic spread of the disease is via the inguinofemoral lymph nodes, but the tumor can also spread hematogenous. Metastasis, especially inguinofemoral, can already occur, when the depth of the tumors infiltration is just exceeding 1 mm.(36)

Therapy

In the early stage of the disease, radical surgery or observance is the main treatment for vulvar cancer. (30, 35, 37) The surgery can involve a radical vulvectomy with “en block” bilateral inguinal and femoral lymphadenectomy (IFL). After the surgery, a chemoradiation or an adjuvant radiation is performed. If the disease is further spread, a resection of the vagina, anus and urethra such as a pelvic exenteration can be necessary. If the tumor is not further advanced, a three-incision or other more limited surgery with a sentinel node extraction, can replace the extensive resection.(36, 37) Even though the effectiveness of these surgeries is high, alternatives are being sought after, due to the complications after surgery.

Those complications include short and long time morbidity, such as a bad influence of the quality of life in those women.(37) Especially after IFL, women often suffer from the emerged wound. Often cellulitis, wound infection, lymphoceles, lymph edema or erysipelas develops.(36) Furthermore, they might suffer from urinary stress incontinence and negative changes of their own body image and sexual function.(38) A radiation therapy performed preoperatively, can help to lower the recurrence rate of the disease. A chemoradiation therapy with a weekly given cisplatin and gemcitabine hydrochloride additionally to an intensity-modulated radiation therapy of 6400 cGY could present an alternative to surgery.(37)

Methods

The main aim of this thesis was - to give an overview - on how different diseases of the vulva affect the quality of life and sexuality in affected women. Due to these diseases involving a very intimate area of the female body and being rarely openly talked about, the degree of suffering in affected women often remains unclear. The current thesis is focusing on the quality of life indicators such as sexuality of women suffering from a vulvar disease and are undergoing therapy. Those vulvar diseases include dermatoses (vulvar lichen sclerosus, vulvar lichen planus and vulvar lichen simplex chronicus), vulvar intraepithelial neoplasia and vulvar carcinoma. Firstly, a knowledge of basic information was gained of each disease. Six basic aspects were chosen for the description of each disease, including clinical characteristics, pathogenesis, symptoms, diagnosis, prognosis and therapy of each disease. Secondly, a basic knowledge on the sexuality and quality of life in the affected women was gained through a more specialized PubMed search. An impaired sexuality and quality of life was assumed, due to the wide range of symptoms of each disease. Thirdly, a comparable factor was searched for and questionnaires being used in different studies, were evaluated for that purpose. Fourthly, the questionnaires were described and their usage listed. Fiftly, the effects of a vulvar disease on the female sexuality and quality of life, measured via questionnaires, were assessed. Sixtly, a direct comparison of sexuality and quality of life in women with a vulvar disease was performed. Additionally, conservative and surgical therapies, used in the evaluated publications, were described and a more detailed information on their effect on women with a vulvar disease was listed. Furthermore, the individual usage of each questionnaire for either surgical or conservative treatment was listed.

Literature search

Basic Information

The first step was to gain a basic knowledge on vulvar anatomy and diseases. For this reason, a literature search was performed using Pubmed Library, Cochrane Library and Google Scholar and gynecologist specialist books were looked at.(2-12, 14-17, 19-36, 38-41) Therefore, the catchwords “Lichen Sclerosus”, “Lichen Planus”, “Lichen Simplex Chronicus”, “Vulvar intraepithelial neoplasia” and “vulvar

carcinoma" have been used. The included papers were published between 2004 and 2017. Abstracts and Full texts of those papers, which included detailed information on one of the 5 diseases, appearing in the vulva of women, were downloaded and assessed. After comparing published articles and books, a composition of the most prevalent shown aspects of each disease was established. The basic aspects of each vulvar disease included the characteristics, pathogenesis, symptoms, diagnosis, prognosis and therapy of each vulvar disease.

Sexuality and Quality of Life

Now that the basic aspects of each disease had been found, another literature search was initiated, concerning the sexuality and quality of life in women with one of the 5 vulvar conditions.

This research was performed using PubMed library. This time, the used catchwords were the name of the disease plus the word "sexuality" and "quality of life". In order to receive only vulvar dermatoses, the specific names: vulvar lichen sclerosus, vulvar lichen planus and vulvar lichen simplex chronicus were used for information on dermatoses. A timeframe of 10 years, ranging from 2008-2018 was set. Only German and English publications were included for further evaluation. The search was further limited to include the females of the human species. Questionnaires were chosen for evaluation of sexuality and quality of life in women with a vulvar disease.

Questionnaire Evaluation

All publications including a questionnaire on sexuality or quality of life and a vulvar disease were evaluated. Questionnaires, concerning sexuality and quality of life, revealing results, either comparing different therapy approaches or the status of the condition itself, were included. Self-designed questionnaires, psychological questionnaires, concerning depression, questionnaires only appearing in literature reviews, revealing no results on vulvar diseases, only mentioning a questionnaire, including men, or only using parts of a questionnaire, were excluded. All included questionnaires were divided into questionnaires on sexuality and questionnaires on quality of life. Both were listed, shortly described and their usage counted.

Comparison of questionnaires

Each vulvar condition (Vulvar dermatoses, vulvar intraepithelial neoplasia and vulvar cancer) and its questionnaires on sexuality and quality of life were counted and described.

Vulvar Dermatoses and Sexuality

Questionnaires, including vulvar dermatoses (vulvar lichen sclerosus, vulvar lichen planus, vulvar lichen simplex chronicus) and sexuality were listed. Its results, concerning sexuality, were divided into whether they evaluated the status of the disease or a measurement of treatment and presented in tables for comparison. Additionally, a summary of the evaluated results was appended.

Vulvar Dermatoses and Quality of Life

Questionnaires, including vulvar dermatoses and quality of life were listed. Its results, concerning quality of life, were divided into whether they evaluated the status of the disease or a measurement of treatment and presented in tables for comparison. Additionally, a summary of the evaluated results was appended.

Vulvar Intraepithelial Neoplasia and Sexuality

Questionnaires, including vulvar intraepithelial neoplasia and sexuality were listed. Its results, concerning sexuality, were divided into whether they evaluated the status of the disease or a measurement of treatment and presented in tables for comparison. Additionally, a summary of the evaluated results was appended.

Vulvar Intraepithelial Neoplasia and Quality of Life

Questionnaires, including vulvar intraepithelial neoplasia and quality of life were listed. Its results, concerning quality of life, were divided into whether they evaluated the status of the disease or a measurement of treatment and presented in tables for comparison. Additionally, a summary of the evaluated results was appended.

Vulvar Cancer and Sexuality

Questionnaires, including vulvar cancer and sexuality were listed. Its results, concerning sexuality, were divided into whether they evaluated the status of the disease or a measurement of treatment and presented in tables for comparison. Additionally, a summary of the evaluated results was appended.

Vulvar Cancer and Quality of Life

Questionnaires, including vulvar cancer and quality of life were listed. Its results, concerning quality of life, were divided into whether they evaluated the status of the disease or a measurement of treatment and presented in tables for comparison. Additionally, a summary of the evaluated results was appended.

Comparison of diseases

Overall scores of questionnaires, which have been evaluated for all diseases, including dermatoses, VIN and vulvar cancer, were searched for and presented in tables for comparison.

Information on Therapy

After listing each disease with its questionnaires on sexuality and quality of life, further research began on quality of life and sexuality in women with a vulvar condition (dermatoses, vulvar intraepithelial neoplasia, vulvar cancer) and its individual therapy approach. This research included all publications, that had been used for earlier comparisons of sexuality and quality of life in women with a vulvar condition. Dermatoses, VIN and vulvar cancer were divided into whether conservative or surgical treatment was performed. Publications on the status of a disease, not evaluating a therapy approach, were excluded. Each treatment strategy was shortly described and the results, especially on sexuality and quality of life, of the included studies were presented.

Additional Information

After evaluating the surgical and conservative therapy approaches with all included questionnaires, their individual usage for either treatment was listed.

Results

Publications assessing Sexuality and Quality of Life

The results of the literature search using the catch words “lichen sclerosus”, “lichen planus”, “lichen simplex chronicus”, “vulvar intraepithelial neoplasia” and “vulvar cancer” along with “sexuality” and “quality of life” are shown in Table 1.

Table 1 Publications assessing Sexuality and Quality of Life

	Dermatoses			Vulvar Intraepithelial Neoplasia	Vulvar Cancer
	Vulvar Lichen Sclerosus	Vulvar Lichen Planus	Vulvar Lichen Simplex Chronicus		
Publications on sexuality total	12	3	2	17	56
excluded	2	1	/	1	/
included	10	2	2	16	56
Publications on quality of life total	45	82	9	31	129
excluded	7	45	/	1	/
included	38	37	9	30	129

Exclusion criteria: publications with a self-designed questionnaire; psychological questionnaires, concerning depression; questionnaires appearing only literature reviews; without revealing results on vulvar diseases; only mentioning a questionnaire; including men; or only using parts of a questionnaire.

Questionnaires on sexuality

3 questionnaires including vulvar dermatoses, vulvar intraepithelial neoplasia or vulvar cancer and sexuality, complying with all inclusion criteria, were found. Those questionnaires were:

- Female Sexual Function Index(42)
- Female Sexual Distress Scale(43)
- Sexual Activity Questionnaire(44)

Female Sexual Function Index (FSFI)

Questionnaire

The Female Sexual Function Index is a questionnaire, concerning the sexuality of women suffering from a vulvar condition. It was constructed and validated in 2000,

by comparing two groups of women (women with sexual arousal disorder and healthy controls), resulting in a differentiation in all of the six domains, that are included in the FSFI. Those domains include subjective arousal, desire, orgasm, satisfaction, lubrication and pain or discomfort referring to the previous 4 weeks. It includes 19 questions: 2 desire questions, 4 arousal questions, 3 orgasm questions, 2 satisfaction questions and 3 pain questions. Each question has an answering possibility from either 0 or 1 to 5. The Maximum points are 36, the Minimum points are 2. Scores of 26.5 points have been proposed to be the cut point. Women with a higher score ought to not suffer from sexual dysfunction. Further, it must be mentioned, that each domain can be counted separately by summing up its items and multiplying it with a given factor. This factor is 0.6 for the desire domain, 0.3 for the arousal domain, 0.3 for lubrication and 0.4 for the domain of orgasm, satisfaction and desire.(42, 45-53) Farmer et al.(53) implied, that the pain domain can be counted separately as well. Women achieving lower scores than 3.20 ought to be suffering from “high pain”, while women with scores from 5.20 to 3.60 were considered to suffer from “low pain”. Women with even higher scores than 5.20 were considered to suffer from “no pain”.(53) The only domain, resulting in sexual desire dysfunction when counted alone, is the desire domain, with a cutoff point of either equal or lower than 5.(54) The FSFI should not be used as a measurement for sexual experience, attitudes, interpersonal functioning or sexual knowledge of women. (42, 45-53)

Usage

The Female Sexual Function Index appeared in 26 publications of this literature research(12, 46, 49, 53-75). 14 publications(46, 53-58, 65, 66, 68-71, 75) were excluded, because they either only mentioned the FSFI, did not give any information on the results, concerned non-vulvar diseases or were literature researches. 12 publications(12, 49, 53, 59-64, 67, 72-74) were included.

Female Sexual Distress Scale (FSDS)

Questionnaire

The Female Sexual Distress Scale is a 12-item questionnaire, self-administered and regards to various aspects of sexual distress. It was constructed and validated

in 2002, by measuring different aspects of sexual functioning of approximately 500 women. The questionnaire has already been translated into many different languages. It includes possible feelings and problems, that might have occurred to women during the last 30 days concerning their sexuality. It measures the distress occurring to women with sexual dysfunction. Each question has possible answers reaching from “Never” (0 points), “Rarely” (1 point), “Occasionally” (2 points), “Frequently” (3 points) to “Always” (4 points). The Maximum score is 48 and the Minimum Score is 0. A higher score indicates a higher level of sexual distress. The Female Sexual Distress Scale-revised (FSDS-R) 2005 is identical to the FSDS except for one additional question. This question includes low sexual desire and asks women, if they are bothered by it. Scores higher than 11 distinguish between women with a sexual dysfunction and women without. (43, 76, 77)

Usage

The Female Sexual Distress Scale appeared in 8 publications of this literature research.(15, 49, 55, 58, 68, 71, 74, 78) 5 publications(15, 49, 68, 71, 78) were excluded, because they either only mentioned the FSDS, did not reveal results or were literature researches. 3 publications (55, 58, 74)revealed results for further evaluation.

Sexual Activity Questionnaire (SAQ)

Questionnaire

The Sexual Activity Questionnaire was invented for women suffering from breast cancer, undergoing a tamoxifen therapy. It was constructed and validated in 1996, by comparing the sexual function of women with tamoxifen therapy and a higher risk of developing breast cancer to women without tamoxifen therapy and no risk for developing breast cancer. Nowadays, it is also used for other gynecological disorders to measure the influence of a treatment on the sexual function. The questionnaire is organized into 3 components. The first one includes the sexual activity of a woman, the second assesses reasons for sexual inactivity and the third is laid out for sexual active women only and is also known as the SAQ-F, concerning the sexual functioning. The questionnaire contains 10 questions relating to the sexual habits, sexual discomfort and sexual pleasure of a women,

referring to the last month compared to the last several months. 9 out of those 10 questions have answering possibilities ranging from “Not at All” (0 points) to “Very Much” (3 points). The results of this questionnaire indicate higher pleasure and frequency, if a higher score is achieved and a higher level of discomfort, if a lower score is achieved.(44, 79-82)

Usage

The Sexual Activity Questionnaire appeared in 5 publications(56, 65, 69, 80, 83) 3 publications(56, 69, 83) were excluded, because they either only mentioned the SAQ, did not reveal results or included non-vulvar diseases. 2 publications(65, 80) revealed results for further evaluation.

Questionnaires on Quality of Life

6 questionnaires including vulvar dermatoses, vulvar intraepithelial neoplasia or vulvar cancer and quality of life were found. Those questionnaires were:

- Dermatology Quality of Life Index(84)
- Short Form 36(85)
- Short Form 12(86)
- Skindex 29(87)
- EORTC QLQ 30(88)
- Functional Assessment of Cancer Therapy-Vulvar(89, 90)

Dermatology Life Quality Index (DLQI)

Questionnaire

The Dermatology Life Quality Index consists of 10 questions, concerning the impact of a skin disease and its used treatment. It was constructed and validated in 1994, by comparing quality of life in patients of a skin disease to healthy controls. It includes 6 domains, dealing with feelings and symptoms, leisure, daily activities, school and work, treatment and personal relationships. Each question has 5 possible answers: Very much/A lot/A little/Not at all/Not relevant. Only question 7 has a Yes/No/Not relevant option in the answers, followed by another

question with the answers Very much/A lot/A little. The scoring ranges from Very Much- counting 3, to Not relevant or unanswered- counting 0. The maximum points are 30, minimum points 0.
After summating the points of the results, the preserved number can be evaluated. 30-21 points result in an extremely large effect on a patient's life, 20-11 points mean, that there is a very large effect on a patient's life, 10-6 points result in a moderate effect on a patient's life, 5-2 points mean, that there is a small effect on patient's life and 1-0 points mean, that there is no effect at all on a patient's life. (84, 91-93)

Usage

The Dermatology Quality of Life Index appeared in 11 publications(12, 58, 67, 74, 78, 92, 94-98). 6 publications (67, 78, 92, 94, 95, 97, 98)were excluded, because they either only mentioned the DLQI, included men or non-vulvar diseases. 5 publications(12, 58, 74, 96) included the DLQI and a vulvar disease, revealed results and were taken for further evaluation.

Short Form-36 Health Survey (SF-36)

Questionnaire

The Short Form-36 Health Survey questionnaire is a widely used instrument for the evaluation of the health-related quality of life. It was constructed and validated in 1992, by comparing healthy controls to severe chronic medical ill patients and psychological ill patients. It comprises 36 questions and is a self-administered questionnaire. The SF-36 includes 8 main dimensions. Those include: physical function affected by possible health problems, social functioning affected by either physical or emotional problems, role limitations for physical problems and role limitations for emotional problems, bodily pain, general mental health, vitality and general health perception. The SF-36 should be able to detect negative and positive states of health. For each dimension a special process of coding, transforming and summing up takes place to reveal a number on a scale from 0, meaning worst health, to 100, best health. All those dimensions can be further divided and contribute differently into the Physical Component Scale (PCS) or the Mental Component Scale (MCS). For a correct calculation, special algorithms are

required, which are precisely managed by a private company. (85, 99-101)

Usage

The Short Form-36 Health Survey appeared in 17 publications Publications(49, 67, 69-71, 75, 83, 102-112). 14 publications(69-71, 75, 83, 102-110) were excluded, because they only mentioned the SF-36, did not reveal necessary results or were literature reviews. 4 publications(49, 67, 111, 112) included the SF-36 and were further evaluated.

Short Form-12 Health Survey (SF-12)

Questionnaire

The Short Form-12 Health Survey is a questionnaire, including 12 questions, concerning the health-related quality of life and general health of patients suffering from any illness. It was constructed and validated in 1996, by using the same criteria, that have been used to validate the SF-36. Its eight domains were compiled from the Short Form-36. Those domains include the health outcomes, concerning vitality (VT), physical functioning (PF), bodily pain (BP), social functioning (SF), mental health (MH), general health (GH), role-physical (RP) and role-emotional (RE). It can be answered by oneself, via face-to-face interview, over the telephone or the computer. The answering process only takes two minutes, while remaining accurate. The questions have responding possibilities ranging from two to six answers. Those include categorical questions, that can be answered with “yes” or “no”. Further, it includes questions with a three-point scale, questions with a five-point scale and questions with a six-point scale. For the analysis of this test, a program called “Medical Outcomes Study (MOS) SAS software program”, should be used. A higher score of indicates better well-being, less dysfunction, pain or impairment. (86, 113-116)

Usage

The SF-12 questionnaire appeared in 9 publications.(60, 61, 69, 70, 102, 106, 107, 117, 118) 3 publications(69, 102, 107) were excluded, because they either only mentioned the SF-12, included non-vulvar diseases or were literature reviews. 6 publications(60, 61, 70, 106, 117, 118) included the SF-12 and were further evaluated.

Skindex 29

Questionnaire

The Skindex 29 questionnaire was developed to observe the effect of a skin disease on the quality of life. It was constructed and validated in 1996, by comparing patients with isolated lesion to patients with inflammatory dermatoses and via exploratory factor analysis. It is build up by a concept of three dimensions including symptoms of a skin disease, function and emotion, which affect the quality of life. Patients are asked to notify on how often a described item appeared during the last 4 weeks. Possible answers are “never”, “rarely”, “sometimes”, “often” and “all the time”. There are 7 items concerning the symptoms, 10 items concerning the emotions and 12 items concerning the function. After completing, the responses are transformed on a linear scale reaching from 0, meaning that it has no effect, to 100, meaning that the effect appears all the time. (87, 119) Prinsen et al.(120, 121) suggested 100 to 44 points as “severe impact”, 32 to 43 as “moderate impact” and 31 to 25 as “mild impact” on quality of life. Each dimension further has its own scale score. The Skindex-29 has been broadly used an its results for specific conditions can be compared with each other.(87, 119)

Usage

The Skindex-29 appeared in 7 publications.(78, 106, 110, 122-125) 4 publications(78, 110, 124, 125) were excluded, because they only mentioned the Skindex-29, included non-vulvar diseases or men, or were literature reviews. 3 publications(106, 122, 123) included the Skindex-29 and were further evaluated.

EORTC-QLQ30

Questionnaire

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 helps to measure the quality of life in cancer patients. It was constructed and validated in 1993, by measuring quality of life in patients with nonresectable lung cancer, including 13 different countries. It includes five functional scales (cognitive, emotional, social, physical and role functioning), three symptom scales (pain, fatigue, nausea and vomiting), a global health status/quality

of life scale, various single items, which refer to additional symptoms of cancer patients (insomnia, loss of appetite, diarrhea, constipation and dyspnea) and the budgetary impact of the disease. All questions can be answered from 0-4(not at all-very much) except the global health status/quality of life scale, which can be answered from 0-7(very poor-excellent). Higher scores in the functional scale indicate higher levels of functioning. Further a high score in the quality of life scale indicates higher levels of quality of life. On the symptom scale, a lower level would be desirable, meaning that there are not many symptoms or problems. (88, 126-128)

Usage

The EORTC-QLQ30 appeared in 25 publications.(9, 57, 59, 65, 67, 69, 83, 104, 105, 107-109, 111, 128-139) 16 publications (9, 57, 65, 67, 69, 83, 104, 105, 107, 129, 130, 132, 136-139) were excluded, because they either only mentioned the EORTC-QLQ30, revealed not the necessary results, or were literature reviews. 9 publications(59, 108, 109, 111, 128, 131, 133-135) included the questionnaire and were further evaluated.

Functional Assessment of Cancer Therapy-Vulvar (FACT-V)

Questionnaire

The Functional Assessment of Cancer Therapy-Vulvar is a questionnaire to measure the quality of life in vulvar cancer patients or women, who are currently undergoing radical vulvar surgery. It was constructed in 2004 and validated in 2005, by comparing results to the patient's subjective performance status, measured by the Eastern Cooperative Oncology Group Performance Status Rating, and the Hospital Anxiety and Depression Scale(140).(89, 141) It combines the FACT-G (Functional Assessment of Cancer Therapy-General) and the Vulvar Cancer Scale (VSC) to ask general questions about the quality of life in addition to vulvar specific changes, caused by vulvar cancer. It includes 7 questions, concerning the physical-wellbeing, 7 questions on social/family-wellbeing, 6 questions on emotional-wellbeing and 7 questions on functional- wellbeing in additions to 19 vulvar specific questions. All questions can be answered with 0 (not at all) – 4 (very much) points. Higher scores indicate better well-being.(89, 90, 141,

142)

Usage

The Functional Assessment of Cancer Therapy-Vulvar appeared in 12 publications.(60, 61, 102, 107, 132, 135, 138, 142-146) 10 publications(60, 61, 102, 107, 132, 138, 143-146) were excluded, because they only partially included the FACT-V, included non-vulvar diseases or were literature reviews. 2 publications(135, 142) included the FACT-V and were further evaluated.

Comparison of Questionnaires

Comparison of Questionnaires evaluating dermatoses and sexuality

9 publications(12, 55, 58, 62, 63, 72-75) with questionnaires on vulvar dermatoses and sexuality were found. 8 papers(12, 58, 62, 63, 72-75) included the FSFI and dermatoses and 3 papers(55, 58, 74) included the FSDS and dermatoses. The results of the status of the disease or a measurement of treatment are shown in Table 2, Table 3, Table 4 and Table 5.

Table 2 FSFI and dermatoses: Studies measuring the effect of an intervention on sexual health

Author/Year	Study design	Disease	Number of Women*	Procedure	Results
Gordon et al.(63), 2016	Cross-sectional study	VLS, VLP	16 VLS; 8 VLP	Comparison: VLS/VLP and vaginitis and vestibulitis	Lower overall scores in sexual functioning, orgasm and satisfaction in women with VLS and VLP, but not statistically significant. Women with a vulvar condition are at higher risk though, to suffer from sexual dysfunction.
Van de Nieuwenhof et al.(74), 2010	Not revealed	VLS	215	Questionnaires: VLS vs. healthy controls	Significant impairment of sexual function in all domains (lubrication, arousal, pain, satisfaction, orgasm and desire) in women with VLS. ($p<0.001$, except desire $p=0.016$)

Table 3 FSFI and dermatoses: Studies measuring the effect of an intervention on sexual health

Author/Year	Study design	Disease	Number of Women*	Procedure	Results
Boero et al.(12), 2015	Experimantal Study	VLS	36	Fat Grafting	Significant improvement of sexual function achieved by a fat grafting therapy. (p< 0001)
Goldstein et al.(62), 2015	Double-blind, placebo-controlled study	VLS	30	Human Fibroblast Lysate Cream (HFLC)	No significant changes between the sexual function before and after treatment with HFLC. (p=0.98)
Skrzypulec et al.(72), 2009	Clinical trial study	VLS	37	Photodynamic Therapy	Significant decrease of sexual functioning in women with VLS after photodynamic therapy. (p=0.009) Especially, a decrease of lubrication (p=0.00002), arousal (p=0.015) and orgasm(p=0.002).
Suzuki et al.(73), 2013	Retrospective survey	VLP	11	Lysis of vulvovaginal adhesions in VLP women vs. healthy controls	Greater impairment of sexual functioning in women with lysis after VLP adhesions, especially in satisfaction. (p=0.004)

Table 4 FSDS and dermatoses: Studies measuring the effect of the condition on sexual health

Author/Year	Study design	Disease	Number of Women*	Procedure	Results
Cheng et al.(58), 2017	prospective observational study	VLS, VLP	48 VLS; 17 VLP	Questionnaires	Significant sexual distress in women with VLS and VLP.

Van de Nieuwenhof et al.(74), 2010	Not revealed	VLS	215	Questionnaires: VLS vs. healthy controls	Significant sexual distress in patients with VLS. (p<0.001)

Table 5 FSDS and dermatoses: Studies measuring the effect of an intervention on sexual health

Author/Year	Study design	Disease	Number of Women*	Procedure	Results
Burrows et al.(55), 2011	double-blind trial	VLS	36	Clobetasol vs. Pimecrolimus	Significant sexual distress remains in women with VLS, despite adequate treatment. Clobetasol and Pimecrolimus lead to significant improvement of sexual function though. (p=0.001).

Summary

The research revealed an enormous negative impact of dermatoses on female sexual function. Lubrication, orgasm, arousal, desire, satisfaction and pain are all negatively influenced by the disease. Furthermore, women are suffering from sexual distress, meaning that they feel less happy, more frustrated, embarrassed, worried, dissatisfied, stressed, sexually inadequate, angry and inferior. The severity of the constant itch seems to play a relevant role for the degree of suffering. Also, pain and soreness achieved by the easily tearing skin negatively affect their sexuality. While being married/being in a relationship did not change sexuality in one study, it did result in an improvement of such in another. (58, 63, 74) Although, an impact of dermatoses on sexuality was already assumed, the research showed the enormous impact of specific treatment strategies on female sexual function. Fat grafting positively affected the sexual functioning. The study itself did, however, suggest fat grafting as an additional treatment to topical steroids of women, whose vulvar architecture has been changed, since it does not influence the activity of dermatoses. It can also not be used for severe vulvar changes, which require vulvar flap reconstruction.(12) Pimecrolimus and clobetasol also showed a positive effect on sexual functioning. Nevertheless, sexual dysfunction persisted in women, even after the application of pimecrolimus and clobetasol.(55) Burrows et al.(55) suggested surgical treatment for an

increase of clitoral sensation and a decrease of dyspareunia, but lysis of adhesion revealed an even lowered sexual functioning. (73) The frequency of sexual intercourse increased after lysis, but sexual satisfaction remained low. Nevertheless, women in the study recommended it to others.(73) Human Fibroblast Lysate Cream did neither increase nor decrease the female sexual functioning.(62) Photodynamic therapy resulted in a reduction of lubrication, arousal and orgasm.(72)

Comparison of Questionnaires evaluating dermatoses and Quality of Life

7 publications on dermatoses (Vulvar lichen sclerosus, vulvar lichen planus and vulvar lichen simplex chronicus) and a questionnaire on quality of life were found. 3 publications included the DLQI and dermatoses, one included the SF-12 and dermatoses and 3 included the Skindex 29 and dermatoses. Results on the status of the disease or measurement of treatment are shown in Table 6, Table 7, Table 8, Table 9 and Table 10.

Table 6 DLQI and dermatoses: Studies measuring the effect of the condition on quality of life

Author/Year	Study design	Disease	Number of women	Procedure	Results
Cheng et al.(58), 2017	prospective observational study	VLS, VLP	17 erosive VLP, 48 VLS, 12 vulvar dermatitis	Questionnaire: erosive VLP vs. VLS vs. vulvar dermatitis	Moderate effect on quality of life in women with erosive VLP. Significantly more women with VLS reported small effect on quality of life. (p = .009)
Van de Nieuwenhof et al.(74), 2010	Not revealed	VLS	212	Questionnaires: VLS status	Large effect on quality of life in women with VLS. (mean score: 11.92) Most influence on sexual functioning, least on working or studying.

Table 7 DLQI and dermatoses: Studies measuring the effect of an intervention on quality of life

Author/Year	Study design	Disease	Number of women	Procedure	Results
Boero et al.(12), 2015	Experimental study	VLS	36	Fat grafting	Significant improvement of VLS women's quality of life after fat grafting. (p<0001)

Table 8 SF-12 and dermatoses: Studies measuring the effect of the condition on quality of life

Author/Year	Study design	Disease	Number of women	Procedure	Results
Lansdorp et al.(106), 2013	cross-sectional study	VLS	262	Questionnaires: VLS vs. healthy controls	Worse quality of life in women with VLS, than healthy controls.

Table 9 Skindex 29 and dermatoses: Studies measuring the effect of the condition on quality of life

Author/Year	Study design	Disease	Number of women	Procedure	Results
Lansdorp et al.(106), 2013	cross-sectional study	VLS	262	Questionnaires: VLS vs. healthy controls	More symptoms, most frequently soreness, impediment of sexual life and concerns about the disease, are associated with worse quality of life. (P <0.001)

Table 10 Skindex 29 and dermatoses: Studies measuring the effect of an intervention on quality of life

Author/Year	Study design	Disease	Number of women	Procedure	Results
Terras et al.(123), 2014	Randomized Clinical Trial	VLS	26	UV-A1 Phototherapy vs Clobetasol Propionate, 0.05%	Significant increase of quality of life after Clobetasol treatment. (P=0.009) Better response of Clobetasol than UV-A1 (p=0.05)

Summary

All studies, measuring the quality of life of women with dermatoses, revealed a reduction of quality of life. Especially discontentment with sexual function, concerns about the disease and soreness negatively affected the quality of life and

vice versa. Furthermore, women worried about the development of vulvar cancer and if their family members might also develop dermatoses. Dermatoses less impaired going to work or studying. A higher number of symptoms correlated with a higher burden on quality of life.(74, 106) The only treatment strategies evaluating quality of life via questionnaire were fat grafting, clobetasol and UV-1A therapy. Fat grafting increased the quality of life. It can be used as an additional therapy to increase quality of life and sexual function in women, who received a topical steroid therapy and whose vulvar architecture is not severely changed. Women after Clobetasol treatment mostly complaint about symptoms and emotions, which lowered their quality of life. Their symptoms included burning, pain and itching/scratching, although a symptom reduction occurred after treatment. A higher frequency and intensity was correlated with worse quality of life. Women felt angry, frustrated of the effect the disease had on their sex life and worried about cancer development. UV-A1 therapy reduced burning and pain, did however not significantly affect the pruritus as a main factor of lower quality of life. This occurred, because the UV-A1 treatment lead to a dehydration of the skin.(122, 123)

Comparison of Questionnaires evaluating Vulvar Intraepithelial Neoplasia and Sexuality

3 publications on VIN and a questionnaire on sexuality were found. 2 included the FSFI and VIN and one included the SAQ and VIN. One of them did not differentiate between VIN and vulvar carcinoma. One compared VIN to vulvar cancer. Due to the higher number of vulvar cancer patients, they were listed under Table 14 and Table 15. The result of the remaining publication is shown in Table 11.

Table 11 SAQ and VIN: Studies measuring the effect of the condition on sexual health

Author/Year	Study design	Number of women	Procedure	SAQ results
Nagele et al.(80), 2016	observational study	30	Questionnaire: HPV-related VIN vs. HPV-related CIN vs HPV-related VAIN	Lower scores of sexual activity in the VIN group, but not significant.

Summary

Only one study included the sexuality of women, suffering from VIN, without testing a specific therapeutic approach. It stated a decreased sexual functioning in VIN women, reasoning to feeling less attractive and fear of dyspareunia. The study included only HPV-related VIN, which also caused women to worry about infecting their partner or not being able to have children. Women were further worried about the development of cancer. VIN patients after surgery still suffered from sexual dysfunction, especially sexual desire was lowered. Further, recurrence of the disease negatively affected sexual activity. The risk of recurrence does remain present after surgery of a HPV-related VIN due to the immune system not eliminating the HPV virus.(80) Forner et al.(60) tested, whether resection or sparing of the clitoris would influence sexual functioning, resulting in an equally balanced sexual function and dysfunction. However, it mainly included vulvar cancer patients and might therefore not be valid for VIN patients. There was lack of information on physical symptoms, except surgical complications, influencing the sexual functioning of VIN patients. Nevertheless, it can be derived from the study, that women suffering from VIN also suffer from sexual dysfunction.

Comparison of Questionnaires evaluating Vulvar Intraepithelial Neoplasia and Quality of Life

5 publications on vulvar intraepithelial neoplasia and quality of life were found. One publication included the DLQI and VIN, 2 publications included the EORTC-QLQ30 and VIN, one publication included the SF-36 and VIN and one publication included the SF-12 and VIN. Results are shown in Table 12 and Table 13, except publications with the SF-36 and SF-12, because they included higher numbers of vulvar cancer patients and were therefore listed under Table 17 and Table 18. (60, 112)

Table 12 DLQI and VIN: Studies measuring the effect of the condition on quality of life

Author/Year	Study design	Number of women	Procedure	Results
McFadden et al.(96), 2009	prospective observational study	8	Questionnaires: VIN status	Negative effect of VIN on quality of life. (no significant results)

Table 13 EORTC-QLQ30 and VIN: Studies measuring the effect of an intervention on quality of life

Author/Year	Study design	Number of Women	Procedure	Results
Van Seters et al.(109), 2008	placebo-controlled, double-blind, randomized clinical trial	52	Imiquimod vs. placebo	No significant difference between quality of life in women treated with imiquimod or placebo.
Terlou et al.(108), 2011	randomized clinical trial	24	Imiquimod long term effects: Long term responders vs. residual disease/recurrence of disease	Significant improvement of quality of life in women with complete long-term response to imiquimod, compared to women with residual disease or recurrence of it. (p=0.025)

Summary

Only one publication included the measurement of quality of life in VIN patients, without testing surgical or conservative therapy approaches. It stated, that newly diagnosed women suffered from lowered quality of life and sexual dysfunction. Symptoms of VIN like burning and itching were responsible for the lower contentment. Furthermore, the fear of not knowing how the disease will develop and changes of body image negatively influenced quality of life and sexuality.(96) Further, Imiquimod and surgery were tested as possible therapies. Despite women under imiquimod therapy suffering from side effects post application or one day after (including burning and pruritus, erythema, edema and erosion), they revealed a significant symptom relief of burning and pruritus after 20 weeks of treatment and their quality of life, sexuality or body image did not negatively change. A long-term research on imiquimod demonstrated better quality of life, if there was better response to treatment.(108, 109) Forner et al.(60) also tested the quality of life in women after clitoris-sparing or resecting surgery. Results might not be valid for VIN patients, reasoning to the small number of VIN patients, but it did not reveal a difference in quality of life for either the clitoris-resected, or clitoris-spared women. Kobleder et al.(112) included VIN and vulvar cancer patients, revealing less

impairment in women with a vulvar intraepitheal neoplasia. Women with VIN received less radical surgery and showed better quality of in physical functioning and role functioning. The study suggested, that a likely reason reporting better quality of life could also result in the younger age of VIN patients.

Comparison of Questionnaires evaluating vulvar cancer and Sexuality

6 publications on vulvar cancer and a questionnaire on sexuality were found. 5 included the FSFI and vulvar cancer and one included the SAQ and vulvar cancer. Results of the status of the disease and measurement of treatment are shown in Table 14, Table 15 and Table 16.

Table 14 FSFI and vulvar cancer: Studies measuring the effect of the condition on sexual health

Author/Year	Study design	Disease	Number of women	Procedure	Results
Grimm et al.(64), 2016	Cross-sectional study	Vulvar Cancer, VIN	34 Vulvar Cancer, 24 VIN	Questionnaires: Vulvar Cancer vs. VIN	Insignificant better sexual functioning in women with VIN. (p=0.421) Impairment of sexual function in both groups. Significant impairment of sexual functioning with higher age. (p=0.013)
De Melo Ferreira et al.(59), 2012	Not revealed	Vulvar Cancer	28	Questionnaire: Vulvectomy and inguinofemoral lymphadenectomy vs. healthy controls	No significant difference in sexual functioning in women with vulvar cancer surgery and healthy controls. (p>0.05)

Table 15 FSFI and vulvar cancer: Studies measuring the effect of an intervention on sexual health

Author/Year	Study design	Disease	Number of women	Procedure	Results
Forner et al.(60), 2013	Retrospective study	Vulvar Cancer, VIN	21 vulvar cancer, 3 VIN	Clitoris sparing surgery vs. clitoris resecting surgery	No significant changes in women with or without clitoris sparing surgery. (p=0.93)
Forner et al.(61), 2015	Retrospective study	Vulvar Cancer	21	Wide excision vs. vulvectomy, total inguinofemoral	No significant difference in sexual functioning

				lymphadenectomy vs. sentinel node biopsy	between women with wide excision or vulvectomy (p=0.85). Significant impairment in women with total inguinofemoral lymphadenectomy when compared to sentinel node biopsy. (p=0.03)
Hazewinkel et al.(59), 2012	Cross-sectional study	Vulvar Cancer	76	Long Term Sexual Function: Extensive vs less extensive treatment	No significant difference in long term sexual functioning, regardless of treatment strategy. (p>0.25) (t-test) Physical well-being is associated positively with orgasm(p=0.03).

Table 16 SAQ and vulvar cancer: Studies measuring the effect of the condition on sexual health

Author/Year	Study design	Number of women	Procedure	SAQ results
Grimm et al.(65), 2015	Multicenter cross-sectional study	8	Questionnaires: Vulvar cancer vs. healthy controls	No significant differences in sexual activity of women with vulvar cancer. (p>0.05)

Summary

Two studies compared women, who had undergone vulvar surgery to healthy controls, revealing no significant difference in sexual functioning between them.(59, 65) However, if respecting the cut-off point of the FSFI, women with vulvar cancer surgery reported severe sexual dysfunction.(59, 61, 64) While Forner et al.(60) and Hazewinkel et al.(49) did not detect a difference in sexual functioning after either sparing or resecting the clitoris, Grimm et al.(65) showed more sexual pleasure in women of whom the clitoris had been spared. Grimm et al.(65) further revealed better orgasms, if a wide excision instead of a vulvectomy had been performed, while Forner et al.(61) did not find sexual differences. Hazewinkel et al.(49) also revealed no influence of the extent of the surgery on

sexual functioning. A more radical surgical approach, including lymph nodes, negatively affected sexual function in Forner et al.(61), while it showed no changes in De Melo Ferreira et al.(59). The research did show a tendency of higher age and physical changes of the vulvar architecture having a negative impact on sexuality, while having a partner positively affect sexual activity and contentment about it. Further, women who became sexual active after surgery did show a tendency of regaining their sexual functioning.(49, 64, 65)

Comparison of Questionnaires evaluating vulvar cancer and Quality of Life

14 publications including vulvar cancer and quality of life were found. 2 included the SF-12 and vulvar cancer, 3 included the SF-36 and vulvar cancer, 7 included the EORTC QLQ30 and vulvar cancer and 2 included the FACT-V and vulvar cancer. Results are shown in Table 17, Table 18, Table 19, Table 20, Table 21 and Table 22.

Table 17 SF-12 and vulvar cancer: Studies measuring the effect of an intervention on quality of life

Author/Year	Study design	Disease	Number of women	Procedure	Results
Forner et al.(60), 2013	Retrospective study	VIN, vulvar cancer	3 VIN; 21 vulvar cancer	Clitoris sparing surgery vs. clitoris resecting surgery	Sparing or resecting the clitoris in surgery for VIN and vulvar cancer women, does not influence their quality of life, neither in the physical (p=0.37) nor mental domain (p=0.55).
Forner et al.(61), 2015	Retrospective study	Vulvar cancer	21	Wide excision vs. vulvectomy, total inguinofemoral lymphadenectomy vs. sentinel node biopsy	No significant difference in reduced surgical approach (wide excision vs. vulvectomy) in physical (p=0.97) or mental domain (p=0.92) of quality of life. Further, no significant difference in the physical (p=0.38) or mental

					domains(p=0.46), whether only a sentinel node biopsy is performed or a total inguinofemoral lymphadenectomy.

Table 18 SF-36 and vulvar cancer: Studies measuring the effect of the condition on quality of life

Author/Year	Study design	Disease	Number of women	Procedure	Results
Kobleder et al.(112), 2016	Cross-sectional study	Vulvar Cancer, VIN	42 vulvar cancer, 20 VIN	Questionnaires after surgery, Vulvar cancer vs. VIN	Lower quality of life in women with vulvar cancer, especially in physical function(p=0.013) and role function(p=0.049). A problem with “carrying out daily activities” was asscociated with lower quality of life in almost all domains.
Hazewinkel et al.(49), 2012	Cross-sectional study	Vulvar Cancer	76	Surgery	Only slightly lower scores in quality of the SF-36 scores of women who underwent surgery, compared to the values of the general population. (no significance level available)

Table 19 SF-36 and vulvar cancer: Studies measuring the effect of an intervention on quality of life

Author/Year	Study design	Disease	Number of women	Procedure	Results
Jones et al.(111), 2016	Longitudinal, mixed methods study	Vulvar Cancer	20	Questionnaires after surgery	Significant impairment of women in mental health in advanced vulvar cancer than women in earlier stages (p=0.037) and significant impairment in the physical health 12 months after treatment. (p<0.05)

Table 20 EORTC-QLQ30 and vulvar cancer: Studies measuring the effect of the condition on quality of life

Author/Year	Study	Number of	Procedure	Results

	design	women		
De Melo Ferreira et al.(59), 2012	Not revealed	28	Questionnaire: Vulvectomy and inguinofemoral lymphadenectomy vs. healthy controls	Significant correlation between quality of life, especially in physical, emotional, cognitive, pain, fatigue, financial and social domains and the occurrence of lower lymph edema after surgery. (p<0.05)

Table 21 EORTC-QLQ30 and vulvar cancer: Studies measuring the effect of an intervention on quality of life

Author/Year	Study design	Number of women	Procedure	Results
Gunther et al.(128), 2014	Retrospective single center study	57	Questionnaires: wide local excision vs. radical vulvectomy, LNE vs. inguinofemoral lymphonodectomy	Statistical significant impairment of quality of life in women with radical vulvectomy in domains of pain and social functioning(p<0.05), further in global health, physical-, role-, emotional-, financial-, congnitive function, diarreah and appetite loss. (no significance level shown) Higher rates of lymphedema in women with inguinofemoral lymphadenectomy. (p=0.002)
Jones et al.(111), 2016	Longitudinal, mixed methods study	20	Long term influence of vulvar cancer surgery	Worsening of quality of life, especially in social, physical, pain and fatigue domains after 12 months of treatment. (p<0.05)
Li et al.(131), 2015	Case control study	58	Sartorius transposition vs. Sartorius tendon transposition	Significant improve in quality of life in domains of global health(p=0.018), physical(p=0.044) and emotional functioning(p=0.020) and pain(p=0.004) in the sartorius tendon transposition group.
Novackova et al.(133), 2012	Prospective nonrandomized study	29	Questionnaires: inguinofemoral lymphadenectomy vs. sentinel lymph node biopsy	Significant impairment in quality of life in domains of fatigue(p=0.0166), social function(p=0.0474) and dyspnea(p=0.0353) in patients with inguinofemoral lymphadenectomy after 6 months of treatment, when

				compared to sentinel lymph node biopsy.
Novackova et al.(134), 2015	Prospective clinical study	36	Questionnaires: inguinofemoral lymphadenectomy vs. sentinel lymph node biopsy	Significant impairment in quality of life in domains of cognitive function(p=0.032) and body image (p=0.033) in women with inguinofemoral lymphadenectomy when compared to women with sentinel lymph node biopsy 12 months after treatment.
Oonk et al.(135), 2009	Not revealed	62	Questionnaires: sentinel lymph node biopsy procedure vs. inguinofemoral lymphadenectomy	Only significant difference shown in the financial domain of quality of life in women with inguinofemoral lymphadenectomy(p=0.01).

Table 22 FACT-V and vulvar cancer: Studies measuring the effect of an intervention on quality of life

Author/Year	Study design	Number of women	Procedure	Results
Chang et al.(142), 2016	retrospective chart review	6	Quality of Life After Vulvar Reconstruction Using Pedicle PAP Flaps	Good quality of life in women with vulvar cancer after reconstruction with pedicle PAP flaps. (no significance level available)
Oonk et al.(135), 2009	Not revealed	62	Questionnaire: Sentinel lymph node biopsy vs. inguinofemoral lymphadenectomy	Significant impairment in quality of life in women after inguinofemoral lymphadenectomy in the domains of contentment (p=0.04) and edema (p=0.001). Further, the edema associated factors complaints (p=0.01) and stockings (p=0.003).

Summary

Quality of life in vulvar cancer patients was only slightly lowered as measured by Hazewinkel et al.(49), yet a different publication revealed, that the stage of the vulvar cancer also played an important role. (111) A higher stage of the disease negatively impacted the mental health of affected women significantly.(111) Especially physical changes after treatment and pain decreased women's quality of life.(111) Studies revealed that especially carrying out daily activities was often perceived with difficulties and therefore lowered quality of life. Often, this problem

was associated with a more radical approach of cancer management, like vulvectomy and total inguinal lymphadenectomy, resulting in side effects like edema, financial difficulties, pain, change of body image, which lowered the quality of life in women.(59, 112, 128, 133, 134) Oonk et al.(135) revealed only financial difficulties concerning quality of life after total inguinal lymphadenectomy, while Forner et al.(61) did not reveal a difference whether a more radical or less extensive surgery was performed. It has to be noted that Forner et al.(61) included women with a lower stage of vulvar cancer than Oonk et al.(135).

Comparison of diseases

Only one questionnaire, the FSFI was evaluated for all included diseases. The lowest overall scores are shown in Table 23.

Table 23 Comparison of diseases: FSFI overall scores

Dermatoses	VIN	Vulvar Cancer
15.9(72)	16.32(64)	12.74(64)

This comparison results in most impaired sexual functioning in vulvar cancer women, followed by dermatoses and VIN.

Information on Therapy

The research on the different therapy approach, either conservative or surgical, included the 29 publications, that were evaluated for sexuality and quality of life via questionnaires. 7 publications were excluded, because they measured the status of the disease without evaluating treatment. The remaining publications performed research on an either conservative or surgical treatment of a vulvar disease. 5 publications on dermatoses included surgical treatment and 2 publications included conservative therapy. 2 publications on vulvar intraepithelial neoplasia included conservative therapy. 3 publications included VIN and vulvar cancer and surgical treatment. Further, 10 publications included exclusively vulvar cancer and a surgical approach of therapy.

Evaluation of treatment for dermatoses

Conservative Therapy

Human Fibroblast Lysate Cream

Description:

Human Fibroblast Lysate Cream is acquired from human fetal fibroblasts, which have been cultured. It contains anti-inflammatory cytokines (Interleukin 1-, 10- and 13 receptor antagonist), such as wound healing growths factors (epidermal growth factor, vascular endothelial growth factor and fibroblast growth factor). This therapy form still needs to be further tested.(62)

Publication results:

The publication included in this diploma thesis revealed no significant bettering in histopathological inflammation ($p=0.783$) and sexual functioning ($p=0.98$). Further, it showed no significant changes in severity of VLS ($p>0.2$), pruritus reduction ($p=0.226$) or vulvar burning and pain ($p=0.86$), when compared to a placebo group. Further the sexual function did not increase significantly. It showed a tendency of symptom reduction after cream appliance, but a study, including a higher sample size must be performed, to confirm the effect. Hence, Human Fibroblast Lysate Cream should yet not be recommended as treatment for VLS. (62)

Photodynamic Therapy

Description:

Photodynamic therapy involves a topical laser treatment on the skin, which has been treated with a solution, for greater sensitivity. It reveals a cytotoxic effect on the applied area, causing apoptosis of pathological changed cells. It is used for many skin conditions, including basal cell carcinoma. The procedure can be repeated, if necessary. It leads to a relief of clinical symptoms, by reducing pruritus and leads to a softening of the thickened skin structure. It can be used for topical steroid resistant VLS.(72, 147, 148) In the study, included in this diploma thesis, 10ml of a 5% solution of 5-aminolevulinic acid has been used as a photosensitizer. It was applied on vulva 5 hours before laser treatment with an irradiation of 80J/cm2. Irradiance was40–70 mW/cm2 and the used wavelength of the light was 635 nm. The procedure was carried out for three months, including six cycles

every 2 weeks. (72)

Publication results:

Skrzpulec et al.(72) revealed, that sexual activity did insignificantly decrease after therapy($p=0.1$). Sexual functioning significantly decreased after therapy($p=0.009$), especially in the domains of lubrication, arousal and orgasm. Severity of moderate depressive symptoms decreased ($p<0.012$). Women scored 21.6 points on the FSFI overall score before treatment and 15.9 after treatment. The study only mentioned good clinical outcome of photodynamic therapy on VLS, but did not reveal results.(72)

Ultraviolet-A1 Phototherapy

Description:

This therapy involves a radiation treatment of pathological changed cells with UV-A1. Even though, the exact process on how UV-A1 therapy works on sclerotic skin is not known, it seems to influence inflammatory cells and lesional fibroblasts. The collagen production of fibroblasts increases and a decrease of Interleukin 6 and 8 occurs. The treatment can lead to a reduction of the skin thickening, increase the dermal density, soften the skin and better the pigmentation. To this point, information on the exact efficacy of UV-A1 on VLS are still lacking. (15, 123, 149)

Publication results:

Terras et al.(123) revealed, that UV-A1 lead to a significant reduction in clinical symptoms ($p=0.006$), and visual analogue scale symptoms of burning/pain ($p=0.01$). Woman scored 86.2 points before and 80.6 points three months after UV-A1 treatment on the mean Skindex 29 score. However, it did not reduce corium thickness or lead to a reduction of inflammation. It further did not significantly improve symptoms of pruritus ($p=0.16$) or quality of life ($p>0.99$). Hence, Clobetasol should be prior to UV-A1 therapy.(123)

Clobetasol

Description:

Clobetasol 0.05% is a highly potent corticosteroid, which is first line therapy of VLS. It is suggested, that a fingertip of the ointment should be applied on the pathologically changed area once daily for three months, but there is no strict

regimen of the quantity of application. It should lead to a remission of the disease and relief symptoms of pruritus. Frequency of application can be reduced, if the initial treatment lead to a sufficient result. Thinning of the skin, hypopigmentation and scarring can be possible irreversible side effects. (11, 78, 123)

Publication results:

Schwegler et al.(122) stated, that there was a significant correlation between quality of life and the frequency and/or severity of vulvar symptoms, such as pain, itching/burning, scratching and dryness. ($p<0.05$) The study implies a strong therapeutic benefit for women with VLS after Clobetasol treatment and an improvement of quality of life after application. (122)

Burrows et al.(55) showed a significant reduction of sexual distress in women suffering from VLS ($p=0.001$) and a significant decrease of average inflammation, after clobetasol treatment. Nevertheless, women with VLS continued to suffer from sexual dysfunction. Women scored 29 points on the FSDS before and 15 points after treatment. The study also revealed, a greater response of VLS women to clobetasol treatment, than pimecrolimus ($p=0.03$). (55)

Further, Terras et al.(123) showed significant reduction in clinical symptoms ($p=0.001$) (hypopigmentation, edema, erosions, hyperkeratosis, atrophy, erythema and sclerosis), Skindex 29's quality of life measurements ($p=0.009$), visual analogue scale symptoms of burning/pain ($p=0.001$) and pruritus ($p=0.005$) after clobetasol treatment. It further reduced the thickness of the corium ($p=0.003$) and significantly reduced inflammation ($p=0$ .02). Women scored 85.8 points before and 56.3 points after Clobetasol treatment on the mean Skindex 29 score. The publication revealed the prior effect of Clobetasol compared to UV-A1 phototherapy treatment.

Pimecrolimus

Description:

Pimecrolimus, a calcineurin inhibitor, is used as second line treatment of VLS, if prior treatment of topical corticosteroids was ineffective or contraindicated. It is effective in symptom relief and improves the clinical picture of VLS. 3 months after initial application, a follow-up should be scheduled, to examine the clinical picture and symptoms. An advantage of this treatment form is, that it does not affect skin

atrophy. However, local irritations and burning can appear. The higher risk of developing cancer after calcineurin inhibitor usage is still controversial. Recommendations on quantity or amount of application are scarce.(11, 14, 15, 20) The evaluated study of this diploma thesis, measured the application of pimecrolimus twice a day for 12 weeks.(55)

Publication results:

Burrows et al.(55) revealed that pimecrolimus showed a significant reduction of sexual distress in women suffering from VLS (p=0.001). Women continued to suffer from sexual dysfunction after treatment though. Women scored 27 points on the FSDS before and 21 points after treatment. Further, it revealed a significant reduction in average inflammation. Nevertheless, the study indicated a prior effect of Clobetasol treatment than pimecrolimus on VLS(p=0.03).

Surgical Therapy

Fat Grafting

Description:

Fat grafting is mainly used in reconstructive surgery to restore volume, function and disorders of a damaged tissue. The procedure includes the application of purified adipose tissue from surface until the fascial plane. The amount varies, depending on the extent of tissue damage. Antibiotics are required prior to fat grafting. It should not be seen as first line treatment but recommended for women suffering from anatomical changes of the vulva, or women, who are non-responders to corticosteroids. The procedure, however, must be further analyzed.(12)

Publication results:

Boero et al.(12) revealed, that fat grafting can lead to a significant improvement of sexual functioning and quality of life in women with VLS. Further, it leads to better vulvar trophism and elasticity of the tissue. (p<0001) (12)

Lysis

Description:

The main reasons for performing surgery on women with dermatoses are either the development of VIN/vulvar cancer or massive anatomical changes of the

vulva, causing stenosis of the introitus or functional impairment. Those women may benefit from a surgical procedure, but it is not first line treatment for dermatoses. Prior to surgery, the disease should be non-active. A corticosteroid application and dilator use after surgery is recommended to prevent newly stenosis and scarring.(11, 15, 78, 150)

Publication results:

Women with VLP, who underwent lysis, showed a tendency in a decrease of urinary symptoms and infections, genital symptoms and a higher frequency of intercourse. Their satisfaction with sexual functioning remained significantly lower, when compared to healthy controls (p=0.004).(73)

Evaluation of treatment for VIN

Conservative therapy

Imiquimod

Description:

Imiquimod is an immune modulator, which binds to a Toll like receptor, inducing intracellular cascades, like secretion of proinflammatory cytokines and a maturation of cells, presenting antigens. Further, it has a direct apoptotic effect on tumor cells.(109)

An advantage of imiquimod therapy is the possible eradication of HPV 16. Hence, it might reveal a lower recurrence rate. Nevertheless, the risk of not detecting a vulvar carcinoma is given, due to the fact, that a full histological examination is not performed. Its side effect can be severe itching, pain and skin erosions. (67, 151) There is still further knowledge needed on long term effect of imiquimod to distinguish whether it should replace surgical therapy as a first line therapy. (130)

Publication results:

Van Seters et al.(109) showed, that imiquimod significantly reduced the size of the lesions, lead to histological regression and lead to HPV clearance when compared to a placebo group. ($p<0.001$) It further lead to a symptom reduction of pain and pruritus after 12 months of treatment ($p=0.02$ and $p=0.04$) However, treatment did not show significant improvement of quality of life, sexuality of body image. All measurements were taken within 12 months. This study suggested imiquimod as first line therapy for VIN, prior to surgery. (109)

Terlou et al.(108) performed a 7-year follow-up of van Seters et al(109) , measuring the long-term effect of imiquimod therapy in VIN patients. Although no significant changes in mental health, sexuality of body image were found between women, who had been long term responders to imiquimod compared to non-or partial-responders, a significantly better quality of life could be observed. (p=0.025) Out of 24 women, 9 showed a complete response to imiquimod, 10 showed a partial response and 5 showed no response. For partial or non-responders, laser vaporization, local/wide excisions and lymphadenectomy became necessary. The study implied though, that imiquimod is an effective treatment for VIN patients. They strongly recommend prolonged treatment for larger lesions to prevent progression of the disease and annual doctor visits. (108)

Evaluation of treatment for VIN and Vulvar Cancer

Surgical therapy

Depending on the size of the lesion, women with VIN undergo different surgical approaches, while vulvar cancer is mostly treated more radically. Still, surgical approaches range from lazer vaporization, local to wide excision, partial to full vulvectomy and in most cases of vulvar cancer, sentinel node biopsy to inguinofemoral lymphadenectomy. (112, 152) Depending on the involved area and extent of surgery, the clitoris may or may not be resected. A study of Terlou et al.(153) on skinning clitoridectomy revealed promising results on providing the tissue underlying the clitoris, while still resecting the pathological area. Likes et al.(52) revealed worse sexual function and quality of life in women after surgery for VIN women in 2007. No studies evaluating exclusively VIN and surgery met all inclusion criteria for this diploma thesis though. Three studies evaluated in this diploma thesis included a surgical approach of therapy on both, VIN and vulvar cancer women. They did reveal the type of surgery in their collected medical data but did not include results based on the type of surgery. It can be mentioned though, that VIN women received less radical treatment.

Clitoris conserving surgery

Forner et al.(60) included VIN and vulvar cancer women. Quality of life, measured by the SF-12, did not differ significantly in its mental or physical domain and

neither did sexual function in women, regardless of whether the clitoris got resected or spared. (60)

Surgery (including Laser vaporization, local excision, partial vulvectomy, vulvectomy)

Grimm et al.(64) revealed, that VIN and vulvar cancer patients did not statistically differ in their sexual function, based on the FSFI criteria arousal, pain, orgasm, lubrication, desire, lubrications and satisfaction. ($p>0.05$) It did show a tendency of better sexual functioning in the VIN group though. The study did reveal age as a significant factor of sexual activity. Elderly women were less likely to have sexual engagements ($p =0.013$), and scored lower in domains of desire, lubrication, orgasm, arousal and pain. ($p<0.05$) (64)

Surgery (including Local excision, Laser therapy, skinning vulvectomy, partial vulvectomy, radical wide excision, vulvectomy, sentinel node biopsy, lymphadenectomy)

Kobleder et al.(112) revealed, that VIN women suffered less in domains of physical functioning ($p=0.013$) and role functioning($p=0.049$) than vulvar cancer women, revealing better quality of life for VIN women. Especially carrying out daily activities influenced the quality of life in the mental and physical scores of the SF-36. Symptoms, concerning the wound especially affected the physical score, while psychological symptoms affected the mental scores of the SF-36. Women with vulvar cancer were older and had more radical procedures performed on them.(112)

Evaluation of treatment for vulvar cancer

As mentioned earlier, different surgical approaches for vulvar cancer exist. Most commonly, they include local/wide excision, partial/full vulvectomy and additionally a sentinel node biopsy or inguinofemoral lymphadenectomy. 6 studies evaluated in this diploma thesis compared quality of life and/or sexuality of vulvar cancer women, who received a less extensive or more radical surgery. One study compared the long-term effect of surgery on women, suffering from different stages of vulvar cancer and one study compared vulvar cancer women to healthy controls. Another two studies compared different surgical techniques to each other.

Surgery (Radical and less extensive)

Gunther et al.(128) compared vulvectomy and wide local excision with/without lymphadenectomy. The study revealed significant better social functioning and less pain in women after wide local excision compared to women after vulvectomy($p<0.05$). Furthermore, women were more likely to reveal better quality of life, although not statistically significant, in domains of global health, emotional, cognitive, physical and role functioning, after less radical surgery. Women who received a lymphadenectomy were significantly more often affected by the occurrence of lymphedema, than women who did not undergo lymphadenectomy($p=0.002$). The study implied that less radical surgery in vulvar cancer patients should be aimed for.(128)

Forner et al.(61) compared wide local excision, vulvectomy, total inguinofemoral lymphadenectomy and sentinel node biopsy to each other. Sexual functioning was not influenced by the extend of the surgery or age, but significantly decreased, if a lymphadenectomy was performed. ($p=0.04$) Quality of life was only significantly influenced by the age of the patients. Women over the age of 50 years revealed significantly higher scores in quality of life, especially in the mental domains of quality of life. ($p=0.04$)(61)

Novackova et al.(133) compared vulvectomy and radical wide excision with either sentinel node biopsy or lymphadenectomy. It revealed significant worse quality of life in domains of fatigue, dyspnea and social functioning in women after lymphadenectomy, when compared to women with a sentinel node biopsy. ($p=0.0166$, $p=0.0353$, $p=0.0474$) They did however, not statistically differ in the occurrence of lymphedema or other parts of quality of life measured by the EORTC QLQ30. Less radical treatment showed a tendency to better overall quality of life.(133)

Hazewinkel et al.(49) compared radical vulvectomy and radical local excision with inguinal lymph node dissection to radical local excision, with/without sentinel node excision. Both treatments did not reveal significant differences in sexual functioning. Arousal and desire were both lower in older women. Orgasm was negatively associated with adjuvant radiotherapy but correlated positively with physical well-being. Also having a partner positively influenced sexual satisfaction and being more optimistic increased sexual desire.(49)

Novackova et al.(134) included vulvectomy and radical wide excision with either sentinel node biopsy or lymphadenectomy. 12 months after surgery, women with a vulvar surgery and only a sentinel node biopsy showed significantly higher scores in quality of life in domains of body image and cognitive functioning. ($p=0.033$ and $p=0.032$) Further, none of the quality of life domains decreased after vulvar surgery and sentinel node biopsy only. Women with a lymphadenectomy showed significantly higher occurrences of lymphedema. ($p=0.028$) Also, women with lymphadenectomy and an adjuvant radiotherapy showed significantly worse symptom experience, than women without radiotherapy. ($p<0.05$) Sexual function did not differ between radical and less radical surgical approach. Less radical surgery positively influenced quality of life.(134)

Oonk et al.(135) compared vulvectomy and radical wide excision with either sentinel node biopsy or lymphadenectomy. The overall quality of life, measured by the EORTC QLQ 30 did not differ between women after vulvar surgery and inguinofemoral lymphadenectomy or sentinel node biopsy only, except for higher financial difficulties in women after lymphadenectomy. ($p=0.01$) Women after lymphadenectomy also were less content with their treatment ($p=0.04$), showed more discomfort in legs, vulva and groins ($p=0.03$), more often suffered from lymphedema ($p=0.01$) and significantly more often had to wear stockings. ($p=0.003$) Sexual function did not differ.(135)

Long term effect of surgery

Jones et al. included vulvectomy, radical wide local excision, lymphadenectomy, sentinel node excision, adjuvant radiotherapy and chemotherapy. The study revealed long-term effects on women with different surgical approaches in different stages of their disease. After 12 months, the study showed significant worse mental health in women with advanced vulvar cancer compared to early stage cancer. ($p=0.037$) However, quality of life was affected by all women. Especially in domains of fatigue, pain,sexual-, social and physical functioning. ($p<0.05$) Lymphedema and urinary incontinence lead to an inability to carry out daily activities, pain negatively affected mobility and women's relationship with children got affected, due to their inability to carry out leisure activities.(111)

Surgery compared to healthy controls

De Melo Ferreira et al.(59) included vulvectomy and inguinofemoral lymphadenectomy. Patients after vulvectomy and inguinofemoral lymphadenectomy revealed significantly higher severity and occurrence of lymphoedema of the lower extremities, when compared to healthy controls. ($p=0.003$ and $p<0.001$) Furthermore, a higher body mass index and older age were associated with a higher occurrence of lymphedema of the lower extremities. ($p=0.04$ for both) The physical, emotional, social, cognitive, fatigue, sleep, pain, financial domains of quality of life showed significantly decreased scores in women with lymphedema of the lower extremities. ($p < 0.05$) Sexuality and urinary function were not significantly influenced by the surgical procedure.(59)

Vulva defect reconstruction with V-shaped or defect-shaped perfunda artery perforator flaps

All patients showed good FACT-V scores on quality of life. Patients with a V-shaped flap showed higher wound dehiscence. Defect-shaped flaps required less material($p=0.004$) and revealed a more appealing cosmetically outcome. (142)

Vulvectomy with inguinofemoral lymphadenectomy and sartorius tendon vs. sartorius transposition

The study revealed less incidences of chronic lymphedema and wound break and shorter recovery times of inguinal wounds after sartorius tendon transposition. ($p=0.022$, $p=0.012$ and $p=0.026$) Surgical time, amounts of bleeding and recurrences rates, overall survival and progression-free survival did not significantly differ between sartorius and sartorius tendon transposition. Global health, pain, emotional and physical functioning revealed significantly better scores in women after sartorius tendon transposition. ($p<0.05$)(131)

Additional Information

Usage of individual questionnaires

Each questionnaire and its individual usage for either surgical or conservative treatment is shown in

Table 24. The distribution of usage of questionnaires for conservative and surgical treatment is shown in Figure 6.

Table 24 Usage of individual questionnaires

	Conservative treatment	Surgical Treatment
FSFI	2	7
FSDS	1	/
SAQ	/	/
DLQI	/	1
SF-36	/	3
SF-12	/	2
EORTC-QLQ30	2	7
Skindex 29	2	/
FACT-V	/	2

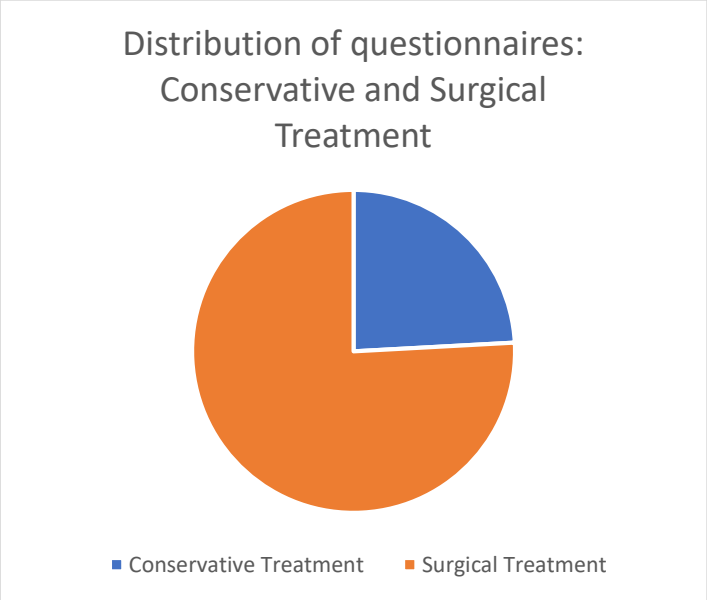

Figure 6 Distribution of questionnaires: Conservative and Surgical Treatment

Discussion

This review has given an overview on the sexuality and quality of life in women suffering from dermatoses, vulvar intraepithelial neoplasia or vulvar cancer, as measured via different questionnaires. It further evaluated different treatment strategies (conservative or surgical) and their influence on quality of life and sexuality of affected women. Although it was already widely assumed that dermatoses, vulvar intraepithelial neoplasia and vulvar cancer are having a strong negative effect on sexuality and quality of life in women, only few studies include comparable questionnaires allowing a conclusion of the most influencing factors and most affected areas in life to be drawn.(5, 20, 75, 89, 152) Many different measurement approaches were found but a comparison was often not possible, because the questionnaires were addressing different aspects of life and sexuality. Furthermore, questionnaires were mostly addressed to women after a specific treatment. Very rarely the influence of the disease itself was discussed. Nevertheless, this literature search was also able to detect a negative impact of vulvar diseases and their therapy on quality of life and sexuality in women.

Dermatoses

This review showed, that sexuality of women suffering from vulvar dermatoses was highly impaired. Despite different medication strategies, such as clobetasol and pimecrolimus aided to achieve more sexual functioning, sexuality remained negatively influenced.(55) It is possible, that women already suffered from architectural changes of the vulva beforehand, which was not cured with the treatment of clobetasol or pimecrolimus itself. All treatment strategies included in this thesis (clobetasol, pimecrolimus, fat grafting, lysis of adhesions, photodynamic therapy and human fibroblast lysate cream), that measured sexuality, either did not reveal results on the exact questionnaire scores or failed to sufficiently help women with dermatoses and their sexuality.(12, 55, 62, 72, 73) It might be helpful, to offer sexual counselling for those women, to inform them on how to manage their sexuality and their disease in order to achieve a regain of their sexual functioning.

Quality of life revealed small to massive effects in all publications. Treatment, like UV-A1, Clobetasol or fat grafting increased quality of life, but either did not reveal

exact questionnaire scores or were not sufficient.(12, 122, 123) Hence, women with dermatoses continued to suffer from an impaired quality of life even after treatment. Schwegler et al.(122) revealed, that especially emotional worries, concern and frustration were influencing quality of life. A better education on dermatoses via their gynecologist, dermatologist or general practitioner might help those women to handle their disease better. Mental support by their supervising doctors, psychiatrist or psychologist could aid to process the diagnosis and handling of the disease.

Vulvar Intraepithelial Neoplasia

VIN women revealed fewer sexual activity and impaired sexual functioning throughout the study. Emotional burden, including the fear of infecting others or developing cancer seemed to be play and important role in reducing sexual functioning. Further, surgery, could still damage the body image of women and increase their anxiety of revealing their body to a partner. Partner counselling, proper education and mental support by gynecologists, general practitioners, psychiatrists or psychologist could help to regain sexual confidence and restore sexual functioning. Less radical surgery in women, which is widely aimed for, and Imiquimod therapy prevented from massive architectural changes of the vulva. Still, they did not result in a regain of sexual functioning.

Quality of life in VIN women seemed negatively affected in all studies. Similarly, sexuality, pruritus and the emotional burden decreased their quality of life. Kobleder et al.(112) revealed less impaired quality of life in VIN-affected women compared to vulvar cancer patients, although it was still decreased compared to healthy individuals. The author explained this finding with the difference in age between VIN patients, who are mostly younger, and vulvar cancer patients who are typically older. Older women might already suffer other from age-related impairments affecting their quality of life. Nevertheless, a good education on the management of vulvar intraepithelial neoplasia should be given to increase quality of life in VIN women.

Vulvar Cancer

Sexual dysfunction, based on questionnaire cut-off points, can be found in women

suffering from vulvar cancer in all included studies. Nevertheless, there were still differences between different surgical approaches result in an equal impairment of sexual function. These surgical approaches included sparing or resecting the clitoris, sentinel node excision or lymphadenectomy and radical or less extensive surgery. (49, 59-61, 65) A prospective study, including a larger sample size of women and a sexual questionnaire would be necessary to address conflicting findings.

All studies revealed an impairment of quality of life in vulvar cancer patients. Jones et al.(111) revealed higher stages of the disease resulting in even lower quality of life than earlier stages, which may be explained by more radical treatment approaches and heavier disease burdens, including greater anxiety and fear of progression. Mental support and education on management of the disease might aid, to increase quality of life in vulvar cancer patients. Improved surgical techniques and reconstructive surgery may further help reduce suffering associated with aggressive surgical therapy.

Comparison of diseases

The FSFI was the only questionnaire, which had been used for all 3 diseases, resulting in the highest influence on sexual functioning provided by vulvar cancer, followed by dermatoses and VIN. This could result from fear of progression in vulvar cancer patients, including metastatic spread or even the death. Furthermore, more radical treatment approaches, including total vulvectomy and total inguinofemoral lymphadenectomy are being used for vulvar cancer women, while VIN-surgery typically only includes the removal of the affected tissue and women, suffering from dermatoses rarely receive surgery at all. Women with vulvar dermatoses typically suffer from a permanent itch, caused by the disease, while VIN often develops asymptomatically. Furthermore, topical cortisone treatment in women with vulvar dermatoses often goes on for many years, while VIN can be cured via surgical removal of the affected tissue, imiquimod therapy or even spontaneous regression of the disease.

Limitations

The determination of sexuality and quality of life is very subjective, questionnaires

might fail to interpret the impact of a vulvar disease on an individual woman. The influential factors of sexuality and quality of life often differed between questionnaires that were included in this diploma thesis. Hence, interpretation of the compared results could be considered to be controversial. Furthermore, the usage of the individual questionnaires varied between disease and treatment strategies, which made a direct comparison more difficult. A concrete conclusion of some treatment strategies could not be given, reasoning to its rare appearance in publications or because the procedure must be further tested. As the FSFI was the only questionnaire to assess sexuality in all three included diseases, a direct comparison based on the disease could only be given for sexual functioning. Quality of life measurement was not performed with the same questionnaire for all three diseases and could therefore not be directly compared.

Conclusion

While multiple publications on dermatoses and vulvar cancer were found, significantly less information was available on vulvar intraepithelial neoplasia. Furthermore, the comparison of the questionnaires assessing patient's quality of life and sexual functioning was often not possible or difficult, due to questionnaires addressing different aspects of quality of life or sexuality. Many questionnaires were not designed for vulvar diseases but cancer or skin diseases. The research also revealed, that questionnaires were more often used for measuring outcome a specific therapy, rather than the actual changes caused by the disease itself. Further it revealed, that there is more variety of questionnaires on quality of life than questionnaires on female sexuality. This might be the case, because sexuality, as a very private topic, is less willingly talked about than general quality of life. Furthermore, the absence of masturbation as an indicator of sexual function within questionnaires may have resulted in difficulties in women self-assessing sexual function independently of respective sexual relationships. Hence, a more exact definition of the female sexuality, including frequency, emotions, pain, orgasm, lubrication and masturbation might help to create a more inclusive questionnaire to measure the female sexual function in women with a vulvar condition. In addition, more studies including the same standardized questionnaire would be necessary to draw valid conclusions. Yet, it can be said, that women with

vulvar dermatoses, VIN and vulvar cancer are all suffering from sexual dysfunction and often reveal an impairment in their quality of life, either through symptoms, caused by the disease itself, or treatment associated side effects.

References

1. Häggström M. Lichen sclerosus on an 82 year old woman, showing an ivory white coloring in the vulva, also stretching downward to the perineum. [accessed 30.05.2018] 2014 [updated 28 July 2014. Available from: https://en.wikipedia.org/wiki/Lichen_sclerosus#/media/File:Lichen_sclerosus.jpg.

2. Davarmanesh M, Samsami Dehaghani A, Deilami Z, Monabbati A, Dastgheib L. Frequency of Genital Involvement in Women with Oral Lichen Planus in Southern Iran. Dermatology Research and Practice. 2012;2012:365230.

3. Kramer F, Hertel H, Hillemanns P. Use of the Sentinel Lymph Node Technique Compared to Complete Inguino-femoral Lymph Node Removal in Patients with Invasive Vulvar Cancer in Germany. Geburtshilfe und Frauenheilkunde. 2013;73(2):142-7.

4. Kim J-M, Lee H-J, Kim S-H, Kim H-S, Ko H-C, Kim B-S, et al. Efficacy of 5% Imiquimod Cream on Vulvar Intraepithelial Neoplasia in Korea: Pilot Study. Annals of Dermatology. 2015;27(1):66-70.

5. Fruchter R, Melnick L, Pomeranz MK. Lichenoid vulvar disease: A review. Int J Womens Dermatol. 2017;3(1):58-64.

6. Breckwoldt MM, Gerhard. Gynäkologie und Geburtshilfe. Stuttgart2008.

7. Weyerstahl TS, Manfred. Gynäkologie und Geburtshilfe. Stuttgart: Thieme; 2013.

8. Clerico C, Lari A, Mojallal A, Boucher F. Anatomy and Aesthetics of the Labia Minora: The Ideal Vulva? Aesthetic plastic surgery. 2017;41(3):714-9.

9. 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. 2012;9(2):361-71.

10. Haefner HK, Aldrich NZ, Dalton VK, Gagne HM, Marcus SB, Patel DA, et al. The impact of vulvar lichen sclerosus on sexual dysfunction. J Womens Health (Larchmt). 2014;23(9):765-70.

11. Kirtschig G. Lichen Sclerosus-Presentation, Diagnosis and Management. Dtsch Arztebl Int. 2016;113(19):337-43.

12. Boero V, Brambilla M, Sipio E, Liverani CA, Di Martino M, Agnoli B, et al. Vulvar lichen sclerosus: A new regenerative approach through fat grafting. Gynecol Oncol. 2015;139(3):471-5.

13. Brauer M, van Lunsen RHW, Laan ETM, Burger MPM. A Qualitative Study

on Experiences After Vulvar Surgery in Women With Lichen Sclerosus and Sexual Pain. The Journal of Sexual Medicine. 2016;13(7):1080-90.

14. Doyen J, Demoulin S, Delbecque K, Goffin F, Kridelka F, Delvenne P. Vulvar skin disorders throughout lifetime: about some representative dermatoses. Biomed Res Int. 2014;2014:595286.

15. Fistarol SK, Itin PH. Diagnosis and treatment of lichen sclerosus: an update. Am J Clin Dermatol. 2013;14(1):27-47.

16. Welz-Kubiak K, Reich A, Szepietowski JC. Clinical Aspects of Itch in Lichen Planus. Acta Derm Venereol. 2017;97(4):505-8.

17. Pérez-López FR, Vieira-Baptista P. Lichen sclerosus in women: a review. Climacteric. 2017:1-9.

18. Borghi A, Minghetti S, Toni G, Virgili A, Corazza M. Combined therapy in vulvar lichen sclerosus: does topical tretinoin improve the efficacy of mometasone furoate? J Dermatolog Treat. 2017:1-8.

19. Criscuolo AA, Schipani C, Cannizzaro MV, Messinese S, Chimenti S, Piccione E, et al. New therapeutic approaches in the treatment of anogenital lichen sclerosus: does photodynamic therapy represent a novel option? Giornale italiano di dermatologia e venereologia : organo ufficiale, Societa italiana di dermatologia e sifilografia. 2017;152(2):117-21.

20. van der Meijden WI, Boffa MJ, Ter Harmsel WA, Kirtschig G, Lewis FM, Moyal-Barracco M, et al. 2016 European guideline for the management of vulval conditions. J Eur Acad Dermatol Venereol. 2017;31(6):925-41.

21. Lynch PJ. Lichen simplex chronicus (atopic/neurodermatitis) of the anogenital region. Dermatologic Therapy. 2004;17(1):8-19.

22. Reyes MC, Cooper K. An update on vulvar intraepithelial neoplasia: terminology and a practical approach to diagnosis. J Clin Pathol. 2014;67(4):290-4.

23. Mazellier S, Dadone-Montaudie B, Chevallier A, Loubatier C, Vitale S, Cardot-Leccia N, et al. Papillomavirus genotyping on formaldehyde fixed paraffin-embedded tissues in vulvar intraepithelial neoplasia. Arch Gynecol Obstet. 2017;296(4):811-7.

24. Bornstein J, Bogliatto F, Haefner HK, Stockdale CK, Preti M, Bohl TG, et al. The 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology of Vulvar Squamous Intraepithelial Lesions. Obstet Gynecol. 2016;127(2):264-8.

25. Yang EJ, Kong CS, Longacre TA. Vulvar and Anal Intraepithelial Neoplasia: Terminology, Diagnosis, and Ancillary Studies. Adv Anat Pathol. 2017;24(3):136-50.

26. Sand FL, Thomsen SF. Clinician's Update on the Benign, Premalignant, and Malignant Skin Tumours of the Vulva: The Dermatologist's View. Int Sch Res Notices. 2017;2017:2414569.

27. Kaushik S, Pepas L, Nordin A, Bryant A, Dickinson HO. Surgical interventions for high-grade vulval intraepithelial neoplasia. Cochrane Database Syst Rev. 2014(3):CD007928.

28. Faber MT, Sand FL, Albieri V, Norrild B, Kjaer SK, Verdoodt F. Prevalence and type distribution of human papillomavirus in squamous cell carcinoma and intraepithelial neoplasia of the vulva. Int J Cancer. 2017;141(6):1161-9.

29. Mitra S, Sharma MK, Kaur I, Khurana R, Modi KB, Narang R, et al. Vulvar carcinoma: dilemma, debates, and decisions. Cancer Manag Res. 2018;10:61-8.

30. Lee LJ, Howitt B, Catalano P, Tanaka C, Murphy R, Cimbak N, et al. Prognostic importance of human papillomavirus (HPV) and p16 positivity in squamous cell carcinoma of the vulva treated with radiotherapy. Gynecol Oncol. 2016;142(2):293-8.

31. Regauer S, Reich O. Etiology of vulvar cancer will impact on treatment options and therapy outcome: Two major pathways of vulvar cancer. Gynecol Oncol. 2013;131(1):246-7.

32. Ralph J. Lellé VK. Kolposkopie in der Praxis. Berlin Heidelberg: Springer-Verlag 2014. 319 p.

33. Comino R, Coronado PJ, Cararach M, Nieto A, Martinez-Escoriza JC, Salamanca A, et al. Spanish consensus on vulvar disorders in postmenopausal women. Maturitas. 2015;80(2):226-33.

34. Shetty AS, Menias CO. MR Imaging of Vulvar and Vaginal Cancer. Magnetic Resonance Imaging Clinics of North America. 2017;25(3):481-502.

35. Greer BE, Koh WJ. New NCCN Guidelines for Vulvar Cancer. J Natl Compr Canc Netw. 2016;14(5 Suppl):656-8.

36. Pouwer AW, Arts HJ, van der Velden J, de Hullu JA. Limiting the morbidity of inguinofemoral lymphadenectomy in vulvar cancer patients; a review. Expert Rev Anticancer Ther. 2017;17(7):615-24.

37. Rao YJ, Chin RI, Hui C, Mutch DG, Powell MA, Schwarz JK, et al. Improved survival with definitive chemoradiation compared to definitive radiation alone in

squamous cell carcinoma of the vulva: A review of the National Cancer Database. Gynecol Oncol. 2017.

38. Woolderink JM, de Bock GH, de Hullu JA, Davy MJ, van der Zee AG, Mourits MJ. Patterns and frequency of recurrences of squamous cell carcinoma of the vulva. Gynecol Oncol. 2006;103(1):293-9.

39. Borghi A, Minghetti S, Toni G, Virgili A, Corazza M. Combined therapy in vulvar lichen sclerosus: does topical tretinoin improve the efficacy of mometasone furoate? J Dermatolog Treat. 2017;28(6):559-63.

40. Brauer M, van Lunsen RH, Laan ET, Burger MP. A Qualitative Study on Experiences After Vulvar Surgery in Women With Lichen Sclerosus and Sexual Pain. J Sex Med. 2016;13(7):1080-90.

41. Rao YJ, Chin RI, Hui C, Mutch DG, Powell MA, Schwarz JK, et al. Improved survival with definitive chemoradiation compared to definitive radiation alone in squamous cell carcinoma of the vulva: A review of the National Cancer Database. Gynecol Oncol. 2017;146(3):572-9.

42. 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. Journal of sex & marital therapy. 2000;26(2):191-208.

43. Derogatis LR, Rosen R, Leiblum S, Burnett A, Heiman J. The Female Sexual Distress Scale (FSDS): initial validation of a standardized scale for assessment of sexually related personal distress in women. Journal of sex & marital therapy. 2002;28(4):317-30.

44. Thirlaway K, Fallowfield L, Cuzick J. The Sexual Activity Questionnaire: A measure of women's sexual functioning. Quality of Life Research. 1996;5(1):81-90.

45. Meston CM. Validation of the Female Sexual Function Index (FSFI) in Women with Female Orgasmic Disorder and in Women with Hypoactive Sexual Desire Disorder. Journal of sex & marital therapy. 2003;29(1):39-46.

46. Eaton AA, Baser RE, Seidel B, Stabile C, Canty JP, Goldfrank DJ, et al. Validation of Clinical Tools for Vaginal and Vulvar Symptom Assessment in Cancer Patients and Survivors. J Sex Med. 2017;14(1):144-51.

47. Gerstenberger EP, Rosen RC, Brewer JV, Meston CM, Brotto LA, Wiegel M, et al. Sexual desire and the female sexual function index (FSFI): a sexual desire cutpoint for clinical interpretation of the FSFI in women with and without hypoactive sexual desire disorder. J Sex Med. 2010;7(9):3096-103.

48. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. Journal of sex & marital therapy. 2005;31(1):1-20.

49. Hazewinkel MH, Laan ET, Sprangers MA, Fons G, Burger MP, Roovers JP. Long-term sexual function in survivors of vulvar cancer: a cross-sectional study. Gynecol Oncol. 2012;126(1):87-92.

50. Giraldi A, Rellini A, Pfaus JG, Bitzer J, Laan E, Jannini EA, et al. Questionnaires for assessment of female sexual dysfunction: a review and proposal for a standardized screener. J Sex Med. 2011;8(10):2681-706.

51. C. Brown PD, U. Tennessee, Memphis, TN; J. Heiman, Ph.D., U. Washington, Seattle, WA.; S. Leiblum, Ph.D. FSFI Scoring Appendix.pdf http://www.fsfiquestionnaire.com/: Bayer AG, Zonagen, Inc. and Target Health Inc.; 2000 [21.02.2018]. Available from: http://www.fsfiquestionnaire.com/.

52. Likes WM, Stegbauer C, Tillmanns T, Pruett J. Pilot study of sexual function and quality of life after excision for vulvar intraepithelial neoplasia. The Journal of reproductive medicine. 2007;52(1):23-7.

53. Farmer MA, Meston CM. Predictors of genital pain in young women. Arch Sex Behav. 2007;36(6):831-43.

54. Ribeiro MC, Nakamura MU, Torloni MR, Scanavino MdT, Scomparini FB, Mattar R. Female Sexual Function of Overweight Women with Gestational Diabetes Mellitus – A Cross-Sectional Study. PLoS ONE. 2014;9(4):e95094.

55. Burrows LJ, Creasey A, Goldstein AT. The treatment of vulvar lichen sclerosus and female sexual dysfunction. J Sex Med. 2011;8(1):219-22.

56. Carter J, Stabile C, Seidel B, Baser RE, Goldfarb S, Goldfrank DJ. Vaginal and sexual health treatment strategies within a female sexual medicine program for cancer patients and survivors. J Cancer Surviv. 2017;11(2):274-83.

57. Cendejas BR, Smith-McCune KK, Khan MJ. Does treatment for cervical and vulvar dysplasia impact women's sexual health? Am J Obstet Gynecol. 2015;212(3):291-7.

58. Cheng H, Oakley A, Conaglen JV, Conaglen HM. Quality of Life and Sexual Distress in Women With Erosive Vulvovaginal Lichen Planus. J Low Genit Tract Dis. 2017;21(2):145-9.

59. de Melo Ferreira AP, de Figueiredo EM, Lima RA, Candido EB, de Castro Monteiro MV, de Figueiredo Franco TM, et al. Quality of life in women with vulvar cancer submitted to surgical treatment: a comparative study. Eur J Obstet Gynecol Reprod Biol. 2012;165(1):91-5.

60. Forner DM, Dakhil R, Lampe B. Can clitoris-conserving surgery for early vulvar cancer improve the outcome in terms of quality of life and sexual sensation? Eur J Obstet Gynecol Reprod Biol. 2013;171(1):150-3.

61. Forner DM, Dakhil R, Lampe B. Quality of life and sexual function after surgery in early stage vulvar cancer. Eur J Surg Oncol. 2015;41(1):40-5.

62. Goldstein AT, Burrows LJ, Belkin ZR, Pfau R, Bremmer M, Goldfinger C, et al. Safety and efficacy of human fibroblast lysate cream for vulvar lichen sclerosus: a randomized placebo-controlled trial. Acta Derm Venereol. 2015;95(7):847-9.

63. Gordon D, Gardella C, Eschenbach D, M. MC. High prevalence of sexual dysfunction in a vulvovaginal specialty clinic. J Low Genit Tract Dis. 2016;20(1):80-4.

64. Grimm D, Eulenburg C, Brummer O, Schliedermann AK, Trillsch F, Prieske K, et al. Sexual activity and function after surgical treatment in patients with (pre)invasive vulvar lesions. Support Care Cancer. 2016;24(1):419-28.

65. Grimm D, Hasenburg A, Eulenburg C, Steinsiek L, Mayer S, Eltrop S, et al. Sexual Activity and Function in Patients With Gynecological Malignancies After Completed Treatment. Int J Gynecol Cancer. 2015;25(6):1134-41.

66. Huffman LB, Hartenbach EM, Carter J, Rash JK, Kushner DM. Maintaining sexual health throughout gynecologic cancer survivorship: A comprehensive review and clinical guide. Gynecol Oncol. 2016;140(2):359-68.

67. Lavoue V, Lemarrec A, Bertheuil N, Henno S, Mesbah H, Watier E, et al. Quality of life and female sexual function after skinning vulvectomy with split-thickness skin graft in women with vulvar intraepithelial neoplasia or vulvar Paget disease. Eur J Surg Oncol. 2013;39(12):1444-50.

68. Lindau ST, Abramsohn EM, Matthews AC. A manifesto on the preservation of sexual function in women and girls with cancer. Am J Obstet Gynecol. 2015;213(2):166-74.

69. Mirabeau-Beale KL, Viswanathan AN. Quality of life (QOL) in women treated for gynecologic malignancies with radiation therapy: a literature review of patient-reported outcomes. Gynecol Oncol. 2014;134(2):403-9.

70. Pilger A, Richter R, Fotopoulou C, Beteta C, Klapp C, J. S. Quality of life and sexuality of patients after treatment for gynaecological malignancies: results of a prospective study in 55 patients. Anticancer Res. 2012;32(11):5045-9.

71. Simpson RC, Thomas KS, Murphy R. Outcome measures for vulval skin conditions: a systematic review of randomized controlled trials. Br J Dermatol. 2013;169(3):494-501.

72. Skrzypulec V, Olejek A, Drosdzol A, Nowosielski K, Kozak-Darmas I, S. W. Sexual functions and depressive symptoms after photodynamic therapy for vulvar lichen sclerosus in postmenopausal women from the Upper Silesian Region of Poland. J Sex Med. 2009;6(12):3395-400.

73. Suzuki V, Haefner HK, Piper CK, O'Gara C, Reed BD. Postoperative sexual concerns and functioning in patients who underwent lysis of vulvovaginal adhesions. J Low Genit Tract Dis. 2013;17(1):33-7.

74. Van de Nieuwenhof HP, Meeuwis KA, Nieboer TE, Vergeer MC, Massuger LF, De Hullu JA. The effect of vulvar lichen sclerosus on quality of life and sexual functioning. J Psychosom Obstet Gynaecol. 2010;31(4):279-84.

75. Wylomanski S, Bouquin R, Hanf M, Winer N, Dreno B, Rouzier R, et al. Sexual well-being in patients with vulvar disease: results from a preliminary prospective matched case-control study. Eur J Obstet Gynecol Reprod Biol. 2015;194:106-10.

76. Carpenter JS, Reed SD, Guthrie KA, Larson JC, Newton KM, Lau RJ, et al. Using an FSDS-R Item to Screen for Sexually Related Distress: A MsFLASH Analysis. Sex Med. 2015;3(1):7-13.

77. Derogatis L, Clayton A, Lewis-D'Agostino D, Wunderlich G, Fu Y. Validation of the female sexual distress scale-revised for assessing distress in women with hypoactive sexual desire disorder. J Sex Med. 2008;5(2):357-64.

78. Kirtschig G, Becker K, Gunthert A, Jasaitiene D, Cooper S, Chi CC, et al. Evidence-based (S3) Guideline on (anogenital) Lichen sclerosus. J Eur Acad Dermatol Venereol. 2015;29(10):e1-43.

79. Vistad I, Fossa SD, Kristensen GB, Mykletun A, Dahl AA. The sexual activity questionnaire: pychometric properties and normative data in a norwegian population sample. J Womens Health (Larchmt). 2007;16(1):139-48.

80. Nagele E, Reich O, Greimel E, Dorfer M, Haas J, Trutnovsky G. Sexual Activity, Psychosexual Distress, and Fear of Progression in Women With Human Papillomavirus-Related Premalignant Genital Lesions. J Sex Med. 2016;13(2):253-9.

81. Stead ML, Crocombe WD, Fallowfield LJ, Selby P, Perren TJ, Garry R, et al. Sexual activity questionnaires in clinical trials: acceptability to patients with gynaecological disorders. BJOG: An International Journal of Obstetrics & Gynaecology. 1999;106(1):50-4.

82. Vermeulen R, Beurden M, Kieffer J, Bleiker E, Valdimarsdottir H, Massuger L, et al. Hormone replacement therapy after risk-reducing salpingo-oophorectomy minimises endocrine and sexual problems: A prospective study2017. 159-67 p.

83. Goncalves V. Long-term quality of life in gynecological cancer survivors. Curr Opin Obstet Gynecol. 2010;22(1):30-5.

84. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. Clinical and Experimental Dermatology. 1994;19(3):210-6.

85. Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36): I. Conceptual Framework and Item Selection. Medical care. 1992;30(6):473-83.

86. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Medical care. 1996;34(3):220-33.

87. Chren MM, Lasek RJ, Quinn LM, Mostow EN, Zyzanski SJ. Skindex, a quality-of-life measure for patients with skin disease: reliability, validity, and responsiveness. J Invest Dermatol. 1996;107(5):707-13.

88. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.

89. Janda M, Obermair A, Cella D, Crandon AJ, Trimmel M. Vulvar cancer patients' quality of life: a qualitative assessment. International Journal of Gynecological Cancer. 2004;14(5):875-81.

90. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1993;11(3):570-9.

91. Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? J Invest Dermatol. 2005;125(4):659-64.

92. Yuksek J, Sezer E, Aksu M, Erkokmaz U. Transcutaneous electrical nerve stimulation for reduction of pruritus in macular amyloidosis and lichen simplex. J Dermatol. 2011;38(6):546-52.

93. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clinical and experimental dermatology. 1994;19(3):210-6.

94. Kouris A, Katoulis A, Christodoulou C, Rigopoulos D, Tsatovidou R, Petridis A, et al. Quality of life and obsessive-compulsive behavior in patients with lichen

simplex chronicus. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG. 2015;13(2):162-3.

95. Lockhart J, Gray NM, Cruickshank ME. The development and evaluation of a questionnaire to assess the impact of vulval intraepithelial neoplasia: a questionnaire study. BJOG. 2013;120(9):1133-42.

96. McFadden KM, Sharp L, Cruickshank ME. The prospective management of women with newly diagnosed vulval intraepithelial neoplasia: clinical outcome and quality of life. J Obstet Gynaecol. 2009;29(8):749-53.

97. Sawant NS, Vanjari NA, Khopkar U, Adulkar S. A study of depression and quality of life in patients of lichen planus. ScientificWorldJournal. 2015;2015:817481.

98. Simpson RC, Littlewood SM, Cooper SM, Cruickshank ME, Green CM, Derrick E, et al. Real-life experience of managing vulval erosive lichen planus: a case-based review and U.K. multicentre case note audit. Br J Dermatol. 2012;167(1):85-91.

99. Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: Scoping review. SAGE Open Med. 2016;4:2050312116671725.

100. Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ (Clinical research ed). 1992;305(6846):160-4.

101. McHorney CA, Ware JE, Jr., Rogers W, Raczek AE, Lu JF. The validity and relative precision of MOS short- and long-form health status scales and Dartmouth COOP charts. Results from the Medical Outcomes Study. Medical care. 1992;30(5 Suppl):Ms253-65.

102. Carpenter KM, Fowler JM, Maxwell GL, Andersen BL. Direct and buffering effects of social support among gynecologic cancer survivors. Ann Behav Med. 2010;39(1):79-90.

103. Ezat SW, Aljunid S. Comparative cost-effectiveness of HPV vaccines in the prevention of cervical cancer in Malaysia. Asian Pacific journal of cancer prevention : APJCP. 2010;11(4):943-51.

104. Flynn P, Kew F, Kisely SR. Interventions for psychosexual dysfunction in women treated for gynaecological malignancy. Cochrane Database Syst Rev. 2009(2):CD004708.

105. Goker A, Guvenal T, Yanikkerem E, Turhan A, Koyuncu FM. Quality of life in women with gynecologic cancer in Turkey. Asian Pacific journal of cancer

prevention : APJCP. 2011;12(11):3121-8.

106. Lansdorp CA, van den Hondel KE, Korfage IJ, van Gestel MJ, van der Meijden WI. Quality of life in Dutch women with lichen sclerosus. Br J Dermatol. 2013;168(4):787-93.

107. Luckett T, King M, Butow P, Friedlander M, Paris T. Assessing health-related quality of life in gynecologic oncology: a systematic review of questionnaires and their ability to detect clinically important differences and change. Int J Gynecol Cancer. 2010;20(4):664-84.

108. Terlou A, van Seters M, Ewing PC, Aaronson NK, Gundy CM, Heijmans-Antonissen C, et al. Treatment of vulvar intraepithelial neoplasia with topical imiquimod: seven years median follow-up of a randomized clinical trial. Gynecol Oncol. 2011;121(1):157-62.

109. van Seters M, van Beurden M, ten Kate FJ, Beckmann I, Ewing PC, Eijkemans MJ, et al. Treatment of vulvar intraepithelial neoplasia with topical imiquimod. The New England journal of medicine. 2008;358(14):1465-73.

110. Simpson RC, Murphy R, Bratton DJ, Sydes MR, Wilkes S, Nankervis H, et al. Systemic therapy for vulval Erosive Lichen Planus (the 'hELP' trial): study protocol for a randomised controlled trial. Trials. 2016;17:2.

111. Jones GL, Jacques RM, Thompson J, Wood HJ, 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. 2016;25(6):656-62.

112. Kobleder A, Nikolic N, Hechinger M, Denhaerynck K, Hampl M, Mueller MD, et al. Perceived Health-Related Quality of Life in Women With Vulvar Neoplasia: A Cross Sectional Study. Int J Gynecol Cancer. 2016;26(7):1313-9.

113. Turner-Bowker D, Hogue SJ. Short Form 12 Health Survey (SF-12). In: Michalos AC, editor. Encyclopedia of Quality of Life and Well-Being Research. Dordrecht: Springer Netherlands; 2014. p. 5954-7.

114. WARE JE, KOSINSKI M, KELLER SD. A 12-Item Short-Form Health Survey: Construction of Scales and Preliminary Tests of Reliability and Validity. Medical Care. 1996;34(3):220-33.

115. Ware J, A. Kosinski M, D. Keller S. SF-12: How to Score the SF-12 Physical and Mental Health Summary Scales1998.

116. Larson CO. Use of the SF-12 Instrument for Measuring the Health of Homeless Persons. Health Services Research. 2002;37(3):733-50.

117. Shylasree TS, Karanjgaokar V, Tristram A, Wilkes AR, MacLean AB, Fiander AN. Contribution of demographic, psychological and disease-related factors to quality of life in women with high-grade vulval intraepithelial neoplasia. Gynecol Oncol. 2008;110(2):185-9.

118. Levin AO, Carpenter KM, Fowler JM, Brothers BM, Andersen BL, Maxwell GL. Sexual morbidity associated with poorer psychological adjustment among gynecological cancer survivors. Int J Gynecol Cancer. 2010;20(3):461-70.

119. Chren MM. The Skindex instruments to measure the effects of skin disease on quality of life. Dermatol Clin. 2012;30(2):231-6, xiii.

120. Prinsen CAC, Lindeboom R, Sprangers MAG, Legierse CM, de Korte J. Health-Related Quality of Life Assessment in Dermatology: Interpretation of Skindex-29 Scores Using Patient-Based Anchors. Journal of Investigative Dermatology. 2010;130(5):1318-22.

121. Prinsen CA, Lindeboom R, de Korte J. Interpretation of Skindex-29 scores: cutoffs for mild, moderate, and severe impairment of health-related quality of life. J Invest Dermatol. 2011;131(9):1945-7.

122. Schwegler J, Schwarz J, Eulenburg C, Blome C, Ihnen M, Mahner S, et al. Health-related quality of life and patient-defined benefit of clobetasol 0.05% in women with chronic lichen sclerosus of the vulva. Dermatology. 2011;223(2):152-60.

123. Terras S, Gambichler T, Moritz RK, Stucker M, Kreuter A. UV-A1 phototherapy vs clobetasol propionate, 0.05%, in the treatment of vulvar lichen sclerosus: a randomized clinical trial. JAMA Dermatol. 2014;150(6):621-7.

124. Toz E, Ozcan A, Balsak D, Avc ME, Eraslan AG, Balc DD. Potential adverse effects of prophylactic bilateral salpingo-oophorectomy on skin aging in premenopausal women undergoing hysterectomy for benign conditions. Menopause. 2016;23(2):138-42.

125. van Cranenburgh OD, Nijland SBW, Lindeboom R, de Korte J, de Rie MA, Ter Stege JA, et al. Patients with lichen sclerosus experience moderate satisfaction with treatment and impairment of quality of life: results of a cross-sectional study. Br J Dermatol. 2017;176(6):1508-15.

126. Fayers P, Bottomley A. Quality of life research within the EORTC—the EORTC QLQ-C30. European Journal of Cancer. 2002;38:125-33.

127. Fayers PM AN, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). European Organisation for Research and Treatment of Cancer. 2001 Brussels

128. 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. 2014;40(7):875-82.

129. Biglia N, Zanfagnin V, Daniele A, Robba E, Bounous VE. Lower Body Lymphedema in Patients with Gynecologic Cancer. Anticancer Res. 2017;37(8):4005-15.

130. Lawrie TA, Nordin A, Chakrabarti M, Bryant A, Kaushik S, Pepas L. Medical and surgical interventions for the treatment of usual-type vulval intraepithelial neoplasia. Cochrane Database Syst Rev. 2016(1):CD011837.

131. Li L, Kou X, Feng X, Liu F, Chao H, Wang L. Clinical application of sartorius tendon transposition during radical vulvectomy: a case control study of 58 cases at a single institution. J Gynecol Oncol. 2015;26(4):320-6.

132. Meads C, Sutton A, Malysiak S, Kowalska M, Zapalska A, Rogozinska E, et al. Sentinel lymph node status in vulval cancer: systematic reviews of test accuracy and decision-analytic model-based economic evaluation. Health Technol Assess. 2013;17(60):1-216.

133. Novackova M, Halaska MJ, Robova H, Mala I, Pluta M, Chmel R, et al. A prospective study in detection of lower-limb lymphedema and evaluation of quality of life after vulvar cancer surgery. Int J Gynecol Cancer. 2012;22(6):1081-8.

134. Novackova M, Halaska MJ, 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. 2015;25(1):166-73.

135. Oonk MH, van Os MA, de Bock GH, de Hullu JA, Ansink AC, van der Zee AG. A comparison of quality of life between vulvar cancer patients after sentinel lymph node procedure only and inguinofemoral lymphadenectomy. Gynecol Oncol. 2009;113(3):301-5.

136. Pepas L, Kaushik S, Bryant A, Nordin A, Dickinson HO. Medical interventions for high grade vulval intraepithelial neoplasia. Cochrane Database Syst Rev. 2011(4):CD007924.

137. Pepas L, Kaushik S, Nordin A, Bryant A, Lawrie TA. Medical interventions for high-grade vulval intraepithelial neoplasia. Cochrane Database Syst Rev. 2015(8):CD007924.

138. Slomovitz BM, Coleman RL, Oonk MH, van der Zee A, Levenback C. Update on sentinel lymph node biopsy for early-stage vulvar cancer. Gynecol Oncol. 2015;138(2):472-7.

139. Wenzel L. Patient-reported outcomes in sentinel lymph node procedure

versus inguinofemoral lymphadenectomy: what is the next step? Gynecol Oncol. 2009;113(3):299-300.

140. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta psychiatrica Scandinavica. 1983;67(6):361-70.

141. Janda M, Obermair A, Cella D, Perrin LC, Nicklin JL, Ward BG, et al. The functional assessment of cancer-vulvar: reliability and validity. Gynecol Oncol. 2005;97(2):568-75.

142. Chang TN, Lee CH, Lai CH, Wu CW, Chang CS, Cheng MH, et al. Profunda artery perforator flap for isolated vulvar defect reconstruction after oncological resection. J Surg Oncol. 2016;113(7):828-34.

143. Doll KM, Snavely AC, Kalinowski A, Irwin DE, Bensen JT, Bae-Jump V, et al. Preoperative quality of life and surgical outcomes in gynecologic oncology patients: a new predictor of operative risk? Gynecol Oncol. 2014;133(3):546-51.

144. Pellegrino A, Damiani GR, Mangioni C, Strippoli D, Loverro G, Cappello A, et al. Outcomes of Bleomycin-based electrochemotherapy in patients with repeated loco-regional recurrences of vulvar cancer. Acta Oncol. 2016;55(5):619-24.

145. Perrone AM, Cima S, Pozzati F, Frakulli R, Cammelli S, Tesei M, et al. Palliative electro-chemotherapy in elderly patients with vulvar cancer: A phase II trial. J Surg Oncol. 2015;112(5):529-32.

146. Perrone AM, Galuppi A, Cima S, Pozzati F, Arcelli A, Cortesi A, et al. Electrochemotherapy can be used as palliative treatment in patients with repeated loco-regional recurrence of squamous vulvar cancer: a preliminary study. Gynecol Oncol. 2013;130(3):550-3.

147. Hillemanns P, Untch M, Prove F, Baumgartner R, Hillemanns M, Korell M. Photodynamic therapy of vulvar lichen sclerosus with 5-aminolevulinic acid. Obstetrics and gynecology. 1999;93(1):71-4.

148. Osiecka BJ, Nockowski P, Jurczyszyn K, Ziolkowski P. Photodynamic therapy of vulvar lichen sclerosus et atrophicus in a woman with hypothyreosis--case report. Photodiagnosis and photodynamic therapy. 2012;9(2):186-8.

149. Kreuter A, Gambichler T, Avermaete A, Happe M, Bacharach-Buhles M, Hoffmann K, et al. Low-dose ultraviolet A1 phototherapy for extragenital lichen sclerosus: results of a preliminary study. J Am Acad Dermatol. 2002;46(2):251-5.

150. Lewis FM, Bogliatto F. Erosive vulval lichen planus--a diagnosis not to be missed: a clinical review. Eur J Obstet Gynecol Reprod Biol. 2013;171(2):214-9.

151. Wallbillich JJ, Rhodes HE, Milbourne AM, Munsell MF, Frumovitz M, Brown J, et al. Vulvar intraepithelial neoplasia (VIN 2/3): comparing clinical outcomes and evaluating risk factors for recurrence. Gynecol Oncol. 2012;127(2):312-5.

152. Likes WM, Russell C, Tillmanns T. Women's experiences with vulvar intraepithelial neoplasia. J Obstet Gynecol Neonatal Nurs. 2008;37(6):640-6.

153. Terlou A, Hage JJ, van Beurden M. Skinning clitorectomy and skin replacement in women with vulvar intra-epithelial neoplasia. J Plast Reconstr Aesthet Surg. 2009;62(3):341-5.