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A comparison of quality of life between vulvar cancer patients after sentinel lymph node procedure only and inguino-femoral lymphadenectomy

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ABSTRACT

Objectives. The SLN-procedure has been introduced in vulvar cancer treatment to reduce morbidity and thereby improve quality of life. Aim of this study was to compare quality of life in vulvar cancer patients who were treated with a SLN-procedure only to those who underwent inguino-femoral lymphadenectomy. Moreover, it was evaluated what patients would advise relatives on the application of the SLN-procedure in light of possible false negative results.

Methods. Patients who participated in the GROningen International Study on Sentinel nodes in Vulvar cancer (GROINSS-V) were invited to fill out three questionnaires: the EORTC QLQ-C30, a vulvar specific questionnaire and a questionnaire about the opinion of patients on new treatment options. Patients who only underwent SLN-procedure were compared to those who subsequently underwent inguino-femoral lymphadenectomy because of a positive SLN.

Results. With a response rate of 85%, 35 patients after the SLN-procedure and 27 patients after inguino-femoral lymphadenectomy filled out the questionnaires. No difference in overall quality of life was observed between the two groups. The major difference was the increase in complaints of lymphedema of the legs after inguino-femoral lymphadenectomy. The majority of patients would advise the SLN-procedure to relatives. Patients after inguino-femoral lymphadenectomy were more reserved concerning the acceptable false negative rate of a new diagnostic procedure.

Conclusions. Patients who underwent the SLN-procedure report less treatment related morbidity compared to those who underwent inguino-femoral lymphadenectomy. However, this did not influence overall quality of life. Furthermore, patients who underwent inguino-femoral lymphadenectomy are more reserved in advising the SLN-procedure to relatives.

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Introduction

The aim of modern vulvar cancer treatment is to minimize treatment related morbidity, without compromising survival rates. The most important prognostic factor in patients with vulvar cancer is the inguino-femoral lymph node status [1]. Until recently inguino-femoral lymphadenectomy was the only possibility to be adequately informed on the lymph node status. However, the morbidity of this procedure is high, while only 25–35% of early stage vulvar cancer patients will have lymph node metastases and thereby benefit from this surgery [1,2]. In the other 65–75% this intervention will (in retrospect) probably be only diagnostic. In order to reduce morbidity the sentinel lymph node (SLN) procedure was introduced in vulvar

cancer treatment with promising results in different accuracy-studies [3–10]. Its safety has recently been shown in the Groningen International Study on Sentinel Nodes in Vulvar cancer (GROINSS-V) with a false negative rate of 2.8% in patients with unifocal early stage disease [11]. Frequently occurring sequelae of inguino-femoral lymphadenectomy are lymphedema, painful legs and recurrent erysipelas. Hence, this procedure will interfere with quality of life. The GROINSS-V showed that both short-term as well as long-term morbidity were significantly decreased in patients who only underwent the SLN procedure compared to those who also underwent subsequent inguino-femoral lymphadenectomy. For lymphedema the percentages were 1.9% vs. 25.2% respectively and for recurrent erysipelas 0.4% vs. 16.2% [11]. Our hypothesis was that patients after a SLN procedure only might have a better quality of life due to less long-term morbidity. In GROINSS-V however assessment of quality of life was not part of the protocol and until now no comparable studies have been performed in vulvar cancer.

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In 2001 de Hullu et al reported on what patients thought about acceptable false-negative rates for the SLN procedure in vulvar cancer. Patients, who themselves had undergone a vulvectomy and inguinofemoral lymphadenectomy, were asked what they would recommend a friend or sister with vulvar cancer: a new technique (the SLN procedure) or the standard therapy (inguinofemoral lymphadenectomy). Remarkably, most patients would not recommend the SLN procedure, although they had experienced themselves severe complications and side effects of the radical treatment they had undergone [12].

Aims of the present study were 1) to compare quality of life in patients with vulvar cancer who were treated by the SLN procedure only with those who underwent inguinofemoral lymphadenectomy and 2) to evaluate what these patients would advise their relatives on the application of the SLN procedure in light of its supposed false-negative rates.

Patients and methods

Patients

Patients who participated in GROINSS-V between March 2000 and December 2005 and who were treated in either University Medical Center Groningen, Radboud University Nijmegen Medical Center or Erasmus University Medical Center Rotterdam were eligible for the study. All eligible patients with a positive SLN treated in the participating centers during this time period were invited to fill out the questionnaires, while an equal number of patients with a negative SLN were age-matched to the eligible patients with a positive SLN. Patients with recurrent disease or with a second malignancy were excluded. No patients with a false negative SLN were included. Also patients who had radiotherapy on the groins instead of an inguinofemoral lymphadenectomy or those who refused inguinofemoral lymphadenectomy in case of a positive SLN were excluded. The questionnaires were sent by mail accompanied by a return envelope and a guidance letter on which a telephone number was noted in case help was needed to answer the questions. No reminders were sent. The surgical procedure has been described in detail previously [11]. In short, the SLN procedure was performed with the combined technique (radioactive tracer and blue dye). When the SLN was negative, no further treatment followed. If metastatic disease was identified in the SLN, an inguinofemoral lymphadenectomy was performed, either during the same operation when found positive by frozen sectioning or during a subsequent procedure if the SLN was found positive at routine pathologic examination or ultrastaging. When more than one intranodal metastasis and/or extranodal growth was detected, post-operative external beam radiotherapy (50 Gy) to the groin/pelvis was recommended. Patients were seen every 2 months at the outpatients' clinic for the first 2 years after primary treatment, and subsequently biannually.

Questionnaires

The questionnaire consisted of three different lists; the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), the vulva specific questionnaire (VSQ) and the patients' opinion questionnaire.

The EORTC QLQ-C30 version 3.0, a cancer-specific questionnaire, is composed of five functional scales (physical, role, emotional, cognitive, social), the global health status and nine symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhea, financial difficulties). The global health status correlates significantly with all the functional and symptom scales [13]. For the functional and global quality of life (QOL) scales a higher score indicates a better level of functioning, for the symptom scales a higher score indicates a worse level of functioning. At present,

vulva specific questionnaires translated into Dutch language are not available. We used a questionnaire based on an existing vulva specific questionnaire in English language (Functional Assessment of Cancer Therapy-Vulvar; FACT-V) [14]. The questionnaire consists of four symptom scales (vulva specific symptoms, sexual functioning, edema, and urinating discomfort) and five functional scales (sexual functioning, physical functioning, body image, future perspective and contentment with procedure). The questionnaire consisted of 17 questions, and answering was according to what the patients experienced the last 7 days. Scale reliability was determined using Cronbach's alpha coefficients, values above 0.70 were considered adequate. The internal consistencies of the subscale data in the EORTC QLQ-C30, evaluated by Cronbach's alpha coefficients were 0.79 for physical functioning, 0.85 for role functioning, 0.87 for emotional functioning, 0.59 for cognitive functioning, 0.89 for social functioning, 0.89 for fatigue, 0.47 for nausea and vomiting, 0.84 for pain and 0.92 for global health status. Cronbach's alpha for the whole questionnaire was 0.87. For the vulvar specific questionnaire they were 0.52 for physical functioning, 0.81 for sexual functioning, 0.58 for vulvar symptoms, 0.57 for edema and – 0.09 for urination. Cronbach's alpha for the whole questionnaire was 0.65. The scales with a Cronbach's alpha below 0.70 were also analyzed per item.

In the patients' opinion questionnaire patients were asked what they would recommend a friend or family member with vulvar cancer: the standard therapy (inguinofemoral lymphadenectomy) with the accompanying side effects or the new technique (SLN procedure) with a chance of missing a metastasis being respectively 10 out of 100, 1 out of 100 or 1 out of 1000. The patients' opinion questionnaire is a non-validated questionnaire that was also used in a previous study from our group [12].

Statistical analysis

All data were analyzed with the Statistical Package for the Social Sciences (SPSS 14). For the quality of life questionnaire, including the vulva specific part, data were analyzed in accordance with the EORTC QLQ-C30 scoring manual [15]. In case of missing values, a scale was scored only if more than half of the items in this scale were answered, and the mean of all items in the concerning scale for that patient was used to score missing items. Patient characteristics between the two surgical groups were compared by using chi-square tests in case of categorical data and the *T*-test in case of continuous data. Due to skewness of data, the Mann Whitney *U*-test was used to compare quality of life between the two types of surgery. *p* values < 0.05 were considered significant.

Results

Patient characteristics

Questionnaires were sent to 37 eligible patients with a positive SLN and 37 age-matched patients with a negative SLN. Sixty-two of 74 patients (84%) returned the questionnaires. The mean age was 69 years (SD 13). Thirty-five patients (56.5%) had a negative SLN and 27 patients (43.5%) had a positive SLN. In all patients with a positive SLN a uni- or bilateral inguinofemoral lymphadenectomy was performed. Postoperative radiotherapy to the groins was given in 10/27 (37%) of the patients with a positive SLN. Patients' clinical characteristics are summarized in Table 1. The median follow-up between surgery and the questionnaire was 33 months (interquartile range: 20–48).

EORTC QLQ-C30

Overall, there was no difference in quality of life between patients who underwent SLN procedure alone and those who underwent an

Table 1
Patients characteristics.

	Total (n = 62)	SLN (n = 35)	CLA (N = 27)	Test	p-value
Age (years)					
Mean	70 (± 13)	71 (± 14)	68 (± 12)	T-test	0.30
Site of groin surgery (%)					
One groin	30 (48%)	16 (46%)	14 (52%)	χ ²	0.63
Both groins	32 (52%)	19 (54%)	13 (48%)		
Vulvar therapy (%)					
Wide local excision	58 (93.5%)	32 (91%)	26 (96%)	χ ²	0.63
Radical vulvectomy	1 (1.5%)	1 (3%)	0 (0%)		
Radiotherapy	3 (5%)	2 (6%)	1 (4%)		
Tumor diameter (mm)					
Mean	23 (± 11)	23 (± 11)	25 (± 10)	T-test	0.44
T1	27 (47%)	17 (49%)	10 (37%)	χ ²	0.36
T2	35 (53%)	18 (51%)	17 (63%)		
Depth of invasion (mm)					
Mean	5.4 (± 3.6)	5.5 (± 4.1)	5.3 (± 2.9)	T-test	0.83

inguinofemoral lymphadenectomy. Only financial difficulties were reported more often by patients who underwent inguinofemoral lymphadenectomy ($p = 0.01$). The quality of life-scores are shown in Table 2. To investigate whether quality of life was influenced by age we compared patients below the age of 69 with those older than 69 years (mean age): better physical functioning ($p = 0.001$) as well as better role functioning ($p = 0.004$) was experienced by the patients below the age of 69. Nausea and appetite loss were more frequently experienced in the older patients ($p = 0.027$ and 0.008 respectively). Other scales did not differ between these two age groups.

Vulvar specific questionnaire

Patients who underwent inguinofemoral lymphadenectomy reported more discomfort in groins, vulva and legs ($p = 0.03$). Complaints of lymphedema ($p = 0.01$) and the need to wear stockings

Table 2
Results of 62 vulvar cancer patients answering the QLQ-C30 questionnaire: SLN procedure ($n = 35$) versus inguinofemoral lymphadenectomy (IFLA) ($n = 27$).

	SLN (n = 35) mean (SD)	IFLA (n = 27) mean (SD)	p-value
Global health status/ QoL	80 (18)	80 (23)	0.62
Functional scales^a			
Physical functioning	84 (21)	80 (19)	0.43
Role functioning	87 (22)	85 (26)	0.87
Emotional functioning	90 (14)	89 (19)	0.63
Cognitive functioning	94 (11)	94 (14)	0.90
Concentration	95 (12)	96 (14)	0.44
Memory	92 (16)	91 (18)	0.83
Social functioning	96 (13)	90 (22)	0.23
Symptom scales^b			
Fatigue	23 (22)	18 (24)	0.23
Nausea and vomiting	3 (11)	2 (10)	0.61
Nausea	6 (19)	4 (14)	0.61
Vomiting	1 (6)	1 (6)	0.85
Pain	15 (21)	14 (24)	0.63
Dyspnoea	12 (24)	12 (21)	0.79
Insomnia	14 (25)	23 (29)	0.15
Appetite loss	10 (24)	9 (22)	0.65
Constipation	7 (16)	5 (15)	0.53
Diarrhea	9 (20)	2 (13)	0.11
Financial difficulties	2 (11)	12 (25)	0.01*

^a A high score on a functional scale represents a high/healthy level of functioning.

^b A high score on a symptom scale represents a high level of symptomatology/problems.

* $p < 0.05$.

Table 3
Results of 62 vulvar cancer patients answering the Vulva Specific Questionnaire: SLN procedure ($n = 35$) versus inguinofemoral lymphadenectomy (IFLA) ($n = 27$).

	SLN mean (SD)	IFLA mean (SD)	p-value
Functional scales^a			
Physical functioning	85 (17)	80 (18)	0.27
Discomfort groins/vulva/legs	86 (20)	69 (32)	0.03
Discomfort sitting	87 (18)	86 (28)	0.46
Discomfort bending	83 (27)	85 (20)	0.83
Sexual functioning ^b	78 (19)	81 (26)	0.67
Future perspective	70 (27)	64 (28)	0.41
Body image	43 (35)	59 (33)	0.09
Contentment	90 (27)	78 (31)	0.04*
Sexual activeness	6 (21)	13 (21)	0.06
Symptom scales^c			
Vulvar symptoms	14 (14)	10 (12)	0.33
Discharge/blood loss	5 (12)	1 (6)	0.17
Fetor	7 (16)	5 (12)	0.77
Itching	24 (26)	16 (19)	0.29
Pain/numbness	22 (28)	20 (27)	0.76
Edema	12 (22)	35 (32)	0.001*
Complaints	12 (24)	27 (29)	0.01*
Stockings	12 (30)	43 (46)	0.003*
Urination	14 (18)	18 (18)	0.30
Incontinence	18 (30)	26 (34)	0.32
Discomfort	10 (21)	10 (18)	0.68

^a A higher score indicates a higher/better level of functioning/contentment.

^b Questions on sexual functioning were only answered by women who were sexually active.

^c A higher score indicates a high level of symptomatology/problems.

* $p < 0.05$

($p = 0.003$) were more often reported by the patients treated with an inguinofemoral lymphadenectomy (Table 3). Patients after the SLN procedure only were more content with the treatment they had undergone ($p = 0.04$). Other functional and symptom scales did not show statistically significant differences. Only 11/62 patients (17.7%) were sexually active, of whom seven only sporadically. The women who had regular sexual intercourse were significantly younger compared to those with sporadically sexual intercourse and those with no sexual intercourse (mean age 43, 68 and 72 years respectively, $p < 0.0001$). No differences in sexual activeness were observed between SLN procedure and inguinofemoral lymphadenectomy. The questions on sexual functioning were only answered by women who were sexually active. Only two patients reported regular complaints with sexual intercourse, both underwent inguinofemoral lymphadenectomy. The other patients reported no or little complaints.

Patients' opinion questionnaire

The questions on what patients would recommend their relatives revealed that patients after inguinofemoral lymphadenectomy were more reserved concerning the acceptable false negative rate of a new treatment compared to patients who had a negative sentinel lymph node. When the SLN procedure would have a false negative rate of 10%, 48% of the patients who underwent inguinofemoral lymphadenectomy and 84% of the patients who underwent a SLN procedure only would recommend it to relatives. These differences were also observed with a suggested false negative rate of 1% and 0.1% (Table 4).

Table 4
Maximum false negative rate of the SLN procedure acceptable to patients ($n = 62$).

Maximum acceptable false-negative rate	Patients who accept the false-negative rate %	SLN (n = 35)	IFLA (n = 27)	p-value*
10%	69%	84%	48%	$p = 0.005$
1%	82%	97%	62%	$p = 0.001$
0.1%	87%	97%	71%	$p = 0.013$

* Tested with chi-square.

Discussion

Our study shows that patients who have been treated for vulvar cancer and underwent an inguofemoral lymphadenectomy experience more often long-term symptoms of lymphedema and discomfort of groins and legs compared to those who only had SLN removal. Also, they are less content with the operative procedure they underwent. On the other, more global quality of life scales (except for financial difficulties, for which we have no clear explanation), no differences were observed between the two groups. A comparable quality of life study comparing these two vulvar cancer patient groups was never performed until now.

Our present study does not support our original idea that a decrease in especially long-term morbidity also translates into an improved overall quality of life for vulvar cancer patients. Several reasons for not finding an improvement in quality of life can be envisioned. An important limitation of our study is the small study population, which unfortunately is often the case in vulvar cancer studies, due to the rareness of this disease. Two studies in breast cancer also reported that the type of axillary surgery (SLN procedure or axillary lymph node dissection) did not seem to affect global quality of life, although axillary lymph node dissection was associated with worse arm/shoulder mobility, more pain and more sensory morbidity [16,17]. Both were relatively small studies ($n = 56$ and $n = 115$, respectively). A recent prospective study in 829 breast cancer patients by Fleissig et al in contrast showed that quality of life was better after SLN procedure compared to axillary lymph node dissection [18]. In another prospective study by Rietman et al. ($n = 181$) it was also shown that 2 years after surgery, breast cancer patients who underwent SLN procedure had significant less treatment related morbidity and less worsening of quality of life compared to those who underwent axillary lymph node dissection [19]. Our study in 62 patients therefore is probably underpowered to detect small differences in global quality of life.

In general data on quality of life in vulvar cancer patients are limited. The main focus of the studies available on vulvar cancer and psychosocial well-being/quality of life is sexual functioning; this domain of quality of life appears to be significantly reduced in vulvar cancer patients [20–24]. Apart from our present study the only other study on vulvar cancer and global quality of life was performed by Janda et al. They developed a vulvar cancer-specific quality of life subscale to accompany the Functional Assessment of Cancer-General (FACT-G) questionnaire. Reductions in emotional functioning, physical functioning, social functioning, sexuality and body image were observed in vulvar cancer patients [25]. In our study, no differences were observed in sexual functioning or sexual activeness between SLN only and full lymphadenectomy patients, which can be explained by the fact that sexual activeness is mainly influenced by the vulvar surgery, which was the same in both groups. Likes et al showed that sexual functioning and overall quality of life were reduced after vulvar excision without groin surgery in patients with vulvar intraepithelial neoplasia [26]. In comparison to healthy women sexual activity was low in our population with only 11/62 women being sexually active (mean age: 57 years). It is well-known that the prevalence of sexual activity in healthy women declines with age: 62% of women between 57 and 64 years, 40% between 65 and 74 years and 17% between 75 and 85 years [27].

We compared the results of the EORTC QLQ-C30 questionnaire in our study to the results of two studies in a general (healthy) population of women aged ≥ 60 years. This indicated that the overall quality of life in our study population is comparable to a general age-matched population [28,29]. A study by Miller et al., comparing healthy patients with those who survived a gynecologic malignancy (51 cervical cancers, 24 uterine cancer and 10 ovarian cancers) showed that there were no overall differences in quality of life [30]. During follow-up after treatment for gynecological cancer an improvement on all quality of life scales was observed [31].

Apparently, the overall recovery from treatment for gynecological cancer is good. Also for other minimal invasive techniques, such as laparoscopic hysterectomy, it was observed that after recovery from primary treatment, no differences were found in quality of life when compared to abdominal hysterectomy. The advantages for less invasive surgery were only significant in the first 6 weeks after treatment [32]. Surviving cancer might also coincide with attitudinal changes. Cancer patients report that the cancer experience changed them in many ways, that it enriched them, deepened the compassion that they felt for others and energized them to look for changes in their environment and the future [33]. These effects of cancer can not be ignored when talking about quality of life issues. Important in this context is the concept of “response shift”. Cancer and its treatment changes patients’ internal standards, values and/or the conceptualization of health related quality of life. These changes are inherent to the process of accommodating to the illness [34].

Finally, a previous study from our group indicated that most vulvar cancer patients treated by inguofemoral lymphadenectomy would not recommend the SLN procedure to relatives in light of different hypothesized false-negative rates [12]. In the present study, we found high percentages of acceptance, even when 10 out of 100 metastases would be missed. Patients who had a metastatic SLN and therefore underwent a full lymphadenectomy were less likely to advise a new method if there was a chance of missing metastases. These patients are likely more willing to accept and live with complications knowing they needed this more extensive approach and would therefore be less willing to trust a new procedure that could potentially underestimate the extent of their disease, not realizing that in fact it reliably revealed their indication for inguofemoral lymphadenectomy. Also, they themselves did not experience the benefits of being treated by the new technique and this puts the low acceptance rate in our first study from our first study in a different perspective. In that study all patients underwent a full lymphadenectomy, which apparently influenced their appreciation of the SLN procedure.

In conclusion, our quality of life study by means of the EORTC-QLQ-C30 and a vulvar specific questionnaire shows that patients who underwent a SLN procedure alone report less treatment related morbidity compared to patients who underwent inguofemoral lymphadenectomy, but this did not influence overall quality of life. Patients who underwent the SLN procedure without inguofemoral lymphadenectomy were more content with the procedure they underwent and were more likely to advise new treatment options to relatives, probably because they themselves experienced the benefits of a new procedure. Our data should be helpful for health professionals when counseling vulvar cancer patients on the pros and cons of a SLN procedure in early stage vulvar cancer.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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