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Vulvar Cancer: Patterns of Recurrence, Quality of Life and Extended Indications for the Sentinel Node Technique

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Stockholm 2023

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Vulvar Cancer: Patterns of Recurrence, Quality of Life and Extended Indications for the Sentinel Node Technique

Thesis for Doctoral Degree (Ph.D.)

By

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The thesis will be defended in public at Karolinska University Hospital Eugeniavägen 3, Jan Lindh Auditorium A4:04, Stockholm, 2nd February 2024, 12.00 noon.

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Popular science summary of the thesis

Vulvar cancer is a rare disease, originating from the outer female genitals. It accounts for only 1% of all malignant diseases in women and affects mostly women older than 70 years of age. The treatment is surgical, comprising the removal of the tumour in the vulva and the lymph nodes in the groin. Advanced disease is treated by a combination of surgery and radiotherapy or by radiotherapy alone. The treatment can have serious local side-effects such as pain, scarring, leg swelling or recurrent infections, as well as problems with urinating or sexual problems. As most women are cured after their treatment and will become long-term survivors of their cancer, it is important to maintain their quality of life. However, knowledge about the course of the disease as well as the development of symptoms and health-related quality of life in vulvar cancer is very limited.

The sentinel node technique implies that, instead of all lymph nodes, only the most important lymph node in a defined area is identified and removed. By this, negative side-effects of groin surgery are reduced. However, the technique is only approved in a subgroup of women with vulvar cancer.

This thesis investigates the patterns of recurrence in women with vulvar cancer, their health-related quality of life over time, and whether more women could be offered the sentinel node technique.

The thesis is a compilation of four nationwide Swedish studies. *Study I* included 489 women with vulvar cancer who were registered in the Swedish Quality Registry for Gynaecologic Cancer between 2012 and 2015. The number and distribution of recurrences were analysed. Furthermore, it was investigated whether removing lymph nodes in the groin had an influence on the risk of recurrence or death. In *Studies II and III*, 153 women with newly diagnosed vulvar cancer between August 2019 and August 2021 completed validated questionnaires which assessed their health-related quality of life, anxiety, depression, and local symptoms. The women completed the questionnaires at the time of diagnosis (baseline), and three and twelve months after treatment. In *Study IV*, 64 women with vulvar cancer and tumours ≥ 4 cm, multifocal tumours (i.e., more than one tumour in the vulva), or a recurrence in the vulva were treated by sentinel node biopsy followed by a removal of all groin lymph nodes, and it was investigated whether the sentinel lymph node correctly predicts metastases in the lymph nodes.

Study I showed that about one in five women suffered from a recurrence, mostly in the vulva (61%). In 30% of the women, the recurrence occurred in groin lymph nodes, and in 9% at another site, e.g., abdominal lymph nodes, lung, or bones. Women who did not undergo surgery in the groins had more recurrences and a higher risk of death compared to women who did undergo groin surgery.

Studies II and III revealed that 42% of the women diagnosed newly with vulvar cancer had elevated levels of anxiety at diagnosis, which decreased to 30% of the women one year after treatment. Women who had sleeping problems, a high need for information, or persistent symptoms in the vulva reported higher levels of anxiety. Furthermore, women with severe vulvar symptoms reported impaired health-related quality of life. Leg swelling became more common after treatment.

In *Study IV,* the sentinel lymph node could be detected in 94-100% of the women and predicted the lymph node status correctly in all investigated groins.

Most women with vulvar cancer will be cured after primary treatment. In case of a recurrence, it is most often a vulvar recurrence. Surgery of the groin should be performed at primary diagnosis. Targeting sleeping problems, unmet needs for information, and persistent vulvar symptoms may decrease anxiety. Most symptoms and health-related quality of life are improved after treatment. The sentinel node biopsy seems to be safe in further subgroups of women with vulvar cancer, and launching a confirmational larger, multinational study seems to be justified.

Abstract

Background: Vulvar cancer is a rare malignancy and few studies have addressed the course of disease and the impact of physical and psychological symptoms on health-related quality of life (HRQOL) over time. In addition, extending the indication for sentinel node biopsy in vulvar cancer requires further evaluation. The overall aim of this thesis was to investigate patterns of recurrence and the trajectory of symptoms and HRQOL in a nationwide population of women with vulvar cancer, and to examine the feasibility of sentinel node biopsy in larger and multifocal tumours.

Methods: *Study I* included all women diagnosed with primary vulvar squamous cell carcinoma (VSCC) from 2012-2015 whose health data were recorded in the Swedish Quality Registry for Gynaecologic Cancer (n=489). The cumulative incidences and survival rates for local, groin, and distant recurrences were calculated. In addition, the potential impact of not performing surgical groin staging on survival was assessed. In *Studies II and III* the relationship between physical and psychological symptoms and HRQOL in a nationwide longitudinal cohort of women with primary vulvar cancer diagnosed from 2019-2021 (n=153) were examined utilizing validated questionnaires (European Organisation for Research and Treatment of Cancer (EORTC)-QLQ C30, the EORTC-QLQ VU34, the Supportive Care Needs Survey, and the Hospital Anxiety and Depression Scale). Anxiety, depression, local vulvar and lymphoedema symptoms and their impact on HRQOL were investigated at the time of diagnosis, as well as 3 and 12 months after treatment. *Study IV* was a nationwide prospective, single-arm interventional pilot study. Women with VSCC and tumours ≥ 4 cm in diameter (Group 1), multifocal tumours (Group 2) or a first local recurrence (Groups 3 and 4) diagnosed between 2019-2022 (total n=64) underwent sentinel node biopsy in addition to standard inguinofemoral lymphadenectomy. Detection rates and negative predictive values were calculated.

Results: In *Study I* after a median follow-up of 52 months, the recurrence rate was 22.3% (vulva 61%, groin 30%, and distant 9%). Groin and distant recurrences occurred primarily within the first two years after treatment, while the incidence of local recurrences increased continuously during follow-up. The median two-year post-recurrence overall survival was 57.8% for vulvar, 17.2% for groin, and 0% for distant recurrences. Omission of surgical groin staging in 23.7% of the patients with presumed stage IB-II disease was associated with poorer survival. In *Studies II and III* 140 (92%) of the women completed at least one questionnaire and 105 (69%) completed all three. At the time of diagnosis, 41.8% of the women reported elevated anxiety, a proportion that declined to 29.5% 12 months after treatment. Insomnia, a high need for information and persistent vulvar symptoms were associated with enhanced anxiety. Vulvar symptoms were associated with impaired HRQOL and improved after treatment, whereas symptoms of leg lymphoedema became more common after treatment. Emotional, role, cognitive, and social functioning, as well as global and mental health became better following treatment. In *Study IV*, the

detection rates in Groups 1 and 2 were 94.1–100% per patient and 84.1–85.3% per groin, respectively. There were no false-negative sentinel nodes, i.e., the negative predictive value was 100% (95% CI 91.2%-100% for Group 1 and 83.9%-100% for Group 2).

Conclusions: Local recurrences are common in patients with vulvar cancer, with a stable incidence throughout the period of surveillance. Lack of surgical groin staging is associated with poorer survival. Women with primary vulvar cancer report a high prevalence of vulvar symptoms, anxiety, and impaired HRQOL at the time of diagnosis. Alleviating vulvar symptoms, insomnia, and unmet needs for information might reduce anxiety. Extending the application of sentinel node biopsy to women with tumours ≥ 4 cm in diameter, as well as to those with multifocal tumours seems feasible.

List of scientific papers

I. Zach D, Åvall-Lundqvist E, Falconer H, Hellman K, Johansson H, Flöter Rådestad A

Patterns of recurrence and survival in vulvar cancer: A nationwide population-based study

Gynecol Oncol. 2021 Jun, 161(3): 748-754
doi: 10.1016/j.ygyno.2021.03.013

II. Zach D, Jensen PT, Falconer H, Kolkova Z, Stenström Bohlin K, Kjølhede P, Åvall-Lundqvist, E, Flöter Rådestad, A

Anxiety and depression among women with newly diagnosed vulvar cancer - A nationwide longitudinal study

Acta Obstet Gynecol Scand. 2023;00:1-11
doi: 10.1111/aogs.14710

III. Zach D, Jensen PT, Falconer H, Kolkova Z, Stenström Bohlin K, Kjølhede P, Raices Cruz I, Åvall-Lundqvist, E, Flöter Rådestad, A

The impact of local symptoms on health-related quality of life in vulvar cancer survivors - A nationwide longitudinal study

In manuscript

IV. Zach D, Stenström Bohlin K, Kannisto P, Moberg L, Kjölhede P

Time to extend the indication for sentinel node biopsy in vulvar cancer? Results from a prospective nationwide Swedish study

Int J Gynecol Cancer. Dec 2023;33(12):1845-1852
doi: 10.1136/ijgc-2023-004790

Contents

List of abbreviations

BMI	Body-mass index
CD	Clavien Dindo
CI	Confidence interval
CIR	Cumulative incidence rate
CRT	Chemoradiotherapy
DEVIL	Differentiated exophytic vulvar intraepithelial lesion
dVIN	Differentiated vulvar intraepithelial neoplasia
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
ESGO	European Society for Gynaecologic Oncology
FACIT.org	Functional assessment of Chronic Illness Therapy Organisation
FIGO	International Federation of Gynaecology and Obstetrics
GEE	Generalised estimated equations
GOG	Gynaecologic Oncology Group
HADS	Hospital Anxiety and Depression Scale
HADS-A	HADS Anxiety scale
HADS-D	HADS Depression scale
HPV	Human papillomavirus
HR	Hazard ratio
HRQOL	Health-related quality of life
HSIL	High grade squamous intraepithelial lesion
IFL	Inguinofemoral lymphadenectomy
ITC	Isolated tumour cells
LLE	Lymphoedema of the lower extremities
LVSI	lymphovascular space invasion
MDT	Multidisciplinary team conference
MID	Minimally important difference
OS	Overall survival
PROM	Patient reported outcome measure

QoL	Quality of life
RCT	Randomised controlled trial
RFS	Recurrence-free survival
RR	Risk ratio
RT	Radiotherapy
SCC	Squamous cell carcinoma
SCNS	Supportive care needs survey
SD	Standard deviation
SGS	Surgical groin staging
SNB	Sentinel node biopsy
SN	Sentinel node
SQRGC	Swedish Quality Registry of Gynaecologic Cancer
TNM	Classification of Malignant Tumours by the Union for International Cancer Control (UICC): T(tumour) N(nodes, i.e., lymph nodes M(metastases)
VAAD	Vulvar acanthosis with altered differentiation
VAM	Vulvar aberrant maturation
VSCC	Vulvar squamous cell carcinoma
WHO	World Health Organisation

1 Introduction

In recent decades, concentrating the care of rare diseases requiring complex treatment to a few highly specialized university hospitals has been a prioritized goal of the Swedish healthcare system. The aim has been not only to improve prognosis and outcome, but also to promote comprehensive health care and research on these diseases.
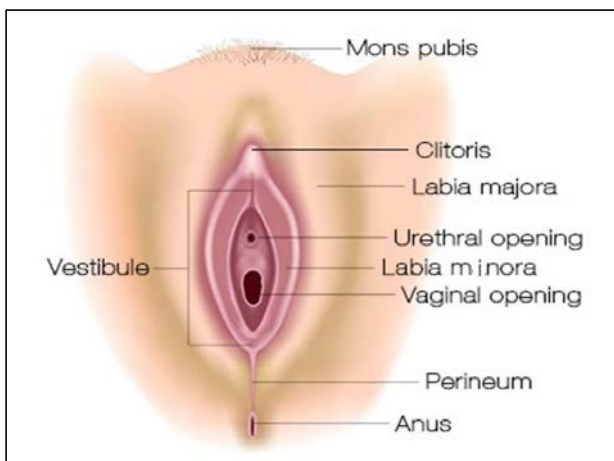
Vulvar cancer, a rare disease affecting mostly elderly women, is diagnosed in approximately 160 women in Sweden every year. Until 2017, these patients were traditionally treated at the closest regional or university hospital, but since then, care for primary and recurrent vulvar cancer care has been centralised to Linköping University Hospital, Skånes University Hospital Lund, Sahlgrenska University Hospital Gothenburg, and Karolinska University Hospital Stockholm, each of which treats 60-80 cases annually. Newly diagnosed and recurrent cases are discussed each week through a digital national multidisciplinary team conference. In addition, representatives from each of the four hospitals meet regularly to discuss national treatment guidelines, which were first published in 2019 and revised in 2023. Treatment outcomes and indicators of quality must be reported to the National Board of Health and Welfare (Socialstyrelsen) each year.

As envisioned, this centralisation of care and access to a national quality registry with almost complete coverage provide excellent possibilities to conduct nationwide studies, four of which are dealt with in the present thesis. This work is dedicated to my patients with the hope that it can help improve understanding of vulvar cancer and the needs of those afflicted.

2 Literature review

2.1 Epidemiology and pathogenesis

Vulvar cancer is an uncommon gynaecological malignancy, arising from the outer female genitals (Figure 1). It is acknowledged as a rare disease by the European Union (1). According to the World Health Organisation (WHO), an estimated number of about 45.000 new cases were diagnosed worldwide in 2020 (2). In Sweden, about 160 women at a median age of 73 years are diagnosed with vulvar cancer each year (3).

Figure 1. Overview over the vulvar anatomy.

Vulvar cancer can arise at any localisation in the vulva, most often on the skin of the labia minora and majora (Figure 1) (4). About 80-90% of the tumours are of squamous cell origin. Malignant melanoma, adenocarcinoma, basal cell carcinoma and Paget's disease are less common histological types (5). In the 2020 published 5th edition of the Classification of Female Genital Tumours, the WHO recommends the division into at least two distinct types of vulvar squamous cell carcinoma (VSCC), human papillomavirus (HPV)-dependent VSCC and HPV-independent VSCC (6). Both entities differ in the means of their aetiology, pathological morphology, precursors, risk factors, and most likely also prognosis. HPV-dependent VSCC develops from a persistent infection with high-risk HPV, predominantly HPV 16, affects younger women with a median age of 54-60 years and is associated with similar risk factors as cervical cancer, such as smoking, multiple sexual partners, and immunosuppression (7–9). The HPV-dependent pathway proceeds from normal vulvar epithelium via high grade squamous intraepithelial lesion (HSIL) to non-keratinising, warty or basaloid VSCC. A risk of about 3-15% for progression from HSIL into VSCC has been estimated (10,11). HPV-dependent VSCC usually shows a strong immunostaining for p16 and is not TP53-mutated. HPV-independent VSCC seems to be triggered by chronic inflammatory vulvar diseases such as lichen sclerosus and is predominantly affecting elderly women with a median age of 71-77 years (7–9,12–18). The pathway proceeds from lichen sclerosus via differentiated vulvar intraepithelial neoplasia (dVIN) to keratinising VSCC, leading to p16-negative tumours which usually are TP53-mutated. dVIN is characterized by a substantial risk of progression to invasive

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cancer (10,19–21). Although only about 10% of all vulvar dysplasia is classified as dVIN, most invasive disease is HPV-independent (7). This might be explained by the rapid progression of dVIN into invasive cancer and the difficulties in diagnosing dVIN. Recently, a third pathway has been proposed, also HPV-independent and associated with lichen sclerosus or lichen simplex (8,15,22,23). Lichen sclerosus or -simplex seems to proceed via vulvar acanthosis with altered differentiation (VAAD) or differentiated exophytic vulvar intraepithelial lesion (DEVIL) to VSCC, often of verrucous type (24). These tumours are p16 and p53 negative (14,22,25). Knowledge about the risk of VAAD or DEVIL to progress to invasive cancer is still limited. There is increasing evidence for a worse prognosis of HPV-independent VSCC compared to HPV-dependent VSCC (13,15,18,20,21,26–28) Figure 2 gives an overview of the three proposed aetiological pathways with their different precursors and characteristics.
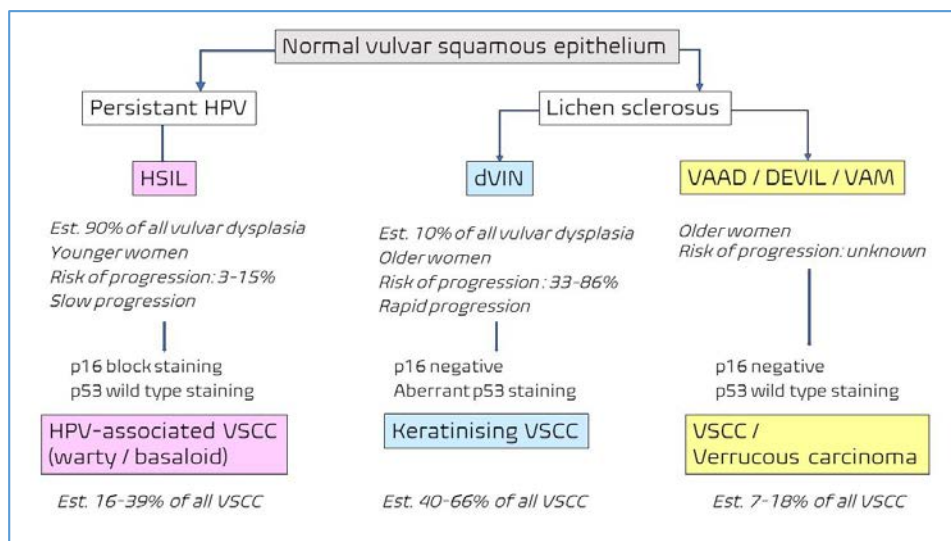
Figure 2. *Overview over the three different aetiological pathways for the development of VSCC* (8,9,13,16,18–22,26,29,30).

Abbreviations: *HPV, human papillomavirus; HSIL, high grade squamous intraepithelial lesion; dVIN, differentiated vulvar intraepithelial neoplasia; VAAD, vulvar acanthosis with altered differentiation; DEVIL, differentiated exophytic vulvar intraepithelial lesion; VAM, vulvar aberrant maturation; VSCC, vulvar squamous cell carcinoma.*

In several countries a rising incidence of VSCC has been described, mostly in younger women, and predominantly explained by an increase in HPV-associated cancers (5,31–38). Although a slight increase of absolute cases in Sweden between 1970 and 2019 can be noted, the age-standardised incidence remained stable (Figure 3, 4).
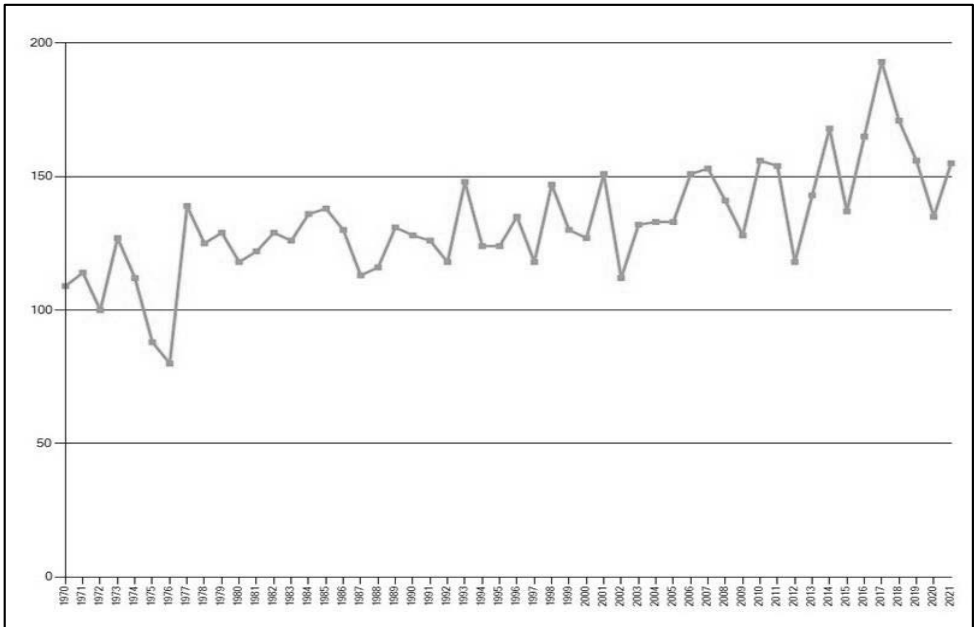
Figure 3. *Newly diagnosed vulvar cancer in Sweden per year, from 1970 until 2021 (absolute cases)* (3).

Figure 4. *Newly diagnosed vulvar cancer in Sweden per year, from 1970 until 2021 (age-standardised incidence per 100.000)*(3).

2.2 Staging

Table 1. Staging of vulvar cancer: Union for International Cancer Control (UICC) TNM classification, 8th edition, 2016 (39); FIGO-staging system, revised version 2021 (40).

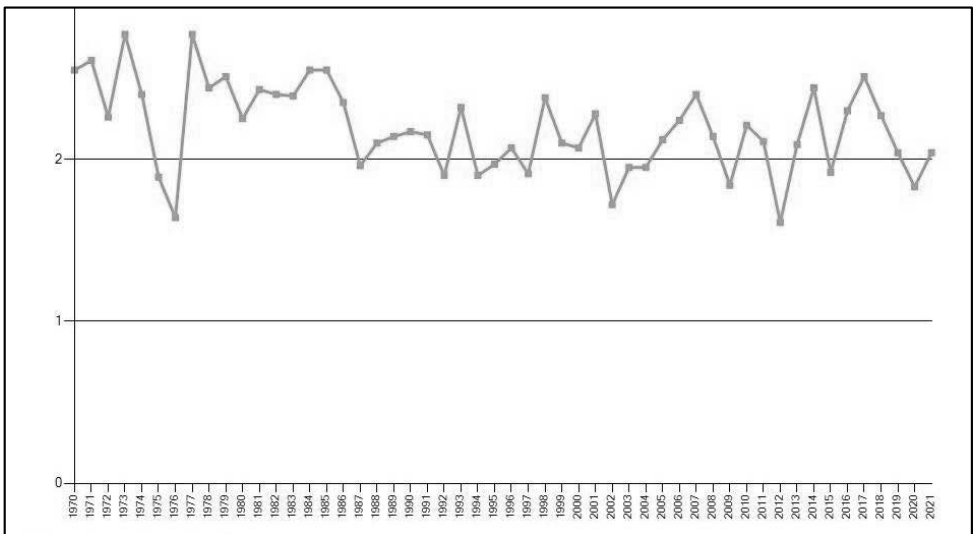| TNM	FIGO	Description
Primary tumour		
T0		No evidence of primary tumour
T1	I	Tumour confined to the vulva
T1a	IA	Tumour size ≤ 2 cm and stromal invasion ≤ 1 mm[a]
T1b	IB	Tumour size > 2 cm or stromal invasion > 1 mm
T2	II	Tumour of any size with extension to lower one-third of the urethra, lower one-third of the vagina, lower one-third of the anus with negative nodes
T3		Tumour of any size with extension to any of the following: upper / proximal 2/3 of urethra, upper / proximal 2/3 of vagina, bladder mucosa, rectal mucosa or fixed to pelvic bone
	III	Tumour of any size with extension to the upper part of adjacent perineal structures
	IVA	Disease fixed to the pelvic bone
Regional[b] lymph nodes		
N0		No evidence of regional lymph node metastases
N1a		1 or 2 lymph node metastases < 5 mm
	IIIA	Regional lymph node metastases ≤ 5 mm
N1b		1 lymph node metastasis ≥ 5 mm
	IIIB	Regional lymph node metastases > 5 mm
N2a		3 or more lymph node metastases each < 5 mm
N2b		2 or more lymph node metastases ≥ 5 mm
N2c	IIIC	Regional lymph node metastases with extracapsular spread
N3	IVA	Fixed or ulcerated regional lymph node metastasis
Distant metastases		
M0		No evidence of distant metastases
M1	IVB	Distant metastasis (including pelvic lymph node metastasis)

[a]*TNM*: Depth of invasion is measured from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

[a]*FIGO*: Depth of invasion is measured from the basement membrane of the deepest, adjacent, dysplastic, tumour-free rete ridge (or nearest dysplastic rete peg) to the deepest point of invasion.

[b] Regional refers to inguinal and femoral lymph nodes.

The most common staging system for vulvar cancer has been provided by the International Federation of Gynaecology and Obstetrics (FIGO) and was revised several times, most recently in 2021 (40). The system is based on surgery and imaging. Local tumour growth, regional lymph node metastasis and distant spread are considered and categorised into four main stages. Alternatively, the disease can be staged according to the Union for International Cancer Control (UICC) TNM classification by T (tumour), N (nodes, i.e., lymph nodes), and M (metastases) (Table 1) (39). Since the last revision of FIGO in 2021, there are distinct differences between the FIGO and the TNM staging, e.g., the way of measuring the depth of invasion and the staging of advanced disease. Between 59% and 71% of all VSCC are diagnosed at early stage, i.e., with the primary tumour limited to the vulva and without regional or distant spread (5,41,42).

2.3 Treatment of VSCC

Surgery is the standard treatment for early-stage VSCC. According to national and international guidelines, it comprises the removal of the primary tumour and a surgical evaluation of the inguinofemoral lymph nodes, traditionally by a vulvectomy with bilateral inguinofemoral lymphadenectomy (IFL) (43–47). In case of lymph node metastasis or tumour-involved margins, adjuvant radiotherapy is advised (48,49). Locally advanced disease, i.e., tumours close to or invading the urethra, vagina, anus, or pelvic bones, is commonly treated by primary radiotherapy, if possible, with concomitant chemotherapy. Primary surgery by pelvic exenteration may be an alternative, and treatment of these rare cases will often be determined on an individual basis (48,49).

Due to the high morbidity of the surgical treatment, several attempts have been made to decrease radicality, without increasing the risk of recurrence. During the recent decades, the following measures were introduced and did not result in higher recurrence rates or impaired survival (50–62):

- Replacing en-bloc vulvectomy and bilateral IFL ("butterfly incision") by separate incisions ("triple incision", Figure 5)
- Replacing vulvectomy by wide tumour excision in most cases
- Reducing the tumour-free margin from 20 mm to 5 mm or less
- Limiting surgical groin staging to the ipsilateral groin in case of lateralised tumours (i.e., at least 1 cm distant from the midline)
- Replacing IFL by sentinel node biopsy (SNB) in selected cases
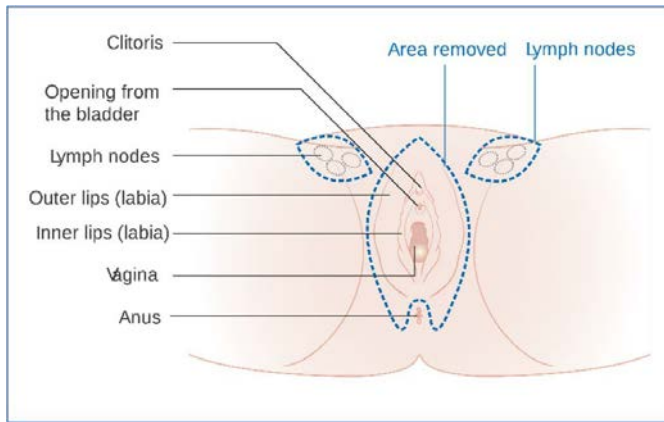
Figure 5. Vulvectomy, bilateral inguinofemoral lymphadenectomy by triple incision.

2.3.1 Vulvar surgery

Current guidelines recommend a local wide excision of the tumour in the vulva with a macroscopic, tumour-free surgical margin of about 5-10 mm as standard treatment (43,45,46). Dysplastic epithelium should be included, and in case of multifocality, a vulvectomy can be advised. Postoperative complications are frequent and reported in 9-58% of cases, comprising wound breakdown, scarring, and narrowing of the vaginal introitus, sexual problems, urinary incontinence, vaginal prolapse, or deviation of micturition (63–66). Particularly larger defects might be difficult to close primarily, thus, various oncoplastic flaps have been described for reconstruction (67–70)
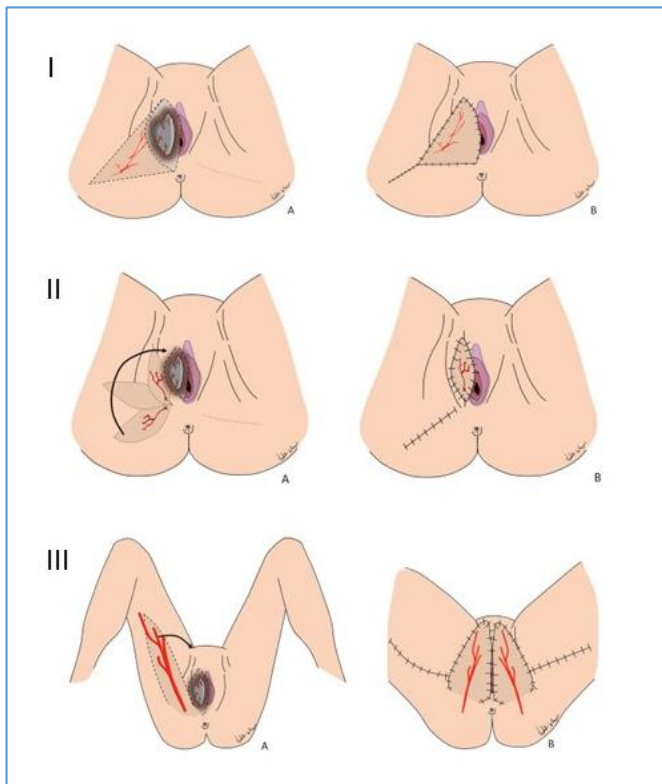
Figure 6. Various types of vulvar reconstructive surgery. I, V-Y advancement gluteal fold flap; II, Lotus petal flap; III, Gluteal thigh flap (68).

(Figure 6). One study indicated that reconstructive surgery instead of primary closure might increase the rate of adequate resection margins and decrease the need for postoperative radiotherapy (71). Furthermore, oncoplastic surgery may decrease the risk of wound breakdown (67,68).

2.3.2 Surgical groin staging in VSCC

After an inguinofemoral lymphadenectomy, 46-77% of the women will develop at least one complication, comprising mainly lymphocysts, infection and wound breakdown in the early phase as well as lymphedema of the lower extremity (LLE) and recurrent erysipelas on the long term (72–76). Particularly the high risk of LLE is a major concern, as numerous studies reported a negative impact of LLE on quality of life (77–79). The reported incidence rates of LLE vary between 10% and 49% (76,80–86). Comparisons between different cohorts and studies are difficult because of different types of groin treatment and a lacking consensus on the definition and assessment of LLE (83,84,87).

On the other hand, surgical groin staging is a central part of primary treatment and has both a diagnostic and therapeutic impact. The detection of metastatic disease in the inguinofemoral region is an indication for adjuvant treatment (43,45–48,88). Early prospective, randomised studies conducted by the Gynaecologic Oncology Group (GOG) during the 1990's showed an additive effect on survival for the surgical removal of the inguinofemoral lymph nodes combined with adjuvant radiation (89,90). Without surgical removal of the lymph nodes and after radiotherapy alone, 18.5% of the women developed a groin recurrence (90). Furthermore, several retrospective reports demonstrated an association between the radicality of surgical groin staging and further prognosis, both in node-negative and in node-positive disease (91–95). In these reports, the risk for groin recurrences was significantly higher in women with fewer lymph nodes removed. Moreover, Baiocchi and co-workers reported in their cohort significantly impaired survival for women with a lower lymph node count compared to women with a higher lymph node count (96).

However, despite the shown benefit of surgical groin staging, several population-based studies reported omission of the procedure in 27% to 45% of the women with newly diagnosed VSCC (97–101). Omitted surgical groin staging was more prevalent at higher age, in women with more comorbidities and a lower income and when the treatment was performed at smaller facilities and not by a gynaecologic oncologist (97,99,102).

The impact of omitted surgical groin staging on recurrence and survival on a population basis is not sufficiently investigated. In a study by Gien and co-workers, the groin recurrence rate was not different between women with and without surgical groin staging, and the procedure was neither associated with improved overall survival (98). However, this retrospective study was conducted before the implementation of the sentinel node

biopsy, with a relatively short follow-up period, and the analyses were not adjusted for FIGO stage.

2.3.3   Sentinel node biopsy

An effective measure to reduce the morbidity related to surgical groin staging is the sentinel node technique. First introduced in malignant melanoma and breast cancer (103,104), it is assumed that tumour cells spread through lymphatic channels to defined sentinel lymph nodes, i.e., lymph nodes which are first reached by possible metastatic cells (105). By identifying these nodes and subjecting them to thorough pathological examination, so-called ultrastaging, metastatic disease can be identified without removing all existing lymph nodes in a basin (105). Furthermore, ultrastaging facilitates the detection of low-volume metastases, such as micrometastases and isolated tumour cells (ITC), which remain largely unidentified by conventional pathohistological examination. Up to 42% of these low-volume metastases are diagnosed only by ultrastaging (58,59). The SNB is accompanied by lower complication rates than radical lymphadenectomies (59,76,106–108). However, when using the technique, it is mandatory to ensure the oncological safety, i.e., a low rate of lymph node recurrences, caused by a false-negative sentinel lymph node. In vulvar cancer, a low rate of false negative sentinel lymph nodes is crucial, as women with negative lymph nodes do not undergo further adjuvant treatment and groin recurrences have a dismal prognosis (109).

Identification of the sentinel lymph node can be facilitated by different tracers, such as radioactive isotopes, blue dye, or fluorescent tracers (Figure 7). A combination of at least two tracers has shown the highest sensitivity in vulvar cancer (110,111). The traditional combination of Technetium-99m (Tc-99m), a metastable nuclear isomer of Technetium-99, and blue dye has been challenged by a recent meta-analysis showing superior detection rates for the combination of Tc-99m with indocyanine green (ICG), a fluorescent cyanin dye (112).

Whatever tracer is used, it is generally acknowledged that the surgical technique is sophisticated and optimal results can first be accomplished after a learning curve (59,113–116). In breast cancer, a number of 20 procedures is usually regarded as sufficient to master the technique (114). In the GROINSS-V-I-study, at least 10 successful SNB procedures per surgeon were regarded as a minimum number to achieve surgical proficiency in VSCC (59). Furthermore, an experienced pathologist and, when using a radiotracer, a nuclear medicine department are important prerequisites.
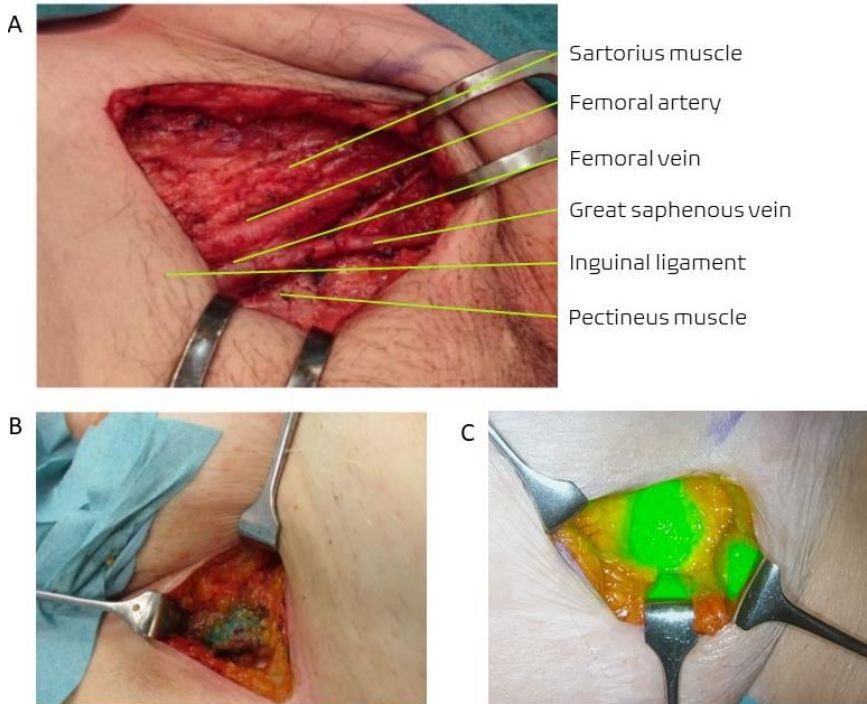
Figure 7. Inguinofemoral lymphadenectomy (A) and sentinel node biopsy (B and C), using blue dye (B) and indocyanine green (C).

2.3.4 Sentinel node biopsy in VSCC

Two large prospective studies confirmed the feasibility and oncological safety of sentinel node biopsy in well-defined patient groups with primary VSCC (58,59).

Van der Zee and colleagues published in 2008 the results of the international, multicentre GROINSS-V-I study on 483 women newly diagnosed with VSCC < 4 cm in diameter who underwent surgical groin staging by SNB only (59). After two years, node-negative women had a groin recurrence rate of 2.3%. Furthermore, postoperative morbidity was significantly reduced in women with SNB compared to IFL. Multifocal tumours which were initially included in the study, were excluded after the occurrence of two groin recurrences within a brief time. Although no further groin recurrences occurred among the hitherto included 19 women with multifocal tumours, the authors concluded that the technique should be restricted to unifocal tumours. It was presumed that multifocality would hamper a proper injection of the tracer with appropriate mapping of all tumour components (59). Since then, only one small prospective study including nine women with multifocal tumours applied the sentinel node to this patient group, resulting in no false-negative sentinel nodes (117).

Four years later, in 2012, Levenback and co-workers published the results of the GOG-173 study, including 452 women with VSCC, treated by SNB in combination with IFL (58). For women with tumours < 4 cm the negative predictive value was 98%, but seven of the 162 women with tumours ≥ 4 cm had a false-negative sentinel node, resulting in a false negative predictive value of 7.4%. It was assumed that due to the large tumour size, an appropriate tracer injection and consequently a representative mapping would be more difficult (58).

Based on the results of the GROINSS-V-I and the GOG-173 study, most international guidelines recommend restricting the sentinel node technique to women with primary VSCC and unifocal tumours < 4 cm in diameter (43–47).

2.4 Prognosis in VSCC

Prognosis in VSCC is mostly dependent on the inguinofemoral lymph node status which underlines the importance of proper groin staging (118). Both the risk for local, groin and distant recurrences is substantially higher in node-positive than in node-negative disease (14).

In a large retrospective German multicentre study, the 3-year disease-free survival and overall survival (OS) was 75% and 90% for node-negative and 35% and 56% for node-positive disease, respectively (119). The long-term-follow-up of the GROINSS-V-I cohort revealed a 10-year disease-specific survival of 91% for node-negative and 65% for node-positive disease (120). Other prognostic factors are age and stage of the disease (102,121–123). Figure 8 displays the 5-year relative survival of a large Swedish population-based cohort stratified by stage and age (102).

Investigation of further factors, such as tumour size, depth of invasion and lymphovascular space invasion (LVSI) yielded ambiguous results. Tumour size has been described as a prognostic factor for disease-free- and overall survival in some small retrospective studies (124–126), however, this finding could not be confirmed in larger cohorts (52,60,94,121,122). Most studies on the prognostic impact of LVSI could not confirm an association with worse disease-free or overall survival (60,127,128). Likewise, depth of invasion seemed to correlate with the risk of lymph node metastases but not with prognosis (60,122,124,127). There is no consensus on the prognostic impact of tumour-free margins. While previous retrospective reports suggested a higher risk for local recurrence for narrow tumour margins, particularly for margins less than 8 mm, this concept was challenged by recent studies showing no difference in prognosis by the margin width (50–52,60,61,129,130). Consequently, recommendations regarding the optimal tumour-free margins vary. In the recently updated European Society for Gynaecologic Oncology (ESGO) guidelines on vulvar cancer treatment, a tumour-free margin without further specification is regarded as sufficient (43). In contrast, the current Swedish national guidelines advise a tumour-free margin of at least 5 mm (45).
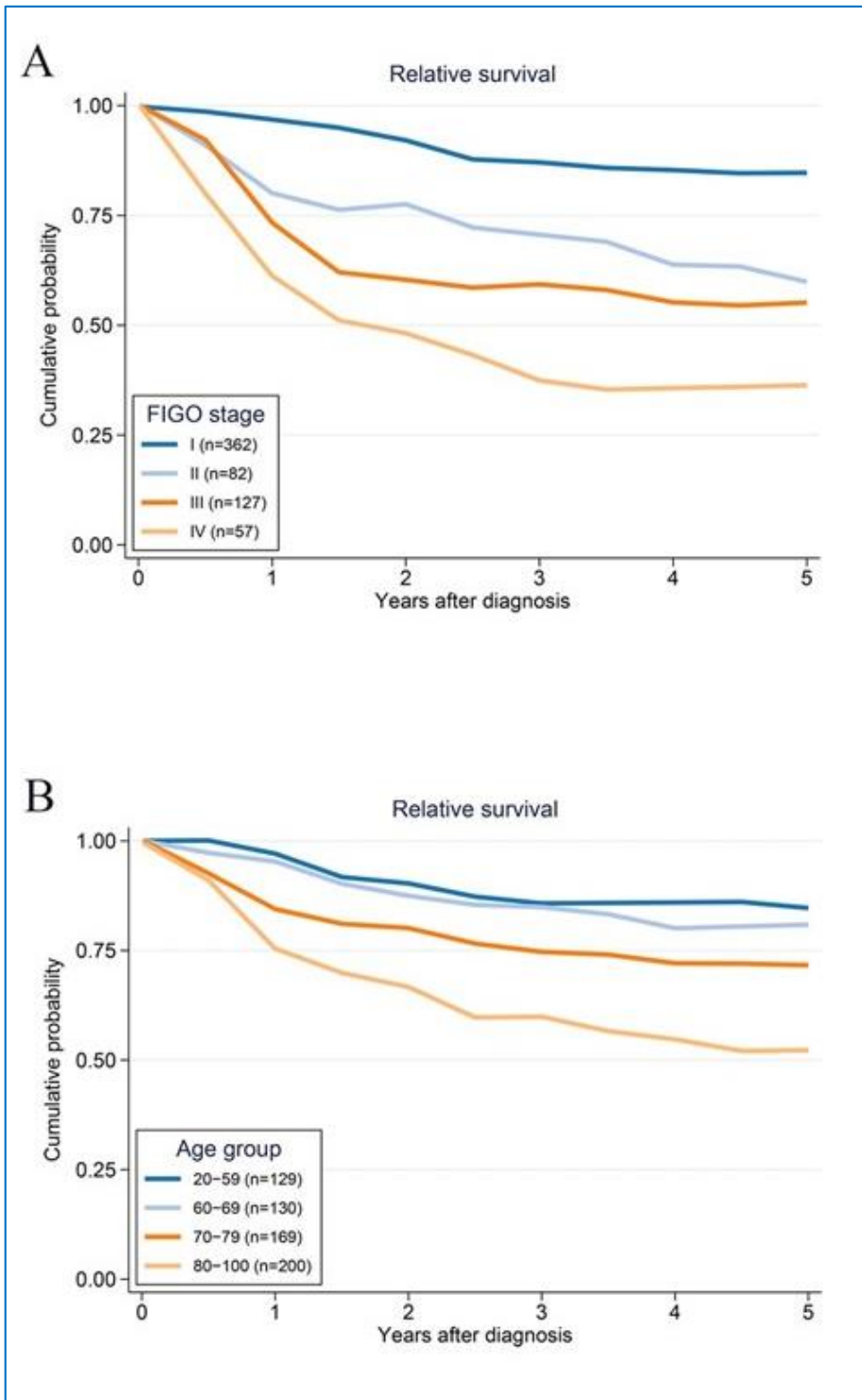
Figure 8. Relative survival stratified by stage (A) and age (B) (102).

Increasing evidence indicate a prognostic impact of the pathogenesis of the tumour. Mainly retrospective studies and one meta-analysis showed significantly worse recurrence-free and overall survival for women with HPV-independent, TP53-mutated tumours (12,26,28,131–134). In a large series by te Grotenhuis and colleagues, the risk for local recurrence was more than doubled in cases where dVIN or lichen sclerosus, the precursors of HPV-independent VSCC, were found in the surgical margin (60). In addition, Thompson and co-workers found significantly worse progression-free survival in women with dVIN in the surgical margin (135).

2.5 Recurrent disease and post–recurrence survival in VSCC

About 12-45% of the women with VSCC will experience a recurrence, predominantly in the vulva (109,120,129,136,137). Most recurrences occur during the first two years after diagnosis (109); however, particularly local recurrences can occur many years after primary diagnosis (120,130,138). Most knowledge about recurrent disease is derived from small retrospective, single-centre studies (14,61,136,139–141).

2.5.1 Local recurrence

Local recurrences are common and account for the majority of recurrent disease (109,119,120,136,137). In a recent update from the GROINSS-V-I study, te Grootenhuis and colleagues reported a local recurrence rate of 27% within five and 40% within 10 years (120). A recently published review estimated an annual local recurrence rate of approximately 4% without reaching a plateau and with a continuously rising cumulative incidence with time (Figure 9) (130).

Figure 9. Local recurrence rate by duration of follow-up time (130).

This may be explained by the remaining risk for new malignant transformation even after removal of the tumour, facilitated by the underlying chronic diseases, e.g., lichen sclerosus, or a persistent or new HPV infection. In most cases, a local re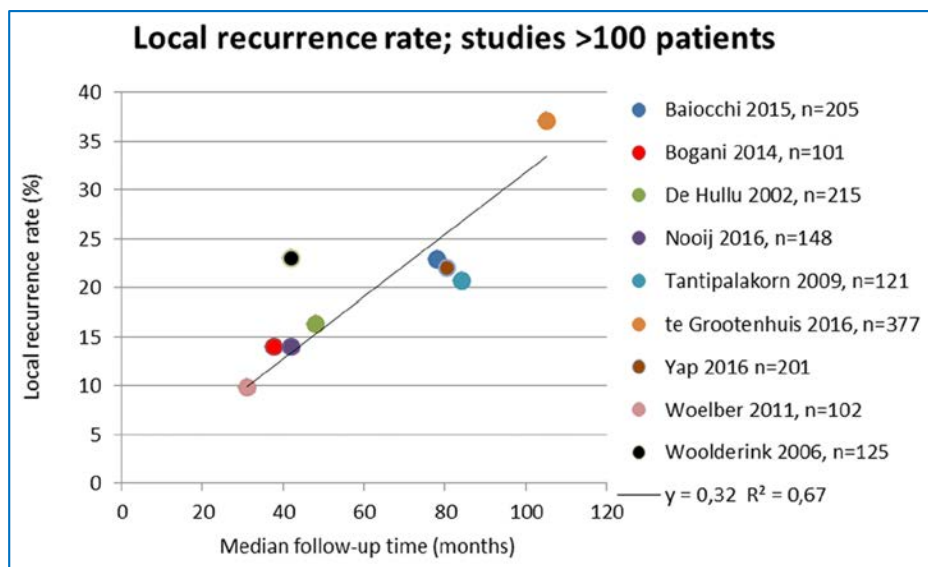currence is treated surgically with curative intention (14,109). Primary radiotherapy might be an alternative option in locally advanced disease (43,45,46).

Even when treated with curative intention, a local recurrence impairs prognosis (109,119,120,142). In a subgroup analysis of the AGO-Care-1-study, 193 of 1249 women with known groin status developed a local recurrence and women with a local recurrence had a 9-fold higher risk of death compared to women without a recurrence. The one-year disease-free survival for this group was 59% (14). Te Grootenhuis and co-workers reported from the GROINSS-V-I node-negative cohort a 10-year disease-free survival of 69% for women with a local recurrence, compared to 91% for women without a local recurrence (120).

2.5.1.1   Surgical groin staging in locally recurrent VSCC

As locally recurrent VSCC might be regarded as a new primary tumour, caused by the underlying vulvar disease, a surgical evaluation of the inguinofemoral lymph nodes is advised, if not performed earlier. Traditionally, an IFL is recommended (43,45).

SNB might be an alternative to reduce treatment-related morbidity. Studies on breast cancer and malignant melanoma confirmed the feasibility of the technique in recurrent disease. Albeit a lower detection rate and a larger proportion of untypically localised sentinel lymph nodes, the procedure is regarded as oncologically safe in these disease entities (143–146).

In VSCC, the feasibility and safety of SNB in local recurrences has not been evaluated prospectively. A small retrospective study from 2016 (147) on 27 women with locally recurrent VSCC who were treated by repeated SNB reported a detection rate of 84% per groin which was lower than the detection rate in primary disease (i.e., 89-95%) (110,148,149). The authors reported no groin recurrences during a median follow-up of 27 months and concluded that the technique might be feasible and oncologically safe in locally recurrent VSCC (147).

2.5.2   Groin and distant recurrences

Inguinofemoral lymph node recurrences comprise 12-30% of all recurrences and occur earlier than local recurrences, most often within 2 years (14,93,109,150). Most studies reported a poor prognosis of groin recurrences with a post-recurrence survival of 0-10%. However, a recent investigation on 30 women with groin recurrences reported an overall survival of 50% after 7 years (140).

Isolated distant recurrences are rare, occur early, and affect most often the pelvic lymph nodes, lung, or bones (139). The few published studies reported dismal survival (139,151–153). In a German study from 2016 following 391 women with primary vulvar cancer, 20 women (5.1%) developed distant metastases after a median follow-up time of 33 months (139). In 60%, the distant relapse was foregone by a local recurrence. The 2-year overall survival after diagnosis of a distant metastasis (including pelvic lymph node metastases) was 11.3% (139).

2.6   Quality of life

The World Health Organisation defines quality of life as "*an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns*" (154). This broad definition highlights two important characteristics of the concept of quality of life. Firstly, quality of life is a construct which consists of multiple different dimensions, such as physical functioning and emotional well-being, but also aspects of an individual's professional, family, and social life, and even economic, religious, gender, political, and financial factors. Secondly, it is subjective, i.e., a person's quality of life has to be assessed by the individual person herself. Health-related quality of life (HRQOL) focusses primarily on health-related aspects, including physical and mental functioning, specific symptoms in relation to certain diseases, or the interaction between patients and caregivers. According to the European Organisation for Research and Treatment of Cancer (EORTC), HRQOL in malignant diseases "*covers the subjective perceptions of the positive and negative aspects of cancer patients' symptoms, including physical, emotional, social, and cognitive functions and, importantly, disease symptoms and side effects of treatment*" (155).

2.7   Measuring health–related quality of life

There is broad consensus that patient-reported outcome measures (PROMs) are suitable tools to measure HRQOL, along with qualitative research methods, such as personal, structured interviews (156). When using a PROM, it is paramount that the instrument is indeed measuring the construct it ought to measure, i.e., is validated. The psychometric validation process of a PROM comprises various aspects, such as content, criterion, and construct validity, reliability, precision, sensitivity, and responsiveness (156).

2.7.1   Instruments / PROM

Many PROMs are not only measuring one dimension, e.g., cognitive functioning, but different dimensions in so called scales. For example, the Hospital Anxiety and Depression Scale (HADS), a validated and widespread PROM, consists of two scales (157). One scale is measuring anxiety, and the other is measuring depression. This structure assumes that anxiety and depression are two different constructs which can be assessed separately by appropriate questions. The questions are called items and a scale can consist of one

(single-item scale) or more items (multi-item scale). In HADS, every scale consists of 7 items.

Various validated PROMs exist for the assessment of HRQOL. The EORTC provides a long-standing, well validated questionnaire to assess general aspects of HRQOL in cancer patients, the EORTC-QLQ C30 (158). Moreover, the EORTC provides cancer-specific modules, e.g., a module for breast cancer, colonic cancer etc. They ought to be used in conjunction with the core module EORTC-QLQ C30.

Until recently, only one vulvar cancer specific questionnaire was available, provided by the Functional assessment of Chronic Illness Therapy Organisation (FACIT.org). The FACT-V(vulva) was validated by Janda and colleagues on 97 Australian women with vulvar cancer in 2005 (159). Lately, also the EORTC developed a vulvar cancer specific module, the EORTC-QLQ VU34 (160). Although still undergoing further psychometric validation, a preliminary version can be used in clinical trials with permission from the EORTC.

2.8   HRQOL in vulvar cancer

Most women with vulvar cancer are diagnosed at early-stage and can expect to be cured. In the Swedish Quality Registry for Gynaecologic Cancer (SQRGC), 70% of all registered primary vulvar cancers between 2012 and 2016 were diagnosed at FIGO stage IA or IB with a 5-year OS of 72.0% (102). However, even in early-stage disease, treatment of vulvar cancer can imply disfiguring local resections with large defects and persisting local symptoms. Surgical groin staging can lead to chronic LLE, recurring erysipelas and disturbed sensations in the groins and upper legs. Radiotherapy may result in long-term tissue fibrosis, sexual, gastrointestinal, and urinary dysfunction. Addressing treatment-related morbidity and maintaining quality of life are important aspects of surveillance.

Most studies investigating HRQOL in women with vulvar cancer are conducted at tertiary care hospitals including only a selected patient cohort. They are predominantly cross-sectional and assess various aspects of HRQOL during surveillance, after a varying timespan since primary treatment. Five longitudinal studies have investigated the development of several aspects of HRQOL in women with vulvar cancer over time. These studies comprised 13, 20, 23, 29, and 36 women with vulvar cancer, respectively (81,159,161–163). Only Janda and colleagues used a vulvar cancer specific questionnaire, the FACT-V (159). In the other studies, generic instruments were used, like the EORTC-QLQ C30, the 36-Item Short Form Health Survey (SF-36), the WHO-5-Well-being-score, Short Sexual Functioning Scale, and the Beck Depression Inventory Scale (161–163). In the study by Novackova and co-workers, the cervical cancer module EORTC-QLQ Cx24 was used (161).

The longitudinal development of local vulvar symptoms from before to two months after treatment was investigated by Janda and co-workers (159). The participating women reported an improvement of symptoms such as itching, burning, pain, or odour over time.

In a cross-sectional study during follow-up vulvar symptoms were prevalent in 7-19% of the women, most commonly numbness and pain (164).

The development of LLE symptoms over time was investigated by Janda and co-workers, and Novackova and co-workers (81,159,161). Both reported a significant deterioration of LLE symptoms after treatment. Further cross-sectional studies during follow-up reported LLE symptoms in 40-73% of the women (77–79,164). Two studies observed a higher risk for LLE in women who underwent IFL compared to SNB (81,165). LLE was associated with a deterioration in physical, role, cognitive, social, emotional functioning, and global quality of life, as well as with more pain, fatigue, and insomnia (77,79).

Reports on the development of physical, emotional, role, and social functioning over time are ambiguous (159,161,162,165). Two longitudinal studies did not find significant changes in physical, role, or social functioning over time (159,161). However, in another study, physical functioning deteriorated significantly from before to one year after treatment (162). Emotional functioning improved over time in all three cohorts (159,161,162). In a Dutch cross-sectional study during follow-up, the participating women reported physical, role, cognitive, social, and emotional functioning comparable to a healthy cohort of Danish and Norwegian women (165). Poorer performance status, higher FIGO stage of disease, and recurrent disease compared to primary disease were associated with poorer HRQOL (159,162). Furthermore, IFL compared to SNB was associated with poorer social functioning (81,161).

The possible impact of vulvar cancer on physical, psychosocial, and mental functioning over time is not fully understood. Furthermore, the severity and trajectory of local vulvar symptoms and their effect on HRQOL are rarely investigated. Reasons for diverging results may be found in the small size of the investigated cohorts, the wide range of instruments being used and the variance in the chosen time points before and after treatment.

2.8.1 Sexual function

Investigations on sexual function in women with vulvar cancer are hampered by the fact that most women did not respond to the questions addressing sexuality (78,79,159,161,165–168). In the cross-sectional study by Alimena and colleagues, 47% of the responding women indicated to be afraid of having sex, and 61% were not interested in sex (164). Most studies during follow-up found worse sexual functioning in women with vulvar cancer compared to healthy women and some showed an association between worse sexual functioning and impaired HRQOL (79,163,169,170). Two longitudinal studies investigating sexual function of women with vulvar cancer over time reported different results (162,163). In the study by Jones and co-workers (162), sexual functioning deteriorated from before to one year after treatment, while in the study by Aerts and colleagues (163) sexual functioning was unchanged between before and one year after treatment.

2.8.2 Anxiety and depression

Very few studies reported on anxiety and depression in women with vulvar cancer. In the longitudinal study by Janda and colleagues, 45% of the women had elevated levels of anxiety at diagnosis, decreasing significantly to 25% after 2 months (159). In a small cross-sectional study, six of nine women were classified as anxious, compared to no woman in the comparison group with endometrial cancer (171). Nineteen to 27% of the women in a cross-sectional study by Alimena and colleagues reported feeling tensed and worried during surveillance (164).

The prevalence of depression differed between studies. In Janda and co-workers' study, 15% of the women had elevated levels of depression before treatment, decreasing to 5% after treatment (159). Alimena and co-workers found symptoms of depression in 16% of the women during follow-up (164) Green and colleagues reported depression being prevalent in 31% of the women in their cohort, with 14% taking antidepressant medication (170).

While not widely investigated in quantitative research, psychological aspects are more intensely studied in qualitative research.

2.8.3 Qualitative research

Jefferies and colleagues conducted a qualitative study in the UK and interviewed 13 patients with vulvar cancer, between six months and five years after primary treatment (172–175). She summoned their complaints under several categories. Most women described a feeling of "Aloneness" because of the rarity of the condition and problems to talk openly about it, "Searching" for help, information and meaning, and "Invisibility" as the vulva and its diseases were experienced as a taboo zone. In general, they expressed a feeling of "All changed" and struggles to get help. Both physical and emotional problems were an important part of their accounts, besides difficulties to discuss these issues with their partners or health care staff. Philp and co-workers described similar findings in their interviews with twelve Australian women with vulvar cancer (176). In a recent study from Germany and Switzerland, 20 women with vulvar cancer or vulvar dysplasia described their experiences six months after treatment (177). The authors identified typical patterns including disturbed body image, lack of information and coping strategies, and affected interpersonal relations. In a study by Jones and colleagues, women described difficulties in carrying out daily activities, persisting pain, local symptoms, fatigue, anxiety, depression, frustration and disturbed relationships with family and friends (162).

2.8.4 Supportive care needs

Due to the various negative effects of a cancer diagnosis on HRQOL (178–181), patients may benefit from a broad range of support, such as physical, social, psychological, informational, and sexual (182). PROMs assessing multimodal supportive care needs can be helpful to identify the most prevalent needs and to guide the delivery of customised

health care. Investigations in different cancer types showed a high need of psychological, comprehensive health care, and information support (85,183–185). The specific supportive care needs of vulvar cancer patients are not investigated hitherto, but mixed cohorts of women with gynaecological cancer, also comprising vulvar cancer patients, reported predominantly psychological, health care, and information needs (186,187).

2.9 Summary

Although vulvar cancer treatment became less radical during the last decades, it still seems to confer a considerable risk of long-term morbidity and may compromise the women's quality of life permanently. Knowledge about the development of HRQOL over time and about the influence of treatment is needed. As most women will survive their cancer, maintaining their quality of life is important. Caregivers should be aware of the physical and psychological needs of the women before treatment and during follow-up. Furthermore, particularly elderly women may not be offered adequate treatment in fear of deteriorating their quality of life, while in fact, we know only little about the effects of treatment on their HRQOL. The existing data show high complication rates and a negative impact of surgical groin staging, specifically IFL, on HRQOL. On the other hand, surgical groin staging is regarded as a paramount part of treatment in primary and locally recurrent disease. It guides adjuvant treatment and seems to improve survival. SNB is an effective measure to decrease treatment-related morbidity but can only be offered to a limited number of women. Extension of SNB to large, multifocal, and locally recurrent tumours would be beneficial in terms of treatment-related morbidity but is currently not advised due to uncertainty regarding the oncological safety.

3 Research aims

The overall aim of this thesis was, on the basis of nationwide studies, to characterize the course of vulvar cancer and associated health-related quality of life, as well as to assess new indications for application of the sentinel node technique.

The specific aims of each individual study were as follows:

Study I   To investigate the patterns of recurrence and post-recurrence survival, in combination with the impact of surgical groin staging on survival in women with VSCC.

Study II   To assess the longitudinal development of psychosocial wellbeing in women diagnosed newly with vulvar cancer and to identify risk factors for elevated levels of anxiety.

Study III   To examine the longitudinal development of symptoms and HRQOL in women diagnosed newly with vulvar cancer and to evaluate the impact of local vulvar symptoms on HRQOL.

Study IV   To analyse the feasibility and oncological safety of the sentinel node biopsy in additional subgroups of women with VSCC.

4 Methods

Table 2. *Overview of the studies compiling this thesis*

Study	I	II	III	IV
Design	Retrospective, nationwide registry-based cohort study	Prospective, longitudinal, nationwide study		Prospective, nationwide, single-arm interventional feasibility study
Participants	Women ≥ 18 years of age diagnosed newly with primary VSCC, registered at the SQRGC	Women ≥ 18 years of age diagnosed newly with primary vulvar cancer, discussed at the weekly national vulvar cancer MDT		Women ≥ 18 years of age diagnosed newly with primary VSCC, ≥ 4 cm or multifocal, or with a first vulvar cancer local recurrence, discussed at the weekly national vulvar cancer MDT
Inclusion period	1st Jan 2012 – 31st Dec 2015	Aug 2019 – Aug 2021		Dec 2019 – Dec 2022
Sample size	N=489	N=153		N=64
Objectives	Patterns of recurrence, survival, and the impact of surgical groin staging on survival	Development of anxiety, depression, emotional and social functioning over time, factors associated with increased anxiety	Development of vulvar and lymphoedema symptoms over time, impact of vulvar symptoms on HRQOL	Feasibility and oncological safety of SNB in VSCC-subgroups where SNB currently is not approved
Intervention	None	Validated questionnaires (EORTC-QLQ C30, EORTC-QLQ VU34, HADS, SCNS-SF34), self-constructed questions		SNB additionally to IFL
Primary outcomes	Distribution and cumulative incidence rates for all types of recurrences	Development of anxiety, depression, emotional and social functioning over time.	Development of local vulvar and lymphoedema symptoms, and HRQOL over time.	Detection rate and negative predictive value of SNB
Secondary outcomes	RFS, OS, post-recurrence OS. Association between surgical groin staging and survival	Factors associated with anxiety	Association between vulvar symptoms and HRQOL	Proportion of metastases detected only by ultrastaging, proportion of ITC and micrometastases

Abbreviations: *VSCC, vulvar squamous cell carcinoma; SQRGC, Swedish Quality Registry for Gynaecologic Cancer; MDT, multidisciplinary team conference; HRQOL, health-related quality of life; RFS, recurrence-free survival; OS, overall survival; SNB, sentinel node biopsy; IFL, inguinofemoral lymphadenectomy; ITC, isolated tumour cells.*

4.1 Study design and setting

Study I

Study I was a retrospective nationwide population-based cohort study, based on the Swedish Quality Registry for Gynaecologic Cancer (SQRGC).

Studies II and III

Studies II and III analysed data from the **PRO**spective **V**ulvar Cancer **E**valuation (**PROVE**)-project, a prospective, longitudinal nationwide study assessing HRQOL in women newly diagnosed with vulvar cancer. All four University hospitals assigned to treat vulvar cancer in Sweden participated in the study, i.e., Linköping University Hospital, Sahlgrenska University Hospital Gothenburg, Skåne University Hospital Lund, and Karolinska University Hospital Stockholm.

Study IV

Study IV was a prospective, nationwide, non-randomised single arm intervention pilot study. All four University hospitals assigned to treat vulvar cancer in Sweden participated in the study.

4.2 Participants

Study I

The study cohort comprised 489 women with primary vulvar squamous cell carcinoma diagnosed between 1st January 2012 and 31st December 2015 and registered in the SQRGC. Inclusion criteria were newly diagnosed primary VSCC, identified by the International Statistical Classification of Diseases and Related Health Problems (ICD) 10th edition topographical codes C51.0, C51.1, C51.2, C51.8 and C51.9, and the International Classification of Diseases for Oncology (ICD-O) morphological codes 8010/3, 8020/3, 8051/3, 8070/3, 8071/3, and 8076/3. All women who were at least 18 years of age irrespective of the stage of disease and treatment modality were included. Exclusion criteria were evidence of residual disease at the end of primary treatment, other histological entities than VSCC, recurrent disease, and metastases from other primary tumours.

Studies II and III

The PROVE study cohort comprised 153 women with newly diagnosed primary vulvar cancer, discussed at the national multidisciplinary vulvar cancer conference between August 2019 and August 2021. Inclusion criteria were newly diagnosed primary vulvar cancer (all stages, all histological subtypes, all treatment modalities), signed informed consent, and age ≥ 18 years. Exclusion criteria were inability to read or write Swedish, serious mental illness, and life expectancy < 6 months.

Eligible women were approached at one of the four treating hospitals during their first visit. Consenting women were asked to complete a questionnaire assessing HRQOL before start of treatment (i.e., after having been informed about their diagnosis, baseline). Follow-up questionnaires were mailed to the women 3 and 12 months after the end of treatment (Figure 10).
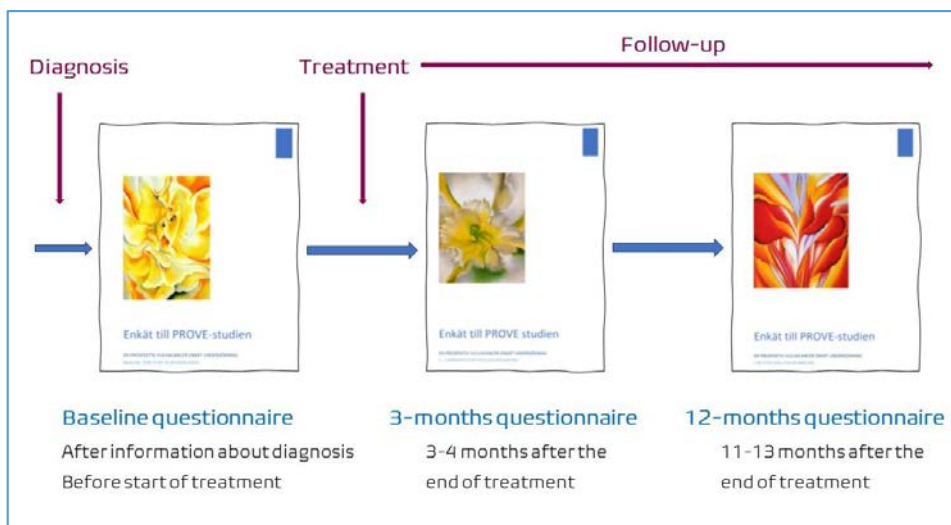
Figure 10. *Timeline of the PROVE-project (studies II and III).*

Study IV

The study cohort comprised 64 women with vulvar cancer, discussed at the national multidisciplinary vulvar cancer conference between December 2019 and December 2022. Inclusion criteria were signed informed consent, age ≥ 18 years; and for Group 1, newly diagnosed VSCC ≥ 4 cm; for Group 2, newly diagnosed multifocal VSCC; for Group 3, first isolated local recurrence of primary vulvar cancer, no previous groin treatment or SNB only; and for Group 4, first isolated local recurrence of primary vulvar cancer, with previous groin treatment by IFL, radiotherapy, or both (Figure 11). Exclusion criteria were performance status ≥ 3, radiological or clinical signs of inguinal lymph node metastases, and ongoing pregnancy. Eligible women were approached at the treating hospital during their first visit.
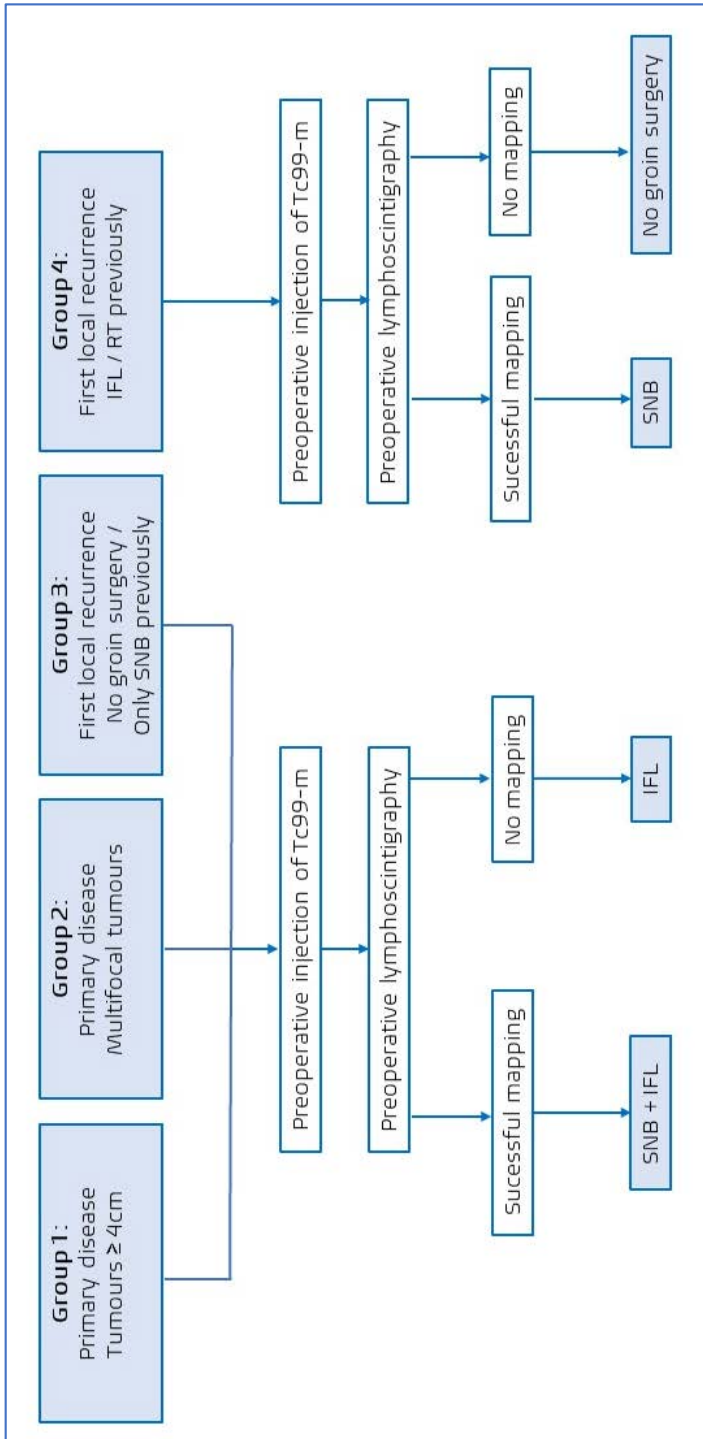
Figure 11. *Flow chart study IV.*

Abbreviations: *SNB, sentinel node biopsy; IFL, inguinofemoral lymphadenectomy; RT, radiotherapy; Tc99-m, Technetium99m.*

4.3 Variables and measures

Study I

Demographic, disease, treatment characteristics and information about recurrence and vital status were retrieved from the SQRGC. The SQRGC is a nationwide registry founded to provide comprehensive information on diagnostics, treatment, and prognosis of gynaecological cancer. It aims on improving quality of care and facilitating research. Registration of vulvar cancer started in 2012. Reporting is voluntary, and women can actively opt out of participating. Demographic data, diagnostic measures, tumour and treatment details and surveillance are prospectively and electronically collected from all six Swedish health care regions. The register is regularly monitored and constantly updated on the patients' vital status. Missing data in the registry were completed by information from the women's hospital charts.

Studies II and III

The following instruments and questions were included in the PROVE-questionnaire:

1. The European Organisation for Research and Treatment of Cancer Quality of life Questionnaire CORE 30 (EORTC-QLQ C30).
2. The European Organisation for Research and Treatment of Cancer Quality of life Questionnaire Vulvar cancer module (EORTC-QLQ VU34).
3. The Hospital Anxiety and Depression Scale (HADS).
4. Fifteen Items from the Supportive Care Needs Survey Short Form (SCNS-SF34).
5. Ten items from the European Organisation for Research and Treatment of Cancer Quality of life Questionnaire Patient Satisfaction (EORTC-QLQ-PATSAT-CORE33).
6. Five self-constructed questions concerning the patients' views and feelings about their vulvar cancer diagnosis.
7. Four self-constructed questions about information sources.
8. Eleven self-constructed questions about basic sociodemographic, lifestyle and medical characteristics.
9. Fifteen self-constructed questions concerning local, sexual, and lymphoedema symptoms, and relationship problems.

The complete questionnaire can be found in the appendix. For this thesis, only a part of the questionnaire was analysed, including selected items from the EORTC-QLQ C30, the EORTC-QLQ VU34, the HADS, the SCNS-SF34, demographic and lifestyle questions, and questions concerning views and feelings about the diagnosis.

EORTC-QLQ-C30, version 3.0

The questionnaire assesses HRQOL in cancer patients and has been validated internationally in various cancer types and languages (158,188–196). It is regarded as a multidimensional, generic instrument which can be applied to any cancer patient

population. The questionnaire is available in Swedish and consists of 30 items, constituting five functional, nine symptom and a global health/QoL scale (Table 3).

Table 3. EORTC-QLQ C30. Scale and item structure, selected items for study II and III.

	Name of the scale	Number of items	Used scales in the studies
Functional scales	Physical functioning	5	Study III
	Role functioning	2	Study III
	Emotional functioning	4	Study II and III
	Cognitive functioning	2	Study III
	Social functioning	2	Study II and III
Symptom scales	Fatigue	3	Study III
	Nausea and vomiting	2	
	Insomnia	1	Study II and III
	Pain	2	Study III
	Dyspnoea	1	
	Appetite loss	1	
	Constipation	1	
	Diarrhoea	1	
	Financial difficulties	1	
Global health status / QoL	global health status/QoL	2	Study III

Abbreviations: QoL, quality of life.

According to the scoring manual, the calculated raw score for every scale has to be transformed into a standardised numeric score which ranges between 0 and 100 for every scale. Higher values represent better functioning in the functional scales but more symptoms in the symptom scales (197). The EORTC does not recommend calculating a total score summary or specific weighting of certain scales or items. However, on behalf of the EORTC QLQ group, Giesinger and co-workers validated different, previously developed summary scales constituting higher order models and reported robust validity for seven of these models (198,199). They have the advantage of less multiple testing and thus, a lower risk for a type-1 error. Besides the functional and Global health/QoL multi-item scales, we used the higher order model Mental health in Study III. It summarizes the functional scales emotional, role, social and cognitive functioning and the symptom scales fatigue, pain, and sleeping disturbances into one scale. The scoring manual of the summary scale was provided by the author professor J. Giesinger (200).

Vulva-module EORTC-VU34

The questionnaire assesses local vulvar, lymphoedema, urinary and bowel symptoms, sexual functioning and body image in vulvar cancer patients and has undergone phase-1, -2, and-3 validation (160). It is currently undergoing formal field testing with psychometric analysis on a cohort of 400 patients with vulvar cancer from different European and non-European countries. The questionnaire is available in Swedish and consists of 34 items in a preliminary scale structure of eight symptom and three functional scales (Table 4). Scores were calculated according to the EORTC-QLQ C30 scoring manual (197).

Table 4. EORTC-QLQ VU34. Scale and item structure, selected items for study II and III.

	Name of the scale	Number of items	Used scales in the studies
Symptom scales	Vulva skin changes	5	Study II and III
	Vulva scarring	2	Study III
	Vulva-vaginal discharge	1	Study III
	Vulva swelling	2	Study III
	Groin lymphoedema	3	Study III
	Leg lymphoedema	4	Study III
	Urine urgency and leakage	4	
	Bowel urgency and leakage	2	
Function. scales	Body image	3	
	Sexual enjoyment	2	
	Sexually related vaginal changes	3	

Hospital Anxiety and Depression Scale, HADS

The questionnaire assesses the prevalence of anxiety and depression and is internationally validated on various populations with malignant and benign diseases (157,201–204). It has been translated into Swedish, and reference values from healthy Swedish women are available (205). It consists of 14 items, divided into two scales:

- Anxiety (A-scale, 7 items)
- Depression (D-scale, 7 items)

According to the scoring manual, the items are summarised to an A-scale-score (between 0 and 21 points) and a D-scale-score (between 0 and 21 points) (157). Missing values

ought to be imputed to avoid a false-low result. According to Bell and colleagues we used the mean value of the completed items in the scale to impute the missing value (206).

While 0-7 points are regarded as "normal", 8-10 points are regarded as "borderline cases" and more than 10 points as "abnormal", i.e., corresponding to a high probability for manifest anxiety disorder or depression, respectively (157).

Supportive Care Needs Survey Short Form, SCNS-SF34

The questionnaire assesses unmet needs and is internationally validated on various cancer patient cohorts (183,184,207–209). It consists of 34 items, divided into five scales (210). To limit the length of the PROVE-questionnaire, only 15 items were included (Table 4). According to previous research (186,187,211,212), the expected most prevalent supportive care needs were chosen, predominantly psychological needs. For study II, four of the 15 items were analysed (Table 5). We hypothesized them to be associated with anxiety.

Table 5. Supportive Care Needs Survey Short Form, SCNS-SF34. Scale and item structure, selected items for study II.

Name of the scale	Number of items	Number of items included in the PROVE-questionnaire	Used items in study II
Psychological needs	10	7	*Learning to feel in control of your situation*
			Fear about the cancer spreading
Health system and information needs	11	3	*Information about important aspects of your care*
Physical and daily living needs	5	3	
Patient care and support needs	5	1	*Hospital staff acknowledging, and showing sensitivity to your feelings and emotional needs*
Sexual needs	3	1	

The questionnaire is not available in Swedish. The EORTC-QLQ group provides recommendations for the translation of PROMs (213). Accordingly, the "forward-backward-technique" was used for translation, i.e., the questionnaire was first translated from English to Swedish by a native English speaker with excellent knowledge of the Swedish language, and then translated back from Swedish to English by a native Swedish

speaker with excellent knowledge in the English language. Remaining incongruities were resolved in collaboration. As we did not use the complete scales, recommendations for scoring could not be applied. Instead, we calculated the proportion of women responding to each of the four response categories for every single item (no need, low need, moderate need, high need).

Self-constructed questions concerning patients' views and feelings about their vulvar cancer diagnosis

Particularly in qualitative research, women with vulvar cancer expressed feelings of isolation and loneliness. They reported difficulties in talking about the disease with family and friends and experienced a lack of knowledge even when talking to health care professionals (172–176). Furthermore, a disease located at the female genitals may sometimes be experienced as shameful, resulting in a reluctance to seek help. These aspects were further explored with three of the self-constructed questions (Table 6).

Table 6. *Self-constructed questions concerning patients' views and feelings about their vulvar cancer diagnosis.*

Wording of the item	Used items in study
I'm feeling lonely and isolated because nobody has knowledge about my disease.	Study II
It feels difficult and shameful to talk about my disease.	Study II
It is difficult to talk with friends / my family about my disease.	Study II
Health care professionals do not have enough knowledge about my disease.	
If I knew the consequences of the treatment for my life, I would have abstained from treatment.	

The whole PROVE-questionnaire was face-to-face validated on 10 vulvar cancer patients attending the Karolinska University Hospital outpatient gynaecological cancer clinic.

Demographic, disease, and treatment characteristics and status of disease at 12 months after treatment were documented in case report files.

Demographic data, diagnostic measures, tumour and treatment characteristics, pathology results and post-operative complications classified according to Clavien Dindo (214) within 60 days were documented prospectively in study specific case report forms.

4.4 Primary and secondary outcomes

Study I

Primary outcomes of *Study I* were the distribution and cumulative incidence rates (CIR) for all types of recurrence (local, inguinofemoral, distant). Secondary outcomes were recurrence-free and overall survival, post-recurrence overall survival, and survival by surgical groin staging.

Study II

In *Study II,* the development of anxiety and depression, emotional, and social functioning over time were primary outcomes, measured by the HADS-A-scale, HADS-D-scale, and the emotional, and social functioning scales from the EORTC-QLQ C30. Secondary outcomes were factors associated with increased anxiety.

Study III

The primary outcomes of *Study III* were the development of local vulvar and lymphoedema symptoms, and HRQOL over time, measured by the EORTC-QLQ VU34 and EORTC-QLQ C30. Secondary outcomes were the effect of local vulvar symptoms on emotional, physical, role, social, cognitive functioning, as well as on global and mental health.

Study IV

In *Study IV,* the detection rate and negative predictive value for each subgroup were primary outcomes. The number of retrieved sentinel lymph nodes, percentage of metastases detected only by ultrastaging, proportion of lymph nodes with isolated tumour cells (ITC) or micrometastases were secondary outcomes. Pathohistological ultrastaging of the sentinel lymph nodes was performed as described in the GROINSS-V-I protocol (59). Each sentinel lymph node not showing signs of metastases in routine haematoxylin and eosin staining (H&E), was cut into three sections per millimetre. The sections were further investigated by H&E and underwent immunostaining with Cytokeratine to detect low-volume metastases, such as ITC or micrometastases. According to the Cancer Staging Manual of the American Joint Committee on Cancer, micrometastases were defined as lymph node metastases > 0.2 mm and ≤ 2 mm in diameter, and isolated tumour cells as tumour cell clusters ≤ 0.2 mm in diameter (215).

4.5 Sample size

Because of the exploratory, descriptive character of *Study I,* without a formal hypothesis testing, no sample size calculation was performed. We included all eligible women from start of registration in 2012. The inclusion period ended in 2015, to obtain an appropriate length of follow-up time for our analyses.

Studies II and III

For *Studies II and III,* data on the prevalence and variance of our endpoints were scarce. Thus, a proper sample size calculation was difficult. We assumed a change of 10 points in the EORTC scores and of 1.5 points in HADS to be clinically relevant (216–219). By accepting a type-I error (α) of 0.05 and a type-II error (β) of 0.2, a sample size of 100 women was deemed sufficient. With an anticipated drop-out rate of 30%, we aimed to include 150 women in 2 years.

Study IV

For *Study IV*, the sample size was calculated as follows: The negative predictive value had to be assessed for each subgroup separately, and, similarly to the previous GOG-173 study by Levenback and colleagues (58), we set the lower boundary of the 95% confidence interval (CI) for the negative predictive value at 95%. This would result in a sample size of at least 150 women with a negative sentinel node in each subgroup. With an estimated number of 10-20 eligible women for each subgroup in Sweden per year, and an expected node-positive rate of up to 40%, it seemed not feasible to conduct the study within a reasonable timeline. Thus, we decided to perform a pilot study with a lower sample size and to continue with a multinational approach if the results supported this effort. We aimed to include at least 20-30 women in each subgroup in two years.

4.6 Statistics

In all studies, characteristics of the study cohorts were presented by summarizing statistics such as mean, standard deviation (SD), median, range, and proportions. Comparisons between independent groups were done by the non-parametric Wilcoxon rank sum test (more than two groups) or the Mann Whitney U test (two groups), as most variables were not normally distributed. The Pearson's Chi square test or Fisher's exact test were applied for comparison of categorical variables. A two-sided p-value of <0.05 was considered as significant.

Study I

Cumulative incidence rates, recurrence-free survival, overall survival, and post-recurrence overall survival were calculated by the Kaplan Meier function, taking competing risks into account. Omitted surgical groin staging as a predictor for worse RFS or OS was

investigated by proportional hazards regression models, crude and adjusted for age, FIGO-stage, tumour size, resection margins and performance status. All analyses were performed with STATA Corp™ Software, version 16.

Study II

Analyses of baseline data were performed on the cohort of women who had returned at least the baseline questionnaire. All longitudinal analyses with repeated measurements were performed on the subgroup of complete responders, i.e., women who had returned the questionnaire at all three time points. Mean scores and standard deviations of the HADS-anxiety- and depression scale were calculated and within-group changes over time were assessed by the paired t-test for changes. Associations between *a priori* defined independent variables and anxiety at baseline and over time were investigated by bivariate and multivariate log-linear regression models, using generalised estimated equations (GEE) with independence working correlation matrices and robust estimators of the variances (220). All analyses were performed with "R" Software, version 4.3.

Study III

All women who had returned at least one questionnaire were included in the analyses. EORTC-QLQ C30 mean scale scores and VU34 mean item scores and standard deviations were calculated for each time point. Unadjusted linear mixed-effects models with patient-specific random intercept were deployed to estimate changes in mean scores over time. Adjusted linear mixed-effects models were used to investigate associations between the most prevalent vulvar symptom and EORTC-QLQ C30 scales. The models included the following covariates as fixed effects:

- Time (baseline *versus* 3 months *versus* 12 months)
- Age (<65 *versus* ≥65 years)
- Treatment (limited vulvar surgery without radiotherapy *versus* extensive vulvar surgery without radiotherapy *versus* vulvar surgery followed by radiotherapy)
- Comorbidities (none *versus* one *versus* more than one)
- The most prevalent vulvar symptom (Not at all *versus* A little *versus* Quite a bit *versus* Very much)

The patient was included in the model as a random effect. Missing values were imputed. All analyses were performed with "R" Software, version 4.3.

Study IV

Detection rates, sensitivity, and the negative predictive values with 95% confidence intervals were calculated by STATA Corp™ Software, version 16.

5 Results

Table 7 shows the main characteristics of the study cohorts of the four studies compiling this thesis. The women were in median 69-73 years old and predominantly diagnosed with early-stage disease. Between 65.6% and 75.2% were treated by surgery only and 20.9-34.4% received adjuvant (chemo-)radiotherapy.

5.1 Study I

Of the 614 women registered in the SQRGC, 555 (91.3%) were classified as VSCC, 34 (5.6%) were malignant melanomas, and 19 (3.1%) showed other rare histological types (*Flow chart of study I see Figure 1 in paper I, page 750).* Sixty-five women (11.7%) were excluded because of residual disease at the end of treatment and in one woman, the status of disease at the end of treatment could not be determined. Thus, 489 women were included in the final study cohort. Clinical and demographic characteristics of the women are described in Table 7.

The median follow-up time of the cohort was 52 months for the calculation of RFS and 64 months for the calculation of OS. During the study period, 109 women (22.3%) suffered from a recurrence, in most cases (61%) an isolated local recurrence (Table 8). Most recurrences were diagnosed among the 113 women with FIGO stage III and IV disease (recurrence rate 44.6% in stage III and 33.3% in stage IV), while of the 94 women with stage IA disease only three suffered from a recurrence (5.3%). Women with a recurrence were significantly older than women without a recurrence (median age 75 versus 70 years, p=0.04).

The overall 2-year and 5-year cumulative incidence rates were 14.5% and 24.4%, respectively and differed between the different types of recurrences (Figure 12). For local recurrences, a steady increase could be observed, while groin and distant recurrences occurred predominantly within the first two years (Figure 12).

The 2-year and 5-year RFS for the whole cohort were 77.9% (95% CI 73.9-81.4) and 56.5% (95% CI 51.1-61.5), respectively. Death was a strong competing event (Figure 12). The 5-year overall survival for the whole cohort was 67% (95% CI 62.1-71.4).

No woman with a distant recurrence was alive after two years, and only 17.2% of the women with a groin recurrence. Of the women with isolated local recurrences, 57.8% (95% CI 43.5-69.7) were alive after two years and 37.4 (95% CI 18.9-24.3) after four years.

Table 7. *Demographic, disease, and treatment characteristics of the study cohorts of the four included studies in the thesis.*

	Participants study I N=489	%	Participants studies II / III N=153	%	Participants study IV N=64	%
Age, years, median	70		69		73	
Range	(23-95)		(43-95)		(38-89)	
ECOG Performance status						
0-1	330	(84.4)	141	(92.2)	58	(90.6)
2-4	61	(15.6)	12	(7.8)	6	(9.4)
Missing	98		0	0	0	
Histology						
SCC	489	(100)	135	(88.2)	63	(98.4)
Malign melanoma	0		6	(3.9)	0	
Other	0		9	(5.9)	0	
Invasive Paget's disease	0		3	(2.0)	1	(1.6)
Tumour size, mm, median	20		24		40	
Range	(0-151)		(10-120)		(3-85)	
FIGO stage						
IA	94	(19.5)	15	(9.8)	0	
IB	213	(44.3)	90	(58.8)	30	(46.9)
II	61	(12.7)	4	(2.6)	1	(1.6)
III	92	(19.1)	30	(19.6)	22	(34.3)
IV	21	(4.4)	5	(3.3)	0	
Not applicable	0		9	(5.9)	11	(17.2)
Missing	8		0		0	
Primary treatment						
Surgery solely	338	(69.2)	115	(75.2)	42	(65.6)
Surgery followed by (chemo)radiotherapy	111	(22.7)	32	(20.9)	22	(34.4)
Definitive (chemo)radiotherapy	32	(6.5)	6	(3.9)	0	
Other	8	(1.6)	0		0	
Extent of vulvar surgery						
Wide excision / partial vulvectomy	380	(85.2)	140	(95.3)	47	(73.4)
Radical vulvectomy	56	(12.6)	3	(2.0)	13	(20.3)
Exenteration	10	(2.2)	4	(2.7)	4	(6.3)
Missing	7		0		0	
Surgical groin staging						
No SGS	175	(39.0)	24	(15.7)	0	
SNB uni- or bilateral	96	(19.5)	81	(52.9)	60	(93.8)
IFL uni- or bilateral	190	(38.9)	48	(31.4)	59	(92.2)
Lymph node sampling	28	(5.6)	0		0	

Abbreviations: *ECOG, Eastern Cooperative Oncology Group; SCC, squamous cell carcinoma; FIGO, International Federation of Gynaecology and Obstetrics; SGS, surgical groin staging; SNB, sentinel node biopsy; IFL, inguinofemoral lymphadenectomy.*

Table 8. Characteristics of recurrent disease.

| | Women with a recurrence | |
	n=109	(%) / Range
Localisation of first recurrence		
Isolated local	61	61.0
Groin (with and without local recurrences)	30	30.0
Distant (with or without local or groin recurrences)	9	9.0
Missing	9	
Median time to first recurrence, in months		
Isolated local recurrences	26	
Groin (with and without local recurrences)	9	
Distant (with or without local or regional recurrences)	7	
Median size of first recurrence, mm (range)		
Isolated local recurrences	15	0-60
Groin (with and without local recurrences)	30	10-120
Symptoms at first recurrence		
Yes	69	75.0
No	23	25.0
Missing	17	
Symptoms at first recurrence, only local recurrences, n	61	
Yes	42	72.4
No	16	27.6
Missing	3	
Recurrence diagnosed at scheduled or unscheduled visit		
At scheduled visit	47	50.5
At unscheduled visit	46	49.5
Missing	16	

Table 9. Isolated groin recurrence rates in the subgroup of women with presumed stage IB-II.

	n	(%)
Isolated groin recurrences, n=26		
Women with SGS, FIGO stage IB-II, n=196	10	5.1
Women without SGS, presumed FIGO stage IB-II, n=61	6	9.8
IFL, n=102	5	4.9
SNB, n=71	5	7.0

Abbreviations: *FIGO, International Federation of Gynaecology and Obstetrics; SGS, surgical groin staging; SNB, sentinel node biopsy; IFL, inguinofemoral lymphadenectomy.*
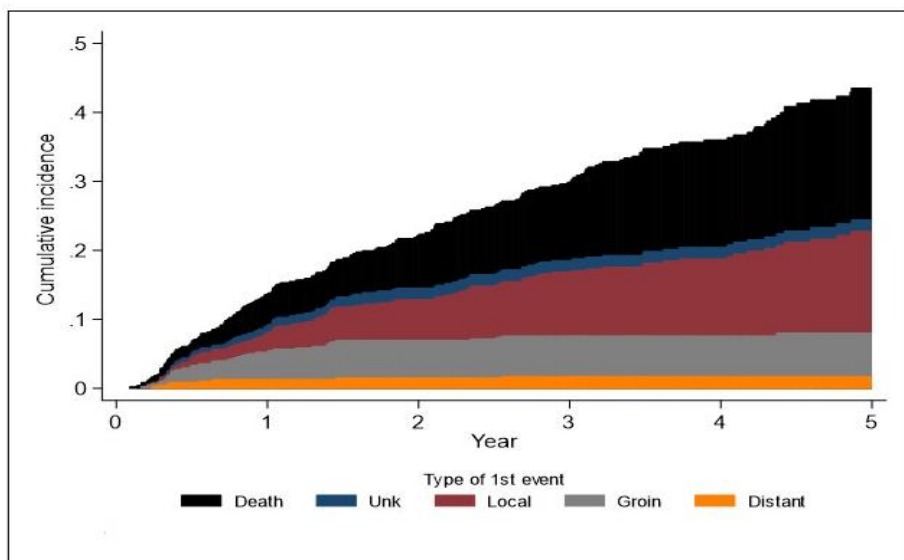
Figure 12. *Cumulative Incidence Rates for different types of recurrence, with death as a competing event.*

2-year-/5-year cumulative incidence rates:
All recurrences: 14.5%/24.4%. Local: 5.9%/14.7%. Groin: 5.5%/6.3%. Distant: 1.5%/1.7%.
Abbreviation*: Unk, unknown*

In a multivariate Cox regression model investigating risk factors associated with worse post-recurrence overall survival, the risk of death was significantly associated with age (Hazard Ratio (HR) 2.19 for age ≥ 75 y *versus* < 75 y; p=0.013), the time to recurrence (HR 2.17 for < 12 months *versus* ≥ 12 months, p=0.019), and the localisation of the recurrence (HR 26.7 for distant *versus* local, p<0.001; HR 2.32 for groin *versus* local, p=0.014). Neither size of the recurrence (HR 1.95 for ≥ 20 mm *versus* < 20 mm, p=0.085) nor whether the recurrence was diagnosed at a scheduled visit or unscheduled visit (HR 1.47 for unscheduled visit *versus* scheduled visit, p=0.228) were associated with post-recurrence survival.

Women with presumed stage IB-II had an isolated groin recurrence rate of 5.1% with surgical groin staging, and 9.8% without surgical groin staging (Table 9). Women with a groin recurrence after IFL had in median four lymph nodes retrieved, in contrast to women without a groin recurrence (seven lymph nodes). Omitted surgical groin staging in women with presumed FIGO stage IB-II disease was associated with a higher risk for recurrence and death, both unadjusted (HR 2.5 for RFS, p<0.001, and HR 3.2 for OS, p<0.001), and adjusted for possible confounders (HR 1.9 for RFS, p=0.004, and HR 2.0 for OS, p=0.04); adjustment for age (>70 *versus* ≤ 70 years), FIGO stage (IB *versus* II), tumour size (continuously), and ECOG performance status (0-1 *versus* 2-4) (*Table 4 in paper I, page 172).*

5.2 Studies II and III
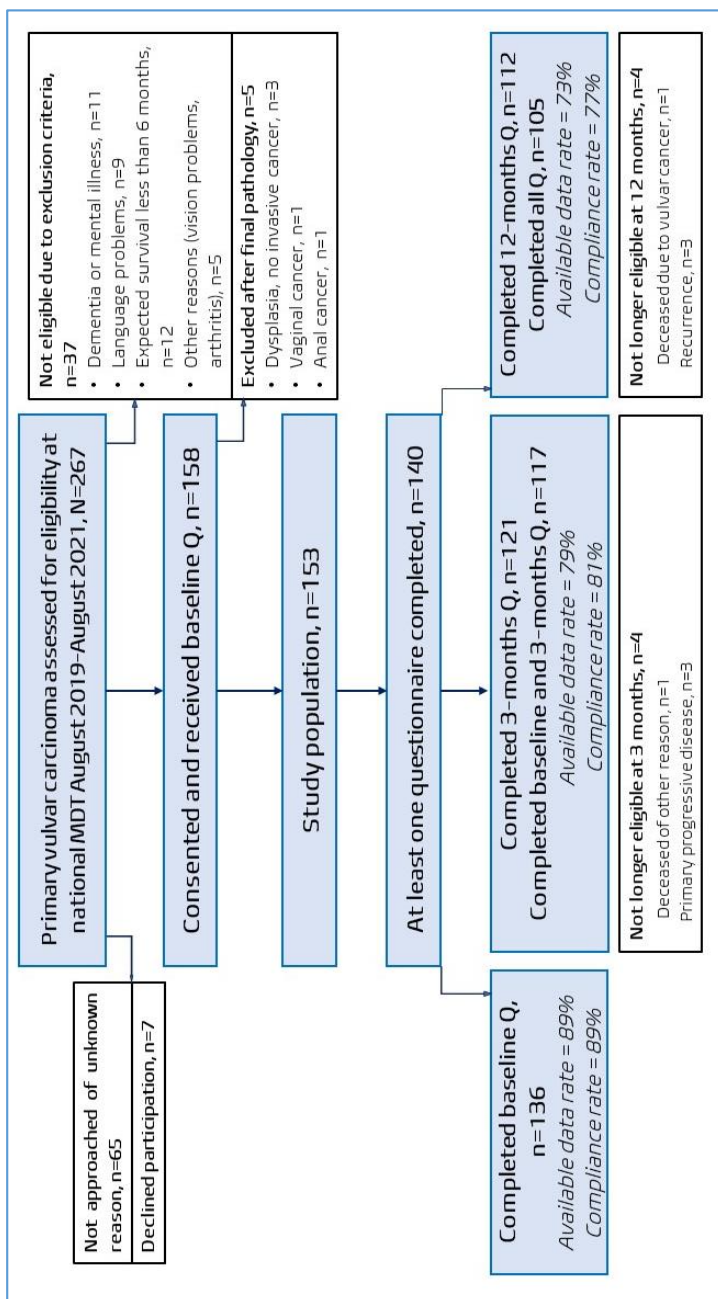
Figure 13. Flow chart studies II and III.

Abbreviations: *Q, study questionnaire; MDT, multidisciplinary team conference.*

Available data rate *= (Number of completed questionnaires at a given time point / Number of included patients at the start of the study) x 100.*

Compliance rate *= (Number of completed questionnaires at a given time point / Number of expected questionnaires at a given time point) x 100 (excluding deceased patients, previous non-responders).*

Of the 153 included women, 136 women (89%) completed the baseline questionnaire, 140 women (92%) completed at least one questionnaire and 105 women (69%) completed all three questionnaires (Figure 13). Clinical and demographic characteristics of the cohort are described in Table 7.

5.2.1 Anxiety

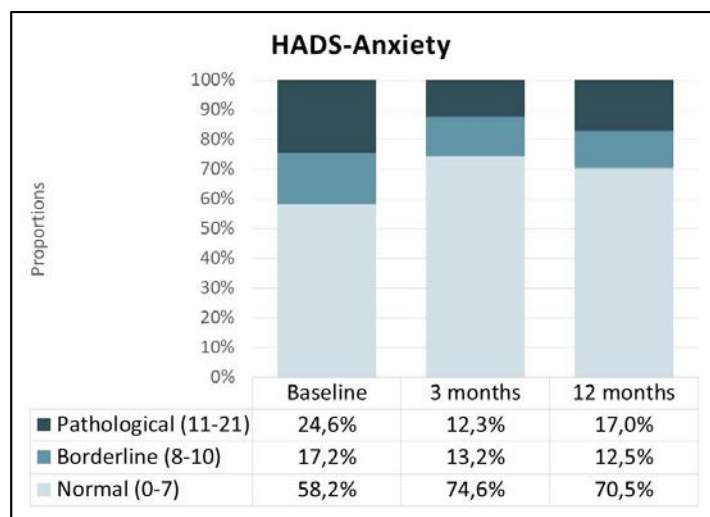The level of anxiety decreased significantly from baseline to 3 months and 12 months. At baseline, 41.8% of the women reported an elevated anxiety level. This proportion decreased to 25.5% three months after treatment, and 29.5% twelve months after treatment (Figure 14). The mean HADS-Anxiety score decreased significantly from 6.9 at baseline to 5.3 at three months, and 5.4 at 12 months (p<0.001) (*Table 2 in paper II, page 7*).

HADS-Anxiety

	Baseline	3 months	12 months
Pathological (11-21)	24,6%	12,3%	17,0%
Borderline (8-10)	17,2%	13,2%	12,5%
Normal (0-7)	58,2%	74,6%	70,5%

Figure 14. Proportions of normal, borderline, and pathological anxiety levels at baseline, 3 months, and 12 months after treatment.

The log-linear regression model revealed a significant association between insomnia and anxiety at baseline (univariate risk ratio (RR) 1.54, p<0.001, multivariate RR 2.21, p<0.001) (Table 10 A). Neither FIGO stage, relationship status, BMI, nor vulvar symptoms were associated with anxiety at baseline in the multivariate analysis. There was a trend towards higher anxiety levels in younger women (RR 1.37, p=0.08).

In the longitudinal multivariate log-linear GEE-model with repeated measurements, insomnia was still significantly associated with elevated anxiety levels (RR 2.09, p=0.012) (Table 10 B). Moreover, persisting vulvar symptoms were associated with increased anxiety (RR 2.71, p<0.001). No association could be found between type of treatment and anxiety. Again, there was a trend towards increased anxiety levels in younger women (RR 1.56, p=0.058).

Table 10. *Uni- and multivariate log-linear regression model investigating associations with anxiety at baseline (A) and over time with three repeated measurements, using generalised estimating equations (GEE) (B). Treatment was not included in model A (before start of treatment), while stage of disease, relationship status, and BMI were not included in model B (not significant at baseline).*

A

Variable	Univariate		Multivariate	
	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
Age				
≥ 65 years	1 (reference)		1 (reference)	
< 65 years	1.48 (1.00-2.18)	0.05	1.37 (0.96-1.94)	0.08
FIGO stage				
Stage I-II	1 (reference)		1 (reference)	
Stage III-IV	0.99 (0.60-1.63)	0.96	0.96 (0.60-1.59)	0.93
Relationship status				
Partner	1 (reference)		1 (reference)	
No partner	1.54 (1.05-2.27)	0.03	1.31 (0.88-1.93)	0.18
Vulvar symptoms[a]				
Low	1 (reference)		1 (reference)	
High	1.41 (0.97-2.11)	0.12	1.17 (0.77-1.78)	0.45
BMI				
<30	1 (reference)		1 (reference)	
≥30	1.43 (0.97-2.11)	0.07	1.19 (0.81-1.74)	0.38
Insomnia[b]				
Low	1 (reference)		1 (reference)	
High	2.62 (1.79-3.84)	<0.001	2.21 (1.44-3.39)	<0.001

B

Variable	Univariate		Multivariate	
	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
Age				
≥ 65 years	1 (reference)		1 (reference)	
< 65 years	1.54 (0.89-2.68)	0.12	1.56 (0.98-2.47)	0.058
Treatment				
Surgery only	1 (reference)		1 (reference)	
Surgery + RT/CRT	1.67 (0.89-3.16)	0.11	1.50 (0.82-2.75)	0.19
Primary RT/CRT	1.79 (1.01-3.20)	0.048	1.53 (0.92-2.54)	0.10
Vulvar symptoms[a]				
Low	1 (reference)		1 (reference)	
High	3.45 (2.11-5.63)	<0.001	2.71 (1.63-4.51)	<0.001
Insomnia[b]				
Low	1 (reference)		1 (reference)	
High	2.97 (1.80-4.89)	<0.001	2.09 (1.18-3.72)	0.012

Anxiety *as binary outcome (yes=borderline or pathological, no=normal level). Measurements at baseline, 3 months, and 12 months included in analysis B.*

[a]*Vulvar symptoms score from the EORTC-VU34 ("Vulvar skin changes", i.e., pain, itchiness, or irritation, tearing or splitting, sore skin, and difficulties in sitting due to problems in the genital area). Low: ≤33, high: >33, score ranging from 0 to 100.*

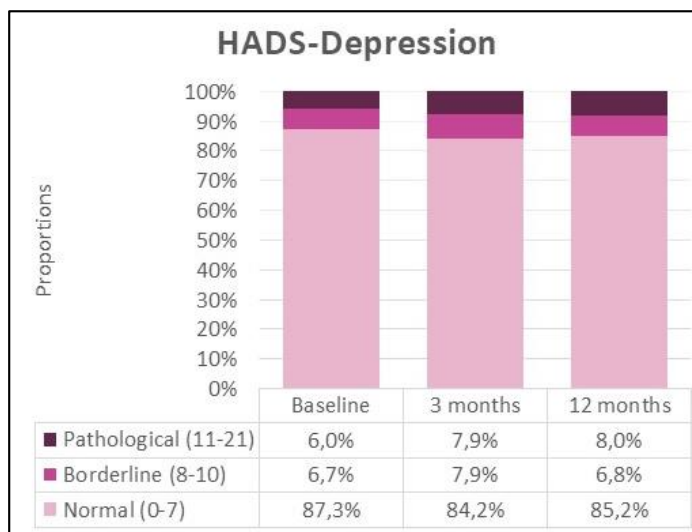[b]*Insomnia score from the EORTC-C30 subscale "Insomnia". Low: ≤50, high: >50, according to Giesinger and co-workers (221).*

Abbreviations: *RR, risk ratio; CI, Confidence interval; BMI, Body-mass index, RT, radiotherapy, CRT, radiochemotherapy.*

In a further log-linear regression model, all four investigated supportive care needs showed a significant association with increased anxiety at baseline (*Table 4 A in paper II, page 9*). Even more pronounced risk ratios between supportive needs and increased anxiety were found in the GEE model with repeated measurements over time (*Table 4 B in paper II, page 9).* Women who needed support because of fear about the cancer spreading, women who needed sensitive hospital staff, women who needed information about their care, and women who needed help to control their situation reported significantly higher levels of anxiety than women not reporting these needs (*Fears about cancer spreading:* RR 3.32 at baseline, p=0.004, and RR 5.19 over time, p<0.001. *Hospital staff acknowledging and showing sensitivity to feelings and emotional needs*: RR 2.78 at baseline, p=0.002, and RR 4.46 over time, p<0.001. *Information about important aspects of care:* RR 2.57 at baseline, p=0.012, and RR 2.72 over time, p<0.001. *Learning to feel in control of the situation:* RR 2.5 at baseline, p=0.001, and RR 3.98 over time, p<0.001).

5.2.2   Depression

At baseline, 87% of the women reported normal depression levels. There were no significant changes in the proportions or mean scores over time. (*Figure 15, Table 2 of paper II, page 7*). Due to the low prevalence, no further analyses were conducted.

Figure 15. Proportions of normal, borderline, and pathological depression levels at baseline, 3 months, and 12 months after treatment.

HADS-Depression	Baseline	3 months	12 months
■ Pathological (11-21)	6,0%	7,9%	8,0%
■ Borderline (8-10)	6,7%	7,9%	6,8%
■ Normal (0-7)	87,3%	84,2%	85,2%

5.2.3   Local vulvar and lymphoedema symptoms

At the time of diagnosis, the most prevalent vulvar symptoms were itching, irritation, pain, sore skin, and swelling of the genital area (Table 11 A, symptoms on item-level). These symptoms improved significantly over time (change in mean scale score between baseline and 12 months -21 for Vulva skin changes, p<0.001; -13 for vulva swelling, p<0.001) (Table 11 B). Narrowing of the vaginal entrance was less prevalent at baseline but increased over time (change in mean score between baseline and 12 months on single-

item level +6). Although groin lymphoedema symptoms worsened initially after treatment (change in mean scale score between baseline and 3 months +7, p=0.005), 12 months after treatment they neither had improved nor deteriorated compared to the time of diagnosis (change in mean scale score from baseline to 12 months -0.2, p=0.923). Leg lymphoedema symptoms increased significantly over time (change in mean scale score between baseline and 12 months +6, p=0.003).

Table 11. *EORTC-QLQ VU34 vulvar and lymphoedema symptoms single-item mean scores (A) and changes in scale mean scores over time (B).*

A

		Mean score at baseline	(SD)	Mean score at 3 months	(SD)	Mean score at 12 months	(SD)
EORTC-QLQ VU34 single items (symptoms)	Pain in the genital area	39	(33)	20	(28)	15	(22)
	Itchy or irritated skin in the genital area	47	(33)	32	(32)	25	(28)
	Sore skin in the genital area	45	(33)	29	(31)	21	(25)
	Tearing / splitting in the genital area	16	(26)	9	(23)	6	(15)
	Difficulties in sitting due to problems in the genital area	38	(36)	26	(35)	12	(22)
	Narrowing / tightness of the vaginal entrance	19	(28)	25	(32)	24	(31)
	Scarring in the genital area	19	(28)	21	(29)	16	(28)
	Unpleasant discharge from the vagina / genital area	19	(28)	10	(20)	9	(21)
	Swelling in the genital area	31	(33)	29	(32)	16	(26)
	Feeling tight in the genital area	27	(29)	27	(32)	16	(25)
	Swelling in the groin	11	(24)	21	(28)	11	(22)
	Sore skin in the groin	15	(28)	20	(28)	13	(23)
	Pain in the groin	12	(24)	18	(29)	11	(23)
	Swelling in one or both legs	9	(21)	20	(28)	19	(28)
	Heaviness in one or both legs	10	(22)	18	(28)	16	(27)
	Skin feeling tight in the legs	7	(19)	13	(27)	11	(22)
	Pain in the legs	10	(23)	17	(28)	15	(28)

B

		Estimated change in scale scores (baseline - 3 months) (95% CI)		p-value	Estimated change in scale scores (baseline - 12 months) (95% CI)		p-value
EORTC-VU34 Symptom scales	Vulvar skin changes[1]	-13	(-18; -9)	<0.001	-21	(-25; -16)	<0.001
	Vulvar scarring[2]	5	(-0.3; 10)	0.065	2	(-3; 7)	0.476
	Vulva swelling[3]	-1	(-6; 4)	0.754	-13	(-18; -7)	<0.001
	Groin lymphoedema[4]	7	(2; 12)	0.005	-0.2	(-5; 5)	0.923
	Leg lymphoedema[5]	8	(4; 12)	<0.001	6	(2; 11)	0.003

Values ranging from 0 to 100 (higher values referring to more symptoms). A negative value reflects improvement.

[1] *Includes the items vulva pain, itching, irritated and sore skin, difficulties to sit, tearing and splitting in the genital area.*

[2] *Includes the items narrowing of the vaginal entrance and scarring of the genital area.*

[3] *Includes the items swelling and feeling tight in the genital area.*

[4] *Includes the items swelling, sore skin, and pain in the groin.*

[5] *Includes the items swelling, heaviness, tight skin, and pain in the legs.*

Abbreviations*: SD, standard deviation; 95% CI, 95% confidence interval.*

Adjusted linear mixed-effects models revealed a significant association between severe vulvar symptoms and impaired HRQOL (*Table 5 of paper III, page 17*). Women with severe vulvar itching/irritation reported significantly worse role functioning (difference in mean score -29, p<0.001), social functioning (difference in mean score -26, p<0.001), mental health (difference in mean score -25, p<0.001), physical functioning (difference in mean score -22, p<0.001), emotional functioning (difference in mean score -21, p=0.001), and cognitive functioning (difference in mean score -18, p=0.001). There was a trend towards impaired global health status (difference in mean score -11, p=0.052). The models were adjusted for age (<65 *versus* ≥65 years), treatment (Limited vulvar surgery without radiotherapy *versus* extensive vulvar surgery without radiotherapy *versus* vulvar surgery followed by radiotherapy), and comorbidities (none *versus* one *versus* more than one comorbidity).

5.2.4 HRQOL

HRQOL, assessed by the EORTC-QLQ C30 functional scales, improved significantly over time (Table 12 A, B). The improvement was most pronounced in emotional functioning (change in mean score between baseline and 12 months +15, p<0.001), role functioning (change in mean score +8, p=0.003), global health (change in mean score +11, p<0.001),

and mental health (change in mean score +8, p<0.001). There was a trend towards a small improvement in physical functioning (change in mean score between baseline and 12 months +3, p=0.051).

Table 12. EORTC-QLQ C30 functional scale mean scores *(A)* and changes in scale mean scores over time *(B)*.

A

	Mean score at baseline	(SD)	Mean score at 3 months	(SD)	Mean score at 12 months	(SD)
Physical functioning	80	(23)	83	(19)	85	(21)
Emotional functioning	65	(25)	76	(26)	79	(25)
Role functioning	74	(32)	82	(27)	83	(28)
Cognitive functioning	82	(23)	86	(23)	86	(23)
Social functioning	79	(27)	82	(24)	84	(25)
Global health status/QoL	61	(26)	68	(24)	72	(23)
Mental health summary scale	72	(22)	78	(22)	81	(22)

B

	Estimated change in scale scores (baseline - 3 months) (95% CI)		p-value	Estimated change in scale scores (baseline - 12 months) (95% CI)		p-value
Physical functioning	2	(-1; 5)	0.233	3	(0; 7)	0.051
Emotional functioning	11	(7; 15)	<0.001	15	(11; 19)	<0.001
Role functioning	7	(2; 13)	0.008	8	(3; 14)	0.003
Cognitive functioning	4	(0.3; 8)	0.032	4	(0.4; 8)	0.029
Social functioning	3	(-1; 7)	0.183	6	(2; 11)	0.004
Global health status/QoL	7	(2; 11)	0.004	11	(6; 15)	<0.001
Mental health summary scale	5	(2; 8)	0.001	8	(5; 11)	<0.001

Values ranging from 0 to 100 (higher values referring to better functioning). A positive value reflects improvement.

Abbreviations: *SD, standard deviation; QoL, quality of life; 95% CI, 95% confidence interval.*

5.2.5 Patients' views and feelings about their vulvar cancer diagnosis

Every fifth woman reported feelings of isolation and loneliness at baseline. Four out of ten women found it difficult to talk about the disease in general and three out of ten to talk about the disease with friends or family at baseline (Table 13). These proportions did not change significantly during surveillance.

Table 13. *Self-constructed questions concerning patients' views and feelings about their vulvar cancer diagnosis (proportions at baseline and 12 months).*

|		Baseline (%)	12 months (%)	*P*-value [a]
I'm feeling lonely and isolated because nobody has knowledge about my disease	Always /often	4.1	5.4	0.49
	Seldom / sometimes	17.6	9.5	
	Never	52.7	60.8	
	Don't know	25.7	24.3	
It feels difficult and shameful to talk about my disease	Always /often	10.8	9.5	0.40
	Seldom / sometimes	28.4	18.9	
	Never	50.0	63.5	
	Don't know	10.8	8.1	
It is difficult to talk with friends / my family about my disease	Always /often	6.8	5.4	0.88
	Seldom / sometimes	25.7	21.6	
	Never	58.1	60.8	
	Don't know	9.5	12.2	

[a] *Chi-square-test*

5.3 Study IV
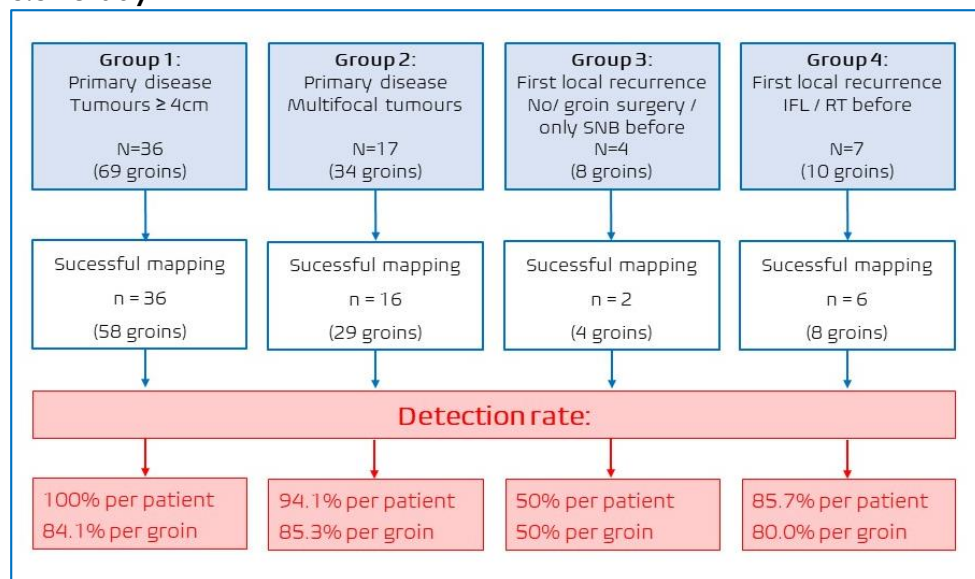
Figure 16. *Inclusion and detection rates for Group 1-4.*
Abbreviations: *SNB, sentinel node biopsy; IFL, inguinofemoral lymphadenectomy; RT, radiotherapy.*

During the study period, 64 women were included, most of them in Group 1 (tumours ≥ 4 cm, 36 women). Seventeen women with multifocal tumours (Group 2) and eleven with a local recurrence (Group 3 and 4) were included (Figure 16). Clinical and demographic characteristics of the cohort are described in Table 7. In 45 women (70%), a combination of a radiotracer and blue dye was used. In 18 women (28%), the sentinel nodes were detected by a radiotracer only, and in one woman (2%), only blue dye was used. In mean 1.5 sentinel lymph nodes and 6 non-sentinel lymph nodes were removed per groin. The detection rates per patient and per groin for the different subgroups are displayed in Figure 16.
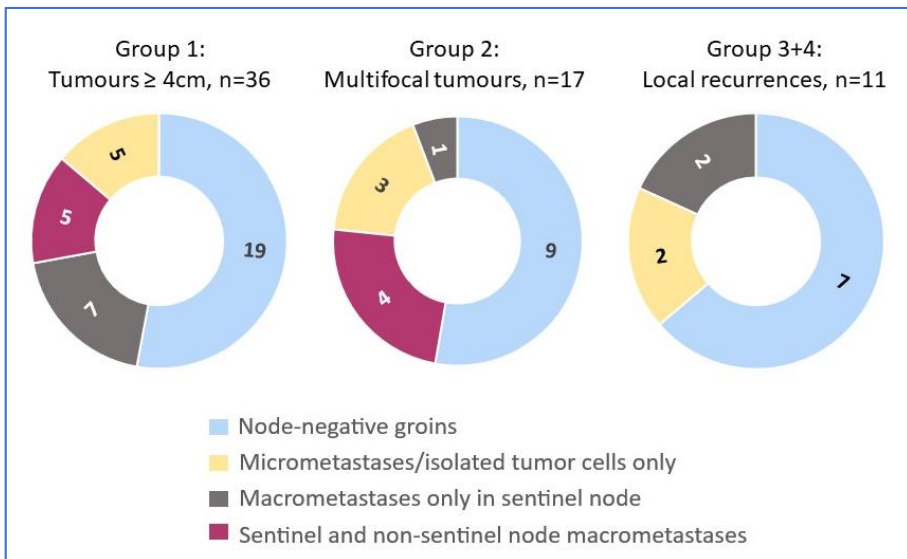

Figure 17. *Distribution of groin metastases in Group 1, Group 2, and Group 3, 4.*

Metastatic disease was found in 17 women (47%) in Group 1, 8 women (47%) in Group 2 and four women (36%) in Group 3 and 4 (Figure 17). In 9 women (26% of the node-positive women), the metastases consisted of micrometastases or ITC only. In 11 women (31%), the metastases were detected by ultrastaging. In 30 of the 35 women with metastases (86%) no further non-sentinel metastases were found. Of 190 removed sentinel lymph nodes, 27 were metastatic (14%). Of 661 removed non-sentinel lymph nodes, 15 were metastatic (2%). Six metastatic sentinel lymph nodes showed extranodal growth. The metastases in these nodes were between 2 and 18 mm in diameter. In four of the 16 non-mapping groins, metastases were diagnosed in the lymphadenectomy specimen. In three of the four groins, the metastases showed extranodal growth.

No false negative sentinel lymph nodes were found, resulting in a negative predictive value of 100% for subgroup 1, 2, and 3 (Table 14). Group 4 (local recurrence with previous inguinofemoral lymphadenectomy and/or radiotherapy) was excluded from the analysis, as women in this group did not undergo an additional IFL, and hence, sensitivity and negative predictive value could not be calculated.

Table 14. Negative predictive value for Group 1 (tumours ≥ 4 cm), Group 2 (multifocal tumours) and Group 3 (local recurrence without or with only limited previous groin treatment).

		SN metastasis[1]		False negative SN	Sensitivity	Negative predictive value
Number of women and groins	SNB	No	Yes	n	% (95% CI)	% (95% CI)
Group 1, 2, 3	Negative	64	0	0	100	100
57 women	Positive	0	27		(87.2 – 100)	(94.4 - 100)
111 groins	Successful mapping: 91 groins					
Group 1	Negative	40	0	0	100	100
36 women	Positive	0	18		(81.5 – 100)	(91.2 – 100)
69 groins	Successful mapping: 58 groins					
Group 2	Negative	21	0	0	100	100
17 women	Positive	0	8		(63.1 – 100)	(83.9 – 100)
34 groins	Successful mapping: 29 groins					
Group 3	Negative	3	0	0	100	100
4 women	Positive	0	1		(5.5 – 100)	(31.0 – 100)
8 groins	Successful mapping: 4 groins					

Abbreviations: *SN, sentinel lymph node; SNB, sentinel node biopsy; CI, Confidence interval.*

[1] *Pathological examination*

Postoperative complications within 60 days occurred in 38 women (59%), mostly Clavien-Dindo (CD) grade 1-2 (29 women, 45%). Eight women developed a complication CD grade 3 (13%), and one woman a CD grade 4 complication (2%). The different types of complications for groin and vulvar surgery can be found in Table 4 of paper IV, page 6. The most common complications after groin surgery were infections (in 32.1% of the women) and lymphocysts (in 24.5% of the women). After vulvar surgery, wound breakdown (in 18.9% of the women) and infection (in 17.0% of the women) were most frequent.

6 Discussion

6.1 Main findings and comments

Study I

In our nationwide cohort of women in Sweden with VSCC, every fifth woman experienced a recurrence, most often in the vulva, as also reported previously (109). However, in contrast to the 4% annual incidence of local recurrences reported by a review published in 2018 (130), the risk we observed for local recurrences was somewhat lower, i.e., 6% after 2 years and 15% after 5 years. This difference might reflect the larger proportion of patients with early-stage disease in our cohort (14,136). In patients with stage IA disease, no more than 5% relapsed within the median follow-up time of 4 years, in contrast to the corresponding value of 33-45% for those with stage III-IV disease. Furthermore, particularly in elderly women, death was a common alternative outcome. At the same time, as described by others, we found that the cumulative incidence of local recurrences rose continuously with time, without reaching a plateau (120,130,136).

The risk for groin recurrences in presumed node-negative disease was higher than anticipated, irrespective of whether an IFL or SNB was performed. A median number of seven lymph nodes per groin were retrieved in women who underwent an IFL and did not experience a groin recurrence. In contrast, in women with a groin recurrence, only four lymph nodes were retrieved. Prior retrospective research has suggested an association between less radical groin surgery and an enhanced risk for recurrence in the groin (91–96).

Limited surgical experience with dissection of lymph nodes may have been one reason for the low number of nodes observed. In the case of breast cancer surgery, performance of 20 procedures is considered to be required in order to master the technique (114) and this number might have been difficult to achieve during our study period, when treatment of VSCC was not centralised. Moreover, differences in the procedures employed in connection with the pathological examination, as well as the quality of this examination, might be another reason. The sentinel node technique was introduced only a few years prior to when our study began. Moreover, these factors may also explain, at least in part, why recurrence in the groin after SNB was seen to be higher here than described in a recent systematic review (110).

We found that every fifth woman with presumed stage IB-II disease did not undergo surgical groin staging and of these, every tenth woman experienced disease recurrence in the groin. Furthermore, absence of groin staging was associated with poorer recurrence-free and overall survival. It appears likely that these women were suffering from occult stage III disease at the time of diagnosis and, consequently, did not receive appropriate treatment. Current imaging techniques are not sufficiently sensitive to

definitively rule out the presence of lymph node metastases, and in particular those of low volume, preoperatively (222–226). Our present findings emphasise the importance of surgical groin staging in connection with the choice of adjuvant therapy.

In our cohort, the rate of survival following disease relapse was alarmingly poor. In this context, Hellman and colleagues observed that women 80 years of age or older underwent less radical primary surgical treatment, received lower doses of radiation, and had a relative survival 4-fold worse than that of women younger than 60 (102). Unfortunately, details concerning the treatment of recurrent disease in our cohort were not available. However, the women with recurrent disease were significantly older than those without recurrence and, as in the case of the study by Hellman and co-workers, our more elderly women might have received suboptimal treatment for their recurrences.

Studies II and III

In this prospective investigation of women diagnosed newly with vulvar cancer, four of ten initially reported borderline or pathological levels of anxiety. Despite a significant decrease in this proportion, every third woman still experienced elevated anxiety 12 months after treatment. To our knowledge, the only previous longitudinal assessment of anxiety in women with vulvar cancer involved 20 Australian women who reported similar levels at the time of diagnosis and two months after treatment (161).

Our current findings reveal that even in the case of vulvar cancer, which affects mainly elderly women and is associated with a generally good prognosis, anxiety is highly prevalent, in particular at the time of diagnosis, and is closely associated with insomnia. It is noteworthy that neither the stage of disease, age at the time of diagnosis, type of treatment, nor relationship status could be used to predict the level of anxiety. However, there was a trend towards more anxiety in younger women. Furthermore, women with high information needs reported increased anxiety.

These findings are in agreement with previous descriptions of associations between a high need for information and impaired emotional functioning in patients with breast and gynaecological cancer (227). A recent meta-analysis identified insomnia as a strong predictor of anxiety (228), and longitudinal studies indicate that insomnia precedes the onset of anxiety and depression, although the exact underlying mechanism remains unclear (229). Sleep appears to be important for emotional and mental processing and psychological learning and sleep deprivation exerts a detrimental effect on both physical and mental health (230–232). Therefore, it is perhaps not surprising that lying awake at night can promote anxiety.

At baseline, the women in our cohort reported poorer overall HRQOL than a cohort of healthy Swedish women of the same age, particularly with respect to emotional, role, and social functioning (233), probably because they already had symptoms of their cancer

and had received their diagnosis. Twelve months later, their HRQOL had improved significantly and was comparable to that of the healthy group.

Local vulvar itching, irritation, swelling, and pain were highly prevalent at baseline and an unexpected and novel finding was that severe vulvar symptoms were associated with high levels of anxiety and impaired HRQOL, both at the time of diagnosis and during surveillance. As described in *Study I*, local recurrences were common and accompanied by symptoms in almost three thirds of the women. During surveillance, women are advised to seek help if they experience local symptoms which might indicate a recurrence and thereby trigger anxiety. Moreover, it is plausible that severe itching and irritation can exert a negative influence on daily social, family, and professional activities, as well as on perception of global health. In addition, such symptoms can disturb sleep and, thereby, promote anxiety and impair HRQOL. As mentioned above, perceived HRQOL improved significantly following treatment, which might have been a result of the treatment itself, the relief of symptoms, and decreasing stress caused by the cancer diagnosis. Furthermore, the women might judge their quality of life differently over time due to response shift.

Narrowing of the vaginal entrance was the only vulvar symptom that became worse during the 12 months after treatment, and this was probably caused by the vulvar surgery. This worsening could have a negative impact, particularly on sexually active women. Although reconstructive surgery with oncoplastic flaps may reduce the risk for vaginal stenosis, this possibility has not yet been investigated.

An increase in the symptoms of LLE over time occurred as expected, most likely as a consequence of groin surgery. An association between LLE and poor HRQOL has been proposed (77–79,81,108). However, the prevalence of such symptoms in our cohort 12 months after treatment was lower than described in earlier studies (59,77–79,81,164). This may reflect the predominantly early stage of disease and the limited radicality of the surgical groin staging in our cohort. Only one-third of the women underwent IFL and more than half of the women a sentinel node biopsy only, while 16% were subjected to no treatment of the groin at all. Furthermore, the different types of measurement and questionnaires employed to assess LLE hamper direct comparisons between studies. To our knowledge, the leg lymphoedema scale of the EORTC-QLQ VU34 has never previously been applied to vulvar cancer patients and, consequently, there are no threshold or reference values available.

Study IV

In this prospective assessment of feasibility, a sentinel lymph node was detected in 100% of the tumours ≥ 4 cm in diameter (Group 1) and 94% of the multifocal tumours (Group 2). Our results are comparable to those reported previously for detection of unifocal tumours < 4 cm in diameter (58,59,110,111). Furthermore, no false-negative sentinel

lymph nodes were observed, i.e., the negative predictive value was 100%. In contrast, for the 162 women with tumours ≥ 4 cm in diameter included in the GOG-173 study, an unacceptably high false-negative predictive value of 7.4% was observed (58).

Certain weaknesses in that study may, at least in part, explain this high failure rate. Firstly, it was conducted in 1999-2009, when the sentinel node technique was just beginning to be performed and many surgeons were still unfamiliar with the procedure. At the same time, there were no formal requirements for participating centres regarding proficiency for carrying out this procedure. Secondly, during the entire 10-year period, only 515 women treated at 47 centres were included, which corresponds to an annual average of one patient per centre. Thirdly, since no formal requirements for preoperative imaging were in place, women with radiologically suspicious lymph nodes might have been included. Preoperative imaging can detect clinically occult metastases in inguinofemoral lymph nodes. By this, false-negative sentinel lymph nodes due to lymph channels obstructed by tumour growth can be avoided. Fourthly, utilization of a radiotracer was not mandatory at the beginning of their study period.

Accordingly, even though our own cohort is much smaller, we are convinced that it presents a better picture of the current standard of the technique. This conclusion is corroborated by a recent small prospective study from a tertiary Italian centre, in which no false-negative sentinel nodes were detected in 12 patients with VSCC and tumours ≥ 4 cm in diameter (117). Although the higher risk for lymph node metastasis in connection with larger tumours probably is associated with a somewhat lower negative predictive value, it might be possible to achieve acceptable oncological safety in these patients as well.

In the case of the GROINSS-V-I study, the exclusion of multifocal tumours following two groin recurrences among the 19 women with multifocal disease may have been premature (59). After early uncertainty, multifocality is no longer considered a hinder for application of the sentinel node technique in patients with breast cancer (234,235). Moreover, in the case of cervical and endometrial cancer, neither the localisation nor focality of the tumour are considered in determining whether to use this procedure and the injection technique is identical (115,236–238). In the Italian study by Garganese and colleagues mentioned above, the negative predictive value was 100% for the 9 women with multifocal tumours (117).

The high proportion of patients with micrometastases and isolated tumour cells, as well as the proportion of metastases diagnosed only through ultrastaging are in agreement with previous findings and provide further evidence for the improvement in lymph node assessment provided by this technique (58,59). As a result of the GROINSS-V-II trial, women exhibiting isolated tumour cells or micrometastases in a sentinel lymph node can be offered adjuvant radiotherapy with an expected inguinofemoral recurrence rate of less than 2%, instead of IFL (239). Although the GROINSS-V-II study included only women

with unifocal tumours < 4 cm in diameter, if the findings of this study are also relevant to large and multifocal tumours, it would have been sufficient to treat 20% of the node-positive women in our cohort with sentinel node biopsy followed by radiotherapy, rather than an IFL. In this manner, along with the 53% of the cohort lacking lymph node metastases, these women could have been spared the morbidity associated with an IFL.

Too few of our women had locally recurrent disease to allow any conclusions concerning safety and feasibility to be drawn. Although over the course of each year, 50-70 women with recurrent vulvar cancer were discussed at the weekly MDT, only a small number of these were considered to be eligible for the study. The most common reasons for exclusion were clinical / radiological signs of regional or distant metastases, poor performance status, or comorbidities. Following previous IFL (a criterion for inclusion in Group 4), many women were already suffering from side-effects of this primary treatment, which made the treating surgeons reluctant to offer participation in a trial that could potentially worsen their condition. Women with no previous groin treatment (a criterion for inclusion in Group 3) were often offered sentinel node biopsy for their local relapse, without complementary IFL.

6.2   Clinical implications

At the time of diagnosis

The high prevalence of anxiety and poor emotional functioning at baseline may motivate screening for a potential need for early psychosocial intervention in connection with the first clinical visit. Moreover, targeting sleeping problems and trying to provide the women with the support they need might alleviate anxiety. In addition, treatment of severe vulvar symptoms and information concerning the risk of vaginal narrowing and its consequences for sexual functioning might help improve HRQOL.

Treatment

The findings documented in _Study I_ support the key relevance of surgical groin staging for primary treatment of VSCC. At present, no non-invasive techniques capable of indicating the status of the lymph nodes with sufficient accuracy are available (240). Although sentinel node biopsy is minimally invasive and highly sensitive, its current application in patients with VSCC is limited to unifocal primary tumours < 4 cm in diameter (58,59). _Study IV_ indicates that further investigation of the safety of this technique in connection with larger and multifocal tumours is well warranted. Moreover, this approach can be utilised to detect even small metastases by ultrastaging, so that women with ITC or micrometastases might be treated effectively by radiotherapy, without the need for an IFL.

The frequent omission of groin staging, high incidence of inguinofemoral recurrences and poor post-recurrence OS documented in _Study I_ underline the importance of surgical

proficiency. In this context the centralisation of treatment of vulvar cancer recently implemented in Sweden could have a positive effect.

It is reassuring that from prior to treatment to 12 months after, women reported improvement in almost all symptoms and in emotional, role, cognitive, and social functioning, as well as in global and mental health. Although our study design does not allow us to determine exactly the role of treatment in this improvement, these findings challenge the common apprehension that, especially in elderly women, treatment might result in more harm than benefit. In *Study I,* the median age of patients who did not undergo surgical groin staging was higher than those who did. The poor survival rate in the former group, probably due to insufficient treatment of stage III disease, motivates efforts to offer appropriate treatment even to elderly women.

Because treatment results in narrowing of the vaginal entrance, measures designed to attenuate the risk for sexual impairment, such as reconstructive surgery and dilating devices, should be explored.

Follow-up

Study I identified certain groups with a low risk for recurrence of vulvar cancer, such as women with stage IA disease. Unfortunately, the SQRGC does not provide information concerning the expression of p16 or p53 in the tumours, which might provide a basis for a more refined risk stratification. However, even women with a low risk for recurrence can benefit from follow-up focussing on psychosocial support and involving caretakers in other disciplines, such as psychologists or specialised nurses.

As revealed by *Study II,* the level of patient anxiety was independent of the stage of their disease or type of treatment. The associations of insomnia, need for support, and vulvar symptoms with elevated anxiety could be utilised to identify women at risk for anxiety and also be valuable to alleviate anxiety. Persistent local vulvar symptoms can be caused by the treatment itself or by an underlying disease in the vulvar skin, such as lichen sclerosus, the prevalence of which among our cohort was unknown.

These findings indicate the potential value of efforts to individualise surveillance of patients with vulvar cancer. Open discussion of the risk of recurrence and attempts to alleviate persistent symptoms, side-effects of the treatment, and anxiety may improve HRQOL considerably. In particular, open-minded discussion of potential sexual difficulties and ways of coping with these could be of great value.

6.3 Methodological considerations

Study I

Study I relies on information retrieved from the SQRGC. Since a previous study found that the quality of information concerning endometrial and ovarian, fallopian tube, peritoneal, abdominal, or pelvic cancers in this registry was adequate (241), we examined the quality of its information concerning vulvar cancer. We compared the information in the register with the medical hospital charts of 31 randomly selected women. In the case of histology, date of death, vital status, state of disease at the end of treatment as well as at last follow-up, and localisation of a recurrence, these two sources were in complete agreement. With respect to the nature of primary treatment, date of recurrence, type of groin surgery, number of retrieved and/or metastatic lymph nodes, and FIGO stage the agreement was 80% and for type of vulvar surgery and histological grading 77%. The corresponding values for the dates of start and termination of treatment, date of diagnosis, tumour-free margins, performance status, and tumour size were 44-70%. Thus, the register data concerning our primary endpoints appear to be reliable, although there might be some bias in regression analyses adjusted for variables such as tumour size or performance status. Furthermore, tumour size was only assessed clinically, even in women who underwent surgery, where a pathological tumour size could have been obtained.

In connection with this comparison, 23.5% of the relevant data were missing from the hospital charts – more specifically, 20.0% in the case of performance status, 23.5% for histological grading, 17.6% for surgical margin, and 11.5% concerning tumour size. However, the information concerning the primary endpoints of our study was almost complete. Rather than making assumptions about missing values, the number of women included in the adjusted regression models was reduced, which introduced the risk of a selection bias.

When comparing the outcomes in two groups, i.e., in *Study I* the survival of women with and without surgical groin staging, biases can be avoided effectively by assigning the subjects randomly to the two different treatment groups. With rare diseases such as vulvar cancer, a randomised controlled trial including an adequate number of subjects is difficult to achieve. The most recent RCTs investigating survival from vulvar cancer, conducted by the Gynaecologic Oncology Group (GOG) in the 1980´s and 1990´s, were characterised by slow acquisition of subjects (89,90,242). Thus, despite the potential influence of known and/or unknown confounders, retrospective analyses in vulvar cancer are common.

A confounder is a factor which is associated with the outcome (in our case RFS and OS) and the exposure of interest (in our case surgical groin staging), but not as a mediator. In our analyses, confounding by indication is possible, as the decision as to whether perform surgical groin staging probably was influenced by factors such as age,

performance status, and comorbidities. Moreover, also the type of hospital where the treatment was performed, and experience and preferences of the treating surgeon might have influenced the treatment decision. Known confounders can be addressed by measures such as stratification, matching, propensity scoring or regression analysis. Unknown confounders are not approachable. The women with and without surgical groin staging differed significantly with respect to age, performance status, and tumour-free margins and these factors were adjusted for in the regression model.

We calculated overall survival from the date of diagnosis until the date of death, data provided accurately by the registry. Recurrence-free survival was calculated from the date of the end of treatment until the date of diagnosis of a recurrence, e.g., by biopsy or imaging. In women without a recurrence, the end of RFS was taken to be the date of the last follow-up without evidence of disease. Occurrence of disease within three months after termination of primary treatment was classified as progression and these cases were excluded from the analysis; whereas every later occurrence was included as a recurrence.

We decided to calculate recurrence-free survival from the date of the termination of treatment, since the average length of treatment differs between surgery alone, surgery followed by radiotherapy, and definitive radiotherapy. In this manner, we avoided an immortal time bias (Figure 18), i.e., a period of time during which an outcome per definition cannot occur. We defined every occurrence of disease during primary treatment as progression and excluded the women concerned. If the duration of primary treatment differs between groups, the group with the longer treatment will thereby be favoured with respect to survival.
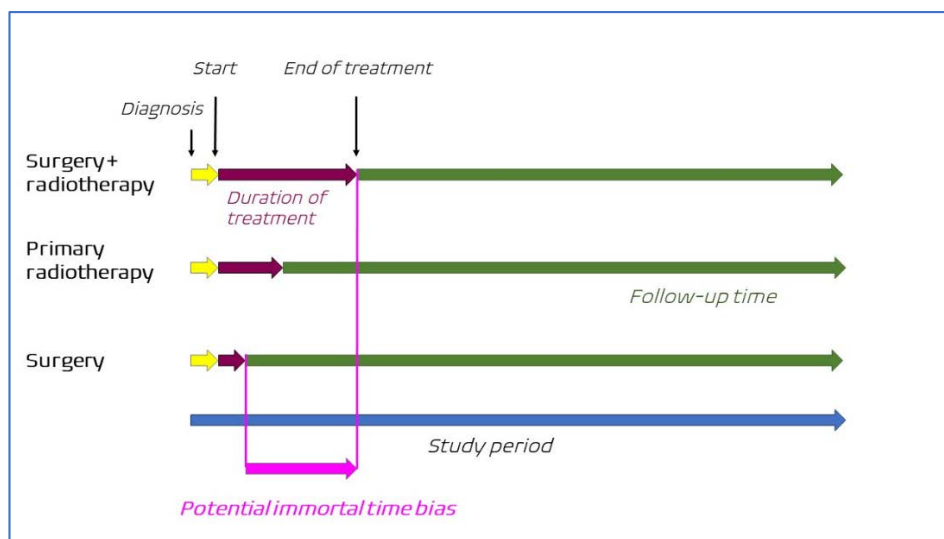

Figure 18. *Schematic illustration of a potential immortal time bias*

On the other hand, in comparison to other studies in which the date of diagnosis or start of treatment was defined as the starting point for RFS, our RFS will be shorter. Furthermore, in our case the median follow-up time for analysis of overall and recurrence-free survival differed.

Studies II and III

Research on quality of life is problematic, especially in the case of rare diseases such as vulvar cancer, which afflicts primarily elderly women and is associated with a high rate of attrition due to recurrence and death. Moreover, many of the accompanying symptoms concern highly private parts of the body. Talking about sexuality and genital organs may be uncomfortable or even taboo for many women and caregivers, which obviously increases the risk of missing information.

Attrition, missing information, and selection bias

Missing information that is due to non-responders and failure to fill in items on a form is probably not random, i.e., bears a risk of a selection bias. Moreover, longitudinal studies involve "natural attrition", i.e., some members of the cohort will not be able to respond because of severe illness, death or simply having moved away. Further non-responding (not returning a questionnaire of unknown reason) should be avoided. In connection with *Studies II and III*, the importance of collecting data that was as complete as possible was emphasised at start-up meetings at all of the hospitals involved, as well as at the regular digital follow-up meetings. After 3 and 12 months, non-responders received one and sometimes two reminders via mail. Women who did not return the questionnaire at baseline were reminded by telephone at the discretion of the treating physician.

There were significant differences in the clinical and demographic characteristics of the women who returned all three questionnaires and those who returned none, only one, or two, indicating a possibility for selection bias. In *Study II,* only information for women who returned all three questionnaires was included in the longitudinal analyses, so there may have been unintentional selection against women with more advanced disease and treatment. In *Study III,* information from all women who returned at least one questionnaire was used in the linear mixed-effects models, with imputation of missing values.

Failure to fill in single items can be accidental, a situation referred to as "missing completely at random" or MCAR. On average, the value for the absent data should be the same as that for the data provided and, therefore, should not introduce a bias, but can weaken the power of the study if not imputed.

Items are defined as "missing at random" or MAR if another variable influences whether they are missing or not. For example, sexually inactive women may leave questions about sexual satisfaction unanswered. MAR values are associated with a risk of bias.

Finally, items can be missing because of their own emotional value ("not missing at random" or NMAR), for example, when women with higher body-mass index more often skip questions about their weight. Such a potential information bias cannot be corrected for completely by imputation.

Missing data can be imputed employing several different approaches, such as multiple imputation, carrying the last observation forward, or using one's individual mean or median of the scale or the median / mean of the entire cohort. The scoring manuals of the EORTC-QLQ C30 and the VU34 module recommend imputation based on the individual's mean of the scale when the values for less than 50% of the items from the scale are missing (197). However, this does not allow imputation of single-item scales. The SCNS-SF34 scoring manual recommends multiple imputation for replacement of missing data when values for less than 50% of the items on the scale are missing (210). In the case of the HADS, imputation is mandatory, since otherwise the summary score will be falsely low (157). Bell and colleagues propose that imputation of the individual's mean value of the subscale (anxiety or depression) is the best approach (206). We imputed values missing from the EORTC-QLQ C30, EORTC-QLQ VU34, and HADS accordingly. In the case of the SCNS-SF34, missing values could not be replaced since the complete scales were not utilized.

Minimally important differences and thresholds for clinical importance

A scale score on the EORTC-QLQ C30 or VU34 is in the range of 0-100. For items concerning functioning, 100 is the best possible outcome; whereas for items concerning symptoms, 0 is most favourable. In the case of HADS, the score for anxiety or depression can vary from 0-21.

For a clinician, it can be difficult to translate these numbers into clinically illustrative values. For HADS, a score of 0-7 is regarded as normal, 8-10 as borderline pathological, and >10 as pathological anxiety or depression (157).

Some support is also provided for the interpretation of the EORTC-QLQ C30 scores and changes in these scores (216,221,243). On behalf of the EORTC-QLQ group, Giesinger and co-workers defined "thresholds for clinical importance" (221). Although these thresholds were developed from data on a heterogenous group of cancer patients, including both men and women, and may not be exactly applicable to our cohort, they were found to be helpful in interpreting the results of Studies *II and III*.

Another working group of the EORTC has developed benchmarks for the interpretation of changes in scores, both between-group differences and within-group changes over time (216,243). Cocks and co-workers have provided values indicating a "minimally important difference" (MID) - "large", "medium" or "small" - for all of the EORTC-QLQ C30 scales, with the exception of the global health scale (216,243). These investigators found small differences between the MIDs for different scales, as emphasised and updated by Musoro

and colleagues in 2023 (217). Furthermore, the MIDs for different types of cancer and for an improvement or deterioration appear to differ slightly. Musoro and co-workers replaced "large", "medium" or "small" by specific cut-off values. For most scales, a MID between 5 and 10 points was determined (217).

Sample size, power, and the risk for a type-II error

A type-II error *(β)* occurs when, even though false, the null hypothesis cannot be rejected. Typically, this happens with small sample sizes or/and extensive variance in the values. For *Studies II and III,* the required sample size could not be calculated properly, since knowledge concerning the prevalence and variance of the condition (e.g., anxiety) was limited. The scatterplot shown in Figure 19 is indicative of a non-linear correlation between anxiety and age at baseline. This could not be confirmed utilizing the log-linear model, although the p-value was close to 0.05. We cannot exclude the possibility that we missed this and/or other associations due to a type-II error.
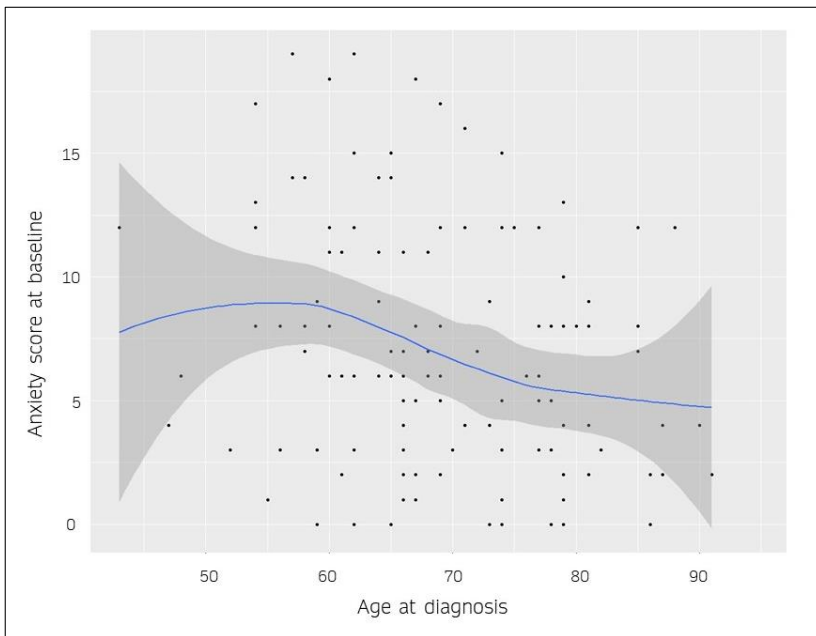

Figure 19. *Scatterplot of the HADS scores for anxiety at baseline (y-axis) and age at the time of diagnosis (x-axis).*

Multiple testing and the risk for a type-I error

Multiple testing is associated with a risk for a type-I error *(α)*, i.e., rejection of the null hypothesis when it actually is true. Upon calculating p-values for 20 different comparisons, at least one will probably be <0.05 simply due to chance. In *Study III* we limited testing by using the scales instead of single items. However, *Studies II and III*

had multiple endpoints and in these cases the possibility of a type-I error cannot be excluded totally.

Ongoing validation of the EORTC-QLQ VU34

The EORTC-QLQ VU34 is currently undergoing phase-4 validation in the field, which may lead to changes in the structure of its scales. We found, for example, that the two items concerning *Vulva scarring* changed after baseline in different ways. While the mean score for *Narrowing of the vaginal entrance* increased from 19 to 24, the mean score for *Scarring in the genital area* decreased from 19 to 16. Thus, we decided to assess vulvar and lymphoedema symptoms primarily on the basis of single items in the EORTC-QLQ VU34, utilizing the scale structure with caution.

Study IV

Sentinel node biopsy can be regarded as an invasive diagnostic test, assessing the risk of metastasis to a lymph node. The sensitivity, specificity, negative and positive predictive value, and false negative rate associated with this procedure can be characterized as shown in Figure 20.

		Condition[1]		Sum	
		Negative	Positive		
Testresult[2]	Negative	a	b	a+b	Negative predictive value
	Positive	c	d	c+d	Positive predictive value
Sum		a+c	b+d		
		Specificity	Sensitiviy		

Figure 20. *A 4-field-contingency table depicting characterization of a diagnostic test*
[1] **Condition** = *lymph node metastasis, assessed by pathological analysis, i.e., the golden standard.*
[2] **Test** = *sentinel node biopsy*

The ideal test would demonstrate 100% sensitivity and 100% specificity. In *Study IV,* each woman served as her own control, so that the specificity of the sentinel node biopsy was by definition 100%, since a metastasis detected in the sentinel node always reflects a metastasis in a lymph node and false positives are impossible. Consequently, sensitivity and negative predictive value were the important properties to be assessed in this case. While the sensitivity of a test is independent of the prevalence of the condition, the negative predictive value takes this prevalence into account. We chose the negative predictive value as our primary endpoint, since this represents the most important

information for the patient, i.e., her individual probability of actually having no metastases in the lymph nodes in her groin when the sentinel node biopsy is negative.

6.4 Internal and external validity

The use of validated PROMs in *Studies II and III* enhanced the internal and external validity of our results. Furthermore, the close cooperation and standardisation of treatment between the participating centres strengthened the internal validity of *Studies II, III, and IV*. In the case of *Study I*, the relatively many missing values and limited agreement between register data and information obtained from hospital charts with respect to certain variables weakened the internal validity, although the information concerning the variables relative to the primary objectives was quite complete and in good agreement.

All of the studies included in this thesis involved nationwide cohorts and high proportions of all eligible women participated in *Studies II, III, and IV*, thereby ensuring good external validity. Furthermore, almost all women with newly diagnosed and recurrent vulvar cancer were identified through screening at the weekly national MDT. It should be noted that the results presented in *Study IV* concern highly proficient and centralised treatment of vulvar cancer and may not be relevant to other systems of healthcare.

6.5 Ethical considerations

All studies were approved by the Swedish Ethical Review Authority (diary numbers 1100-16, T1064-17, and 2019-05887 for *Study I*; 2018/1402-31/1 and 2019-01429 for *Studies II and III;* and 2019-04647 for *Study IV*) and conducted in accordance with the recommendations by the Department of Health And Human Services and International Council for Harmonisation Good Clinical Practice Guidelines (2023) (244), the World Medical Association's (WMA) Declaration of Helsinki (2013) (245) and the European Union General Data Protection Regulation (246). The women who participated in *Studies II, III, and IV* provided their prior written informed consent. In the case of *Study I,* no consent was required, since registration in the SQRGC implies agreement to participate in research, unless the woman asks that her data be removed from this register.

Studies II, III and IV were registered at ClinicalTrials.gov (NCT 04152512 and NCT 04147780).

Centralisation of vulvar cancer was implemented to harmonise treatment, improve outcomes, and facilitate research. The efforts and resources invested in the centralisation call for research into this rare disease.

7 Conclusions

- Local relapses, the most frequent type of recurrence in connection with vulvar squamous cell carcinoma, occur continuously and at a consistent rate during surveillance. Groin and distant recurrences occur early and are characterised by extremely poor survival. Lack of surgical groin staging is associated with poorer survival.

- Women diagnosed newly with vulvar cancer experience high levels of anxiety and poor emotional functioning at the time of diagnosis but exhibit significant improvement after treatment. Insomnia, high needs for information, and persistent vulvar symptoms are associated with increased levels of anxiety both at the time of diagnosis and during the first 12 months of surveillance. Levels of depression are low and stable over time.

- Local vulvar symptoms are highly prevalent at the time of diagnosis but improve significantly after treatment. Severe vulvar itching and irritation are associated with impaired HRQOL. Symptoms of leg lymphoedema increase after treatment. HRQOL is impaired at the time of diagnosis but improves significantly during the first 12 months after treatment.

- It appears to be safe to offer sentinel node biopsy to women with newly diagnosed vulvar squamous cell carcinoma involving tumours ≥ 4 cm in diameter and multifocal tumours.

8 Future Perspectives

The rate of tumour recurrence in the groin in *Study I* was higher than expected and might have been due, at least in part, to limited surgical proficiency at some of the treatment centres. Moreover, the fact that in the case of every fifth patient surgical groin staging was not performed may reflect a lack of familiarity with this disease. *Study I* was conducted prior to the centralisation of vulvar cancer care in Sweden, and it would be of value to examine whether treatment, and in particular groin surgery, has changed since 2017 and, if so, whether this has improved the oncological outcome. Furthermore, the post-recurrence survival in *Study I* was worse than previously reported and the reasons for this require elucidation.

The continuously increasing cumulative incidence of local recurrences during surveillance raises the question of the need for secondary prophylactic measures, such as the treatment of lichen sclerosus or vaccination against human papillomavirus. Such measures might even have a positive impact on the patient's anxiety. In fact, lichen sclerosus and infections with human papillomavirus are important factors in the aetiology of vulvar cancer and should even be considered as potential targets for primary prophylaxis. Previous studies on vaccination against human papillomavirus have focused on invasive cancer and high-grade squamous intraepithelial lesions of the uterine cervix and its potential protection against vulvar high-grade squamous intraepithelial lesions and squamous cell cancer requires further evaluation. In light of the central role played by lichen sclerosus in the development of vulvar squamous cell carcinoma independent of human papillomavirus, the prophylactic effect of corticoids or other types of treatment should be tested.

The high rates of anxiety observed in *Study II* motivate early interventions, such as screening at the time of diagnosis and easy access to psychosocial support. A follow-up study evaluating the effect of such interventions on the patient's anxiety is highly desirable. High levels of anxiety characterise other types of gynaecological cancer as well and such a study could include patients with different diagnoses.

The profound impact of local vulvar symptoms on HRQOL deserves further investigation. In particular, it is important to know whether vulvar symptoms that persist after treatment are due to the treatment itself or underlying vulvar skin diseases such as lichen sclerosus. Furthermore, it would be of value to determine whether vulvar reconstructive surgery following treatment can alleviate vaginal narrowing or other local symptoms.

The accuracy of surgical groin staging by sentinel node biopsy revealed in *Study IV* motivates efforts to investigate the technique further. New tracers such as ICG could be utilised to refine this technique.

Furthermore, reducing the high morbidity of surgical groin staging by inguinofemoral lymph node dissection is an important goal. At primary diagnosis with presumed node-negative disease, less invasive treatment options should be explored. In addition to further development of the sentinel node technique, minimally invasive surgery, such as video endoscopic inguinal lymphadenectomy (VEIL), might be effective in reducing complications and side-effects. In the case of node-positive disease, alternative treatment options to radical surgery and radiotherapy are urgently needed. In this context, molecular-genetic analyses might help to identify potential targets for novel therapeutic agents.

9 Acknowledgements

I am enormously grateful for all the support I received during the last 6 years when working on this thesis. Particularly I want to express my huge gratitude to:

My main supervisor **Angelique Flöter Rådestad** for your never-ending patience, support, and optimism, and navigating me calmly through this incredible journey.

My co-supervisors **Elisabeth Åvall Lundqvist** and **Henrik Falconer**, for your enormous knowledge and experience, as well as your critical input and challenging discussions.

Pernille Jensen for leading me safely through the PROVE data jungle.

Preben Kjølhede for supervising the SNEX project, and to **Conny Kjølhede** for your very warm hospitality.

The head of our clinical department, **Henrik Falconer**, for your generous support and for giving me such immense space and freedom for my development.

My former co-supervisor **Kristina Hellman** for sucessful cooperation in study I.

My **co-authors** for a fruitful and pleasant cooperation.

Malin Holzmann for a fantastic education at the Research school for clinicians in epidemiology, and for - after all - consenting to being chairwoman during my defence.

Hemming Johansson, Eva Hagel, Henrike Häbel, Johan Zetterqvist, Mats Fredriksson, and **Ivette Raices Cruz** for statistical support.

Perihan Inekci from the Clinical Trials Office at Karolinska University Hospital for excellent help with the PROVE questionnaire admission.

All **colleagues, nurses**, and **coordinators** from the participating centres for the support in conducting the studies included in this thesis.

Catharina Beskow, my mentor during the doctoral education, for a very important glass of wine when I really needed it.

All my **colleagues** and **ex-colleagues** at Karolinska Hospital for giving me space, accepting my absences, and supporting my clinical and scientific development.

My **friends** and **family** for love, care, and support.

My **patients** for giving me the feeling of doing something important and meaningful.

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11 List of figures

12 Appendix

PROVE questionnaire at the time of diagnosis (baseline)

Enkät till PROVE studien

EN PROSPEKTIV VULVACANCER ENKÄT UNDERSÖKNING

BASELINE: FÖRE START AV BEHANDLINGEN

Frågeformulär för patienter med vulvacancer (PROVE-studien)

Tack för att du har givit ditt samtycke att delta i denna undersökning!

Syftet med undersökningen är att få mer kunskap om hur patienter med vulvacancer mår under och efter sin behandling och att förbättra omhändertagandet av patienter med vulvacancer.

Vi vill gärna få information om din hälsa och dina besvär i samband med sjukdom och behandling, vilken hjälp som du önskar att få och hur du upplever ditt omhändertagande inom sjukvården. Dessutom har vi några frågor kring din allmänna livssituation. Det finns inga svar som är rätt eller fel. Den informationen du ger kommer att hållas strikt konfidentiell.

Dagens datum: _____

Patient ID: _____

Del 1: Allmänna frågor

Vi vill gärna veta hur din allmänna livssituation och hälsa ser ut. Besvara alla frågor med att sätta ett kryss på det alternativet som stämmer bäst in på dig (ibland flera möjligt).

1. Är du idag:
   - ⭕ Arbetssökande
   - ⭕ Sysselsättning deltid
   - ⭕ Sysselsättning heltid
   - ⭕ Pensionär
   - ⭕ Student
   - ⭕ Långtidssjukskriven / sjukpensionär
   - ⭕ Egen företagare
   - ⭕ Annat

2. Vilken utbildning har du (välj den högsta nivån)?

- ○ Mindre än grundskola
- ○ Grundskola
- ○ Gymnasieavslut / yrkesskola
- ○ Högskoleutbildning / universitetsutbildning

3. Är du för närvarande sjukskriven:

- ○ Ja, pga vulvacancer
- ○ Ja, pga annan anledning
- ○ Nej

4. Är du idag:

- ○ Ensamstående
- ○ Lever i relation / gift

5. Hur bor du?

- ○ Bor ensam
- ○ Bor med partner / familj
- ○ Bor med annan person
- ○ Bor på äldreboende eller annat särskilt boende

6. Var bor du?

- ○ Bor i storstad (Stockholm, Göteborg, Malmö)
- ○ Bor i mellanstad
- ○ Bor på landsbygden

7. Hur mycket väger du: kg

8. Hur lång är du: cm

9. Använder du snus eller röker du:

- ○ Ja,
- ○ Nej

○ Tidigare, men slutat

10. Har du kommit in i menopaus, dvs slutat ha menstruationer sedan minst 12 månader?

○ Ja

○ Nej

11. Använder du någon form av hormonersättning, dvs östrogen?

○ Ja, som tablett, vagitorier eller kräm eller ring i slidan / vulva

○ Ja, som tablett, plåster eller gel eller spray på huden

○ Nej

Plats för egna kommentarer:

Del 2: Allmän hälsa och besvär i samband med din sjukdom / behandling

Vi vill gärna veta om din behandling för vulvacancer har påverkat din allmänna hälsa. Besvara alla frågor genom att sätta en ring runt den siffra som stämmer bäst in på dig.

		Inte alls	Lite	En hel del	Mycket
12.	Har du svårt att göra ansträngande saker, som att bära en tung kasse eller väska?	1	2	3	4
13.	Har du svårt att ta en <u>lång</u> promenad?	1	2	3	4
14.	Har du svårt att ta en <u>kort</u> promenad utomhus?	1	2	3	4

		Inte alls	Lite	En hel del	Mycket
15.	Måste du sitta eller ligga på dagarna?	1	2	3	4
16.	Behöver du hjälp med att äta, klä dig, tvätta dig eller gå på toaletten?	1	2	3	4

Under veckan som gått:

		Inte alls	Lite	En hel del	Mycket
17.	Har du varit begränsad i dina möjligheter att utföra antingen ditt förvärvsarbete eller andra dagliga aktiviteter?	1	2	3	4
18.	Har du varit begränsad i dina möjligheter att utöva dina hobbyer eller andra fritidssysselsättningar?	1	2	3	4
19.	Har du blivit andfådd?	1	2	3	4
20.	Har du haft ont?	1	2	3	4
21.	Har du behövt vila?	1	2	3	4
22.	Har du haft svårt att sova?	1	2	3	4
23.	Har du känt dig svag?	1	2	3	4
24.	Har du haft dålig aptit?	1	2	3	4
25.	Har du känt dig illamående?	1	2	3	4
26.	Har du kräkts?	1	2	3	4
27.	Har du varit förstoppad?	1	2	3	4
28.	Har du haft diarré?	1	2	3	4
29.	Har du varit trött?	1	2	3	4

		Inte alls	Lite	En hel del	Mycket
30.	Har dina dagliga aktiviteter påverkats av smärta?	1	2	3	4
31.	Har du haft svårt att koncentrera dig, t. ex. läsa tidningen eller se på TV?	1	2	3	4
32.	Har du känt dig spänd?	1	2	3	4
33.	Har du oroat dig?	1	2	3	4
34.	Har du känt dig irriterad?	1	2	3	4
35.	Har du känt dig nedstämd?	1	2	3	4
36.	Har du haft svårt att komma ihåg saker?	1	2	3	4
37.	Har ditt fysiska tillstånd eller den mediciniska behandlingen stört ditt familjeliv?	1	2	3	4
38.	Har ditt fysiska tillstånd eller den mediciniska behandlingen stört dina sociala aktiviteter?	1	2	3	4
39.	Har ditt fysiska tillstånd eller den mediciniska behandlingen gjort att du fått ekonomiska svårigheter?	1	2	3	4

Sätt en ring runt den siffra mellan 1 och 7 som stämmer bäst in på dig för följande frågor:

40. Hur skulle du vilja beskriva din hälsa totalt sett under den vecka som gått

   1   2   3   4   5   6   7

   Mycket dålig   Utmärkt

41. Hur skulle du vilja beskriva den totala livskvaliteten under den vecka som gått

1   2   3   4   5   6   7

Mycket dålig   Utmärkt

Plats för egna kommentarer:

Del 3: Lokala besvär efter behandling för vulvacancer

Patienter berättar ibland att de har följande symptom eller problem. Några av dessa gäller underlivet. Ange i vilken utsträckning du har upplevt dessa symptom eller problem, oavsett om du har opererats i underlivet eller inte.

Under veckan som gått

		Inte alls	Lite	En hel del	Mycket
42.	Har du haft smärta i underlivet?	1	2	3	4
43.	Har huden i underlivet känts irriterad eller kliat?	1	2	3	4
44.	Har du känt obehagliga domningar, pirrningar, stickningar eller liknande i huden i underlivet?	1	2	3	4
45.	Har huden i underlivet varit öm?	1	2	3	4
46.	Har huden i underlivet brustit eller spruckit?	1	2	3	4

		Inte alls	Lite	En hel del	Mycket
47.	Har du upplevt att slidöppningen har blivit snävare / trängre?	1	2	3	4
48.	Har ärrbildning i underlivet vållat problem för dig?	1	2	3	4
49.	Har du haft svårigheter att sitta på grund av problem i underlivet?	1	2	3	4
50.	Har du haft obehagliga flytningar från slidan eller underlivet?	1	2	3	4
51.	Har du varit svullen i underlivet?	1	2	3	4
52.	Har huden känts spänd i underlivet?	1	2	3	4
53.	Har du varit svullen i ljumsken?	1	2	3	4
54.	Har huden i ljumsken varit öm?	1	2	3	4
55.	Har du haft smärta i ljumsken?	1	2	3	4
56.	Har du haft bensvullnad i ena eller båda benen?	1	2	3	4
57.	Har du haft tyngdkänsla i ena eller båda benen?	1	2	3	4
58.	Har huden känts trång i ena eller båda benen?	1	2	3	4
59.	Har du haft smärta i ena eller båda benen?	1	2	3	4
60.	Har din sjukdom påverkat hur du väljer dina kläder eller skor (t ex problem att hitta rätta skor eller kläder pga svullnad /lymfödem i ett eller båda ben, skavproblem i ljumskar eller vulva, obehag vid trånga byxor eller liknande)?	1	2	3	4
61.	Har du känt dig mindre fysiskt attraktiv på grund av sjukdomen eller behandlingen?	1	2	3	4

	Inte alls	Lite	En hel del	Mycket
62. Har du känt dig mindre kvinnlig på grund av sjukdomen eller behandlingen?	1	2	3	4
63. Har du känt dig missbelåten med din kropp?	1	2	3	4

64. Har du sedan din vulvacancerbehandling tittat med en spegel på ditt underliv?

○ Ja

○ Nej, eftersom jag vill inte

○ Nej, eftersom jag kan inte (svårt att nå dit)

Plats för egna kommentarer:

65. Har du en urinkateter eller en urinstomipåse (konstgjord urinblåsa)? Nej   Ja

Besvara dessa frågor endast om du INTE har en urinkateter eller en urinstomipåse:

Under veckan som gått:

	Inte alls	Lite	En hel del	Mycket
66. Har du kissat ofta?	1	2	3	4

	Inte alls	Lite	En hel del	Mycket
67. Har du känt smärta eller sveda när du kissar?	1	2	3	4
68. Har du haft urininkontinens?	1	2	3	4
69. Då du kände att du behövde kissa, var du då tvungen att skynda dig till toaletten?	1	2	3	4

	Nej	Ja
70. Har du en tarmstomipåse?	Nej	Ja

Besvara dessa frågor endast om du INTE har en tarmstomipåse:

Under veckan som gått:

	Inte alls	Lite	En hel del	Mycket
71. Har du haft avföringsinkontinens?	1	2	3	4
72. Då du kände att du behövde tömma tarmen, var du då tvungen att skynda dig till toaletten?	1	2	3	4

Plats för egna kommentarer:

Under de senaste 4 veckorna:

	Nej	Ja
73. Har du varit sexuellt aktiv?*	Nej	Ja

Med sexuell aktivitet menas all intim fysisk kontakt, såsom kyss, petting, samlag, erotisk upplevelse, masturbation / eget tillfredsställande mm

74. Om du inte har varit sexuell aktiv senaste månaden, varför inte (flera svar är möjligt)?

○ Jag har ingen partner

○ Jag har inte varit intresserad

○ Jag har varit för trött

○ På grund av min vulvacancerbehandling / sjukdom

○ På grund av fysiska / psykiska problem jag har

○ På grund av fysiska / psykiska problem min partner har

○ Annat:

Besvara dessa frågor endast om du har varit SEXUELLT AKTIV UNDER DE SENASTE 4 VECKORNA:

Under de senaste 4 veckorna:	Inte alls	Lite	En hel del	Mycket
75. Har du oroat dig för att det skulle göra ont att ha sex?	1	2	3	4
76. Har du haft smärta vid samlag eller annan sexuell aktivitet?	1	2	3	4
77. Har slidan känts snäv och / eller trång vid samlag eller annan sexuell aktivitet?	1	2	3	4
78. Har slidan känts torr vid samlag eller annan sexuell aktivitet?	1	2	3	4
79. Har du kunnat njuta av sex?	1	2	3	4

	Alltid / nästan alltid	ofta	Sällan	Aldrig / nästan aldrig
80. Hur ofta har du kunnat få orgasm när du har varit sexuell aktiv?	1	2	3	4

81. Hur nöjd har du varit med ditt sexliv dem senaste fyra veckorna?

1	2	3	4	5	6	7

Mycket dålig   Utmärkt

82. Hur viktigt är sex för dig idag?

1	2	3	4	5	6	7

Inte alls viktigt   Mycket viktigt

83. Om du har en partner: Tycker du att din vulvacancer sjukdom har påverkat din relation?

O Ja, den har blivit bättre

O Ja, den har blivit delvis bättre, delvis sämre

O Ja, den har blivit sämre

O Nej

O Vet ej / inte aktuellt

Plats för egna kommentarer:

Besvara frågor 84 och 85 endast om du har lymfbesvär**:

**Lymfbesvär orsakas av lymfödem, ett kroniskt sjukdomstillstånd med ökad volym och svullnad som kan uppstå i olika grader och som kan ge betydande funktionsnedsättning i form av inskränkt rörlighet, tyngd och spänningskänsla, benägenhet för infektioner, psykologiska och kosmetiska problem. Efter vulvacancerbehandling kan ett lymfödem uppstå i benen eller i underlivet.

84. Använder du något hjälpmedel (flera svar är möjligt)?

○ Ja, jag lägger upp benen regelbundet

○ Ja, jag använder stödstrumpor / kompressionsstrumpor vid vissa tillfällen

○ Ja, jag använder stödstrumpor / kompressionsstrumpor jämt

○ Ja, jag får lymfdränage / sjukgymnastik

○ Ja, annat:

○ Nej, jag använder inga hjälpmedel

85. Nur mycket påverkas du av dina lymfbesvär avseende:

	Inte alls	Lite	En hel del	Mycket
Ditt yrkesarbete?	1	2	3	4
Ditt hushållsarbete?	1	2	3	4
Din personliga hygien?	1	2	3	4
Ditt sexliv?	1	2	3	4
Dina fritids- och sociala aktiviteter?	1	2	3	4
Din kroppsbild?	1	2	3	4

86. Har du haft rosfeber (erysipelas) i underlivet / benen senaste året?

○ Ja

○ Nej

○ Vet ej / inte aktuellt

	Inte alls	Lite	En hel del	Mycket
87. Om ja:	1	2	3	4

Hur mycket besvär har du upplevt i samband med detta (t ex sjukhusvistelse, hög feber, smärtor, sängliggande)?

Plats för egna kommentarer:

Del 4: Ångest och depression

Läs igenom varje påstående och sätt ett kryss i den ruta som bäst beskriver hur du har känt dig den senaste veckan.

Fundera inte för länge över dina svar; din spontana reaktion inför varje påstående är förmodligen mer korrekt än ett svar som du tänkt på länge.

88. Jag känner mig spänd eller nervös:

○ Mestadels

○ Ofta

○ Av och till

○ Inte alls

89. Allting känns trögt:

○ Nästan alltid

○ Ofta

○ Ibland

○ Aldrig

90. Jag uppskattar fortfarande saker jag tidigare uppskattat:

○ Definitivt lika mycket

○ Inte lika mycket

○ Endast delvis

○ Nästan inte alls

91. Jag känner mig orolig, som om jag hade "fjärilar" i magen:

○ Aldrig

○ Ibland

○ Ganska ofta

○ Väldigt ofta

92. Jag har en känsla av att något hemskt kommer att hända:

○ Mycket klart och obehaglig

○ Inte så starkt nu

○ Betydligt svagare nu

○ Inte alls

93. Jag har tappat intresset för hur jag ser ut:

○ Fullständigt

○ Till stor del

○ Delvis

○ Inte alls

94. Jag kan skratta och se det roliga i saker och ting:

○ Lika ofta som tidigare

○ Inte lika ofta nu

○ Betydligt mer sällan nu

○ Aldrig

95. Jag känner mig rastlös:

○ Väldigt ofta

○ Ganska ofta

○ Sällan

○ Inte alls

96. Jag bekymrar mig över saker:

○ Mestadels

○ Ganska ofta

○ Av och till

○ Någon enstaka gång

97. Jag ser med glädje fram emot saker och ting:

○ Lika mycket som tidigare

○ Mindre än tidigare

○ Mycket mindre än tidigare

○ Knappast alls

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98. Jag känner mig på gott humör:

○ Aldrig

○ Sällan

○ Ibland

○ Mestadels

99. Jag får plötsliga panikkänslor:

○ Väldigt ofta

○ Ganska ofta

○ Sällan

○ Aldrig

100. Jag kan sitta stilla och känna mig avslappnad:

○ Definitivt

○ Vanligtvis

○ Sällan

○ Aldrig

101. Jag kan uppskatta en god bok, ett TV- eller radioprogram:

○ Ofta

○ Ibland

○ Sällan

○ Mycket sällan

Plats för egna kommentarer:

Del 5: Behov och önskemål från sjukvården

Vi vill gärna veta om de behov som du kanske har fått på grund av din cancer har blivit tillgodosedda. Målet är att förbättra planeringen av våra tjänster för patienter som har diagnostiserats med cancer.

För varje fråga listad nedan, indikera om du har behövt hjälp för detta på grund av din cancersjukdom och behandling.

Rita en cirkel runt den siffra som bäst beskriver **om du har behövt hjälp** med detta den senaste månaden. Du kan välja mellan 4 olika svar:

Inget behov av hjälp	Litet behov av hjälp!!	Måttligt behov av hjälp	Stort behov av hjälp

Den senaste månaden

Vad var ditt hjälpbehov i fråga om:

		Inget hjälpbehov	Litet hjälpbehov	Måttligt hjälpbehov	Stort hjälpbehov
102.	Smärta	1	2	3	4
103.	Brist på energi / trötthet	1	2	3	4
104.	Oförmåga att klara av det du är van vid att klara själv	1	2	3	4
105.	Oro / ångest	1	2	3	4
106.	Nedstämdhet eller depression	1	2	3	4
107.	Rädsla för att cancern ska spridas	1	2	3	4
108.	Osäkerhet om framtiden	1	2	3	4
109.	Återskapa känslan av att ha kontroll över situationen	1	2	3	4
110.	Känslor och tankar om döden och att dö	1	2	3	4
111.	Förändringar i din sexualitet / sexuellt känsloliv	1	2	3	4
112.	Oro för de som står dig nära	1	2	3	4
113.	Vårdpersonal som bekräftar, och visar empati för dina känslomässiga behov	1	2	3	4
114.	Få skriftlig information om de viktigaste aspekterna av din vård (behandling)	1	2	3	4

		Inget hjälpbehov	Litet hjälpbehov	Måttligt hjälpbehov	Stort hjälpbehov
115.	Få information om aspekter av att klara av din sjukdom och dess bi-effekter hemma	1	2	3	4
116.	Få information om saker du kan göra för att må bättre	1	2	3	4

Plats för egna kommentarer:

Del 6:

Till sist vill vi gärna veta om du tycker att följande påståenden passar in på dig:

		Alltid / ofta	Sällan / ibland	Aldrig / nästan aldrig	Vet ej / icke aktuellt
117.	Jag känner mig ibland ensam och isolerad eftersom ingen känner till min sjukdom	1	2	3	4
118.	Det känns jobbigt / skamligt att prata om min sjukdom	1	2	3	4
119.	Personalen inom sjukvården har otillräcklig kunskap om min sjukdom	1	2	3	4
120.	Det är svårt att prata om min sjukdom med min partner	1	2	3	4

		Alltid / ofta	Sällan / ibland	Aldrig / nästan aldrig	Vet ej / icke aktuellt
121.	Det är svårt att prata om min sjukdom med mina vänner / famij	1	2	3	4
122.	Jag är rädd att sjukdomen påverkar mitt sexliv eller min relation	1	2	3	4
123.	Jag är rädd att inte kunna få en partner igen	1	2	3	4

Plats för egna kommentarer:

TACK FÖR DIN MEDVERKAN!