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

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HIGHLIGHTS

- In this nationwide population-based cohort, the overall recurrence rate was 22.3%.
- The 5-year cumulative incidence rate for isolated local recurrence was only 14.7%.
- Median 4-year overall survival post local recurrence was poor, 37.4%.
- Surgical groin staging was omitted in 23.7% of FIGO stages IB-II.
- Omitting surgical groin staging in FIGO stages IB-II was significantly associated with poor survival.

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ABSTRACT

Objective. To examine the patterns of recurrence and how these patterns are associated with survival in vulvar squamous cell carcinoma. We also explored the survival impact of surgical groin staging (SGS).

Methods. Nationwide population-based study including women diagnosed with vulvar squamous cell carcinoma between 2012 and 2015 and registered in the Swedish Quality Registry for Gynecologic Cancer. Cumulative incidence rates (CIR), recurrence-free (RFS) and overall survival (OS) were calculated by Kaplan Meier estimates. The impact of SGS on RFS and OS was analyzed by proportional hazards models.

Results. 489 eligible women were included. Median follow-up time was 64 months. The overall recurrence rate was 22.3%. Site of recurrence: local in 61.0%, groin in 30.0%, distant in 9.0%. The CIR for local recurrences increased with time (5.9% at 2-years, 14.7% at 5-years) while the rate of groin and distant recurrences was nearly steady (5.5% to 6.3% and 1.5% to 1.7%, respectively). Median 2-year and 4-year OS post-recurrence was 57.8% and 37.4% for local, 17.2%, 10.3% for groin and 0% for distant recurrences, respectively. SGS was omitted in 23.7% of surgically treated women with FIGO stages IB-II and significantly associated with worse RFS (Hazard ratio, HR, 1.9; 95%CI, 1.0–3.5; $p = 0.04$) and OS (HR 2.0; 95%CI, 1.1–3.8; $p = 0.04$) after adjustment for age, FIGO stage, tumor size, resection margins and performance status.

Conclusion. The cumulative incidence of isolated vulvar recurrence was low but for those affected the prognosis was poor. Surgical groin staging is a crucial part of primary treatment and should not be omitted.

1. Introduction

Vulvar cancer is a rare malignancy, comprising about 4% of all gynecological cancer and affecting mostly elderly women [1]. In Sweden, about 160 women are being diagnosed with primary vulvar cancer every year [2]. Approximately 90% are vulvar squamous cell carcinomas (VSCC) and the predominant treatment is surgery, comprising a resection of the primary vulvar tumor and for tumors with an invasion depth of more than one millimeter either a complete inguino-femoral lymphadenectomy (IFL) or a sentinel node biopsy (SNB) in the groins [1,3,4]. Surgical groin exploration is regarded as a central part of primary surgical treatment providing important information for staging, adjuvant treatment and prognosis [5]. Prognosis and the indication for

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adjuvant radiotherapy are highly dependent on the lymph node status in the groins with 5-year-overall survival between 70 and 93% in node-negative and 25–41% in node-positive disease [3,6–8]. Additionally, by removing potential metastatic disease, surgical groin staging (SGS) has shown to improve survival [9–12]. However, a recent population-based study questioned the value of SGS in VSCC where SGS was omitted in 32% of the women, without a negative impact on survival, but women in this cohort were treated before the implementation of the sentinel and the analysis was not adjusted for different FIGO stages [13].

Reported overall recurrence rates range between 12% and 37% with predominantly local recurrences [14]. A recent study showed a local recurrence rate of 25% for node-negative and 33% for node-positive disease within 5 years [15]. Local recurrences are usually treated with a curative intention and median 5-year survival for this group is reported to be between 53% and 76% [14–16]. Groin recurrences occur less often, but carry a markedly worse prognosis, with a 5-year-survival of less than 30% [15,17]. Women without regional spread have a low risk for groin recurrences. Depending on primary treatment of the groins, i.e. if surgical staging is done by IFL or SNB, the groin recurrence rate ranges between 1% and 3% [4,18,19]. Conversely, groin recurrences are common in node-positive women, with reported rates between 9% and 38% [13,15,20]. Surgical proficiency seems to play an important role in the risk for a groin recurrence, both in node-negative and node-positive disease, as various studies could show an inverse association between the number of resected lymph nodes and the risk for a groin recurrence [10–12,21].

Previous studies on recurrent vulvar cancer are retrospective with limited number of women and heterogenous cohorts which probably accounts for the wide variation in the incidence of recurrence [22]. Population-based studies in recurrent vulvar cancer are sparse and, to our knowledge, results from a nationwide cohort are lacking.

We have previously reported on primary treatment patterns by stage and age in a large population-based study of women with VSCC [23]. The aim of the present study was to examine the patterns of recurrence and how these patterns are associated with survival in a nationwide cohort of women with VSCC. Furthermore, we explored the survival impact of SGS.

2. Material and methods

This is a nationwide population-based cohort study using data from the Swedish Quality Registry for Gynecologic Cancer (SQRGC). The SQRGC is a quality registry collecting data on tumor characteristics, treatment, recurrence, and mortality [24]. Registration is voluntary giving women the possibility for opt-out. All six Swedish healthcare regions report electronically and prospectively to the registry while it is continuously monitored by specialized registrars. Information on vital status is regularly updated in the SQRGC, although, without providing the cause of death. Individual patient data can be accessed by the Swedish personal identity number which is allocated to every individual who is registered in the Swedish population registry. This enables linkage to official databases such as the Swedish Cancer Registry (SCR). The SCR is a compulsory nationwide registry which was founded in 1958 and to which notification of all newly diagnosed cancer cases based on a histopathological analysis is mandatory [25]. However, although showing a high coverage, the SCR does not provide data on treatment and recurrence, and consequently, the SQRGC was established in 2008, including registration of vulvar cancer since 2012. From 2012 to 2015, the SQRGC covered 91% of all new vulvar cancer cases reported to the SCR.

2.1. Study cohort

Women diagnosed with primary vulvar cancer between 1st January 2012 and 31st December 2015 were identified through the SQRGC. We included all women with squamous cell carcinoma of the vulva, at least 18 years of age and without evidence of disease at the end of treatment and used the International Classification of Diseases for Oncology (ICD-O-3) for identification, including 8010/3, 8020/3, 8051/3, 8070/3, 8076/3 for morphological and C51.0, C51.1, C51.2, C51.8 and C51.9 for topographical coding.

The following variables were recorded in a case report form: age at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status, histological type, tumor size (assessed clinically at treatment start), histological grading, FIGO-stage, type of primary treatment, extent of primary surgical treatment in the vulva and the groins, date for start and end of primary treatment, pathological tumor-free margins, number retrieved and number of metastatic lymph nodes, disease status at the end of primary treatment, date of recurrence, site of recurrence, date of death and date of last follow-up. Data were obtained from the SQRGC and complemented by review of medical charts if indicated. The revised 2009 FIGO-system was used for staging [26]. SGS was defined as any type of groin surgery, i.e., SNB, IFL or lymph node sampling.

At the time of the study, neither national guidelines nor centralized treatment were in place in Sweden, but treatment and follow-up were performed in accordance with regional guidelines at both university and county hospitals. The most common follow-up program implied clinical examinations 3–4 times per year during the first two years followed by controls twice a year for the next 3 years and did not include any routine radiology or further diagnostics if not otherwise indicated.

The study was approved by the Swedish Ethical Review Authority (ID: 2019–04647).

2.2. Quality assurance

We performed a quality assurance of the vulvar cancer data in the SQRGC to mitigate any information bias. In 31 randomly assigned cases, we compared details from individual medical records with the registered data and found a high concordance for variables such as histology, FIGO-stage, grade, treatment details and recurrence (between 77% and 100%), but a lower concordance for factors such as tumor size, pathological tumor-free margins and ECOG performance status (between 44% and 50%). Further information about the exact results of the audit can be found in the supplementary materials (Table S1). Missing data in the registry was accounted for by extracting these details, if possible, from medical charts.

2.3. Statistical methods

Summarizing statistics such as medians, range (min, max), frequencies and percentages were used to describe distribution of variables in the study groups. Comparison of different distributions were done by non-parametrical tests, i.e., with the Pearson's chi-squared test for binomial and categorical variables and the Wilcoxon rank sum test for continuous variables. We calculated cumulative incidence rates (CIR) – taking competing risks into account - for different first recurrences. Recurrence-free survival (RFS) was calculated from the last day of primary treatment (i.e., date of completed surgical or oncological treatment) to date of first recurrence (i.e., date of diagnostic biopsy or radiology), in order to avoid an immortal time bias in the radiotherapy treated group of women. In recurrence-free women date of death or last follow-up date were used for censoring. Overall survival (OS), comprising death of any cause, was calculated from the date of primary diagnosis to the date of death (in censored women date of study end, i.e., 15th June 2019). Overall survival post first recurrence was calculated from the date of recurrence (i.e., date of biopsy or radiology) to the date of death. We compared characteristics and recurrence rates of women in FIGO stages IB-II treated with or without SGS. Associations between SGS and recurrence-free and overall survival were analyzed by proportional hazards regression models, calculating both crude hazard ratios

(HR) and HR adjusted for different covariates. For all statistical tests, a *p*-value of <0.05 was regarded as significant. All statistical analyses were done by STATA Corp™ Software, version 16.

3. Results

During the study period, 614 women with vulvar cancer were registered in the SQRGC. Of the 555 women with VSCC, 65 (11.7%) had residual tumor and one patient had undefinable disease status after primary treatment. Thus, the study population comprised 489 women with VSCC and no evidence of disease after primary treatment (Fig. 1). Median follow-up time for women still alive at the end of the study was 64 months when calculating overall survival and 52 months when calculating recurrence free survival.

Clinical characteristics of the study population and in subgroups of recurrence-free women and those with recurrent VSCC are shown in Table 1. The overall rate of recurrence was 22.3% ($n = 109$). Women with recurrence were significantly older, had larger tumors, poorer differentiated tumors, were diagnosed more often with stage III disease and had more often several positive lymph nodes as compared with recurrence-free women.

Among the 109 women with recurrent disease, 61.0% had an isolated local recurrence in the vulva, 30.0% in the groins (partly combined with a local recurrence) and 9.0% distant recurrences (partly combined with local recurrences) (Table 1). The latter were predominantly found in pelvic lymph nodes or in the lungs. The overall 2-year and 5-year cumulative incidence rates (CIR) of recurrence were 14.5% and 24.4%, respectively. The CIR of recurrences by site is shown in Fig. 2, with death as a

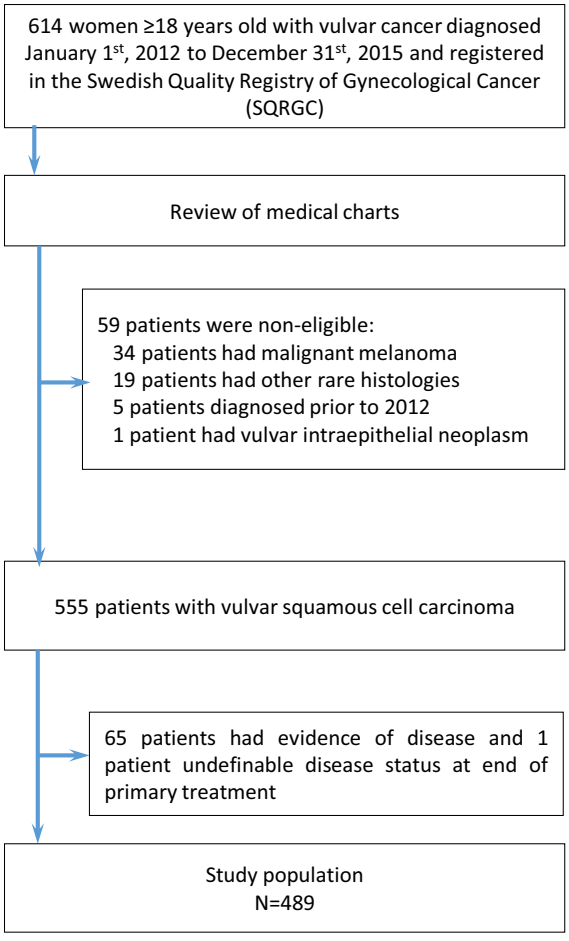

Fig. 1. Flow diagram.

Table 1
Characteristics of study population by women with or without recurrence of vulvar squamous cell carcinoma.

Characteristics	Study population	Recurrence-free	First recurrence	*P*-value
	n = 489	*n* = 380	n = 109	
	N (%)	N (%)	N (%)	
Age, years				
Median (min-max)	70 (23–95)	70 (23–95)	75 (38–93)	0.04[1]
FIGO stage[3]	*481*	*375*	*106*	
IA	94 (19.5)	91 (24.3)	3 (2.8)	<0.001[2]
IB	213 (44.3)	173 (46.1)	40 (37.7)	
II	61 (12.7)	46 (12.3)	15 (14.2)	
III	92 (19.1)	51 (13.6)	41 (38.7)	
IV	21 (4.4)	14 (3.7)	7 (6.6)	
Missing	8	5	3	
Tumor size[4], mm, *n*	*433*	*340*	*93*	
Median (min-max)	20 (0–151)	20 (0–151)	30 (0−100)	<0.001[1]
Missing	56	40	16	
Histological grade, *n*	*374*	*279*	*95*	
Well differentiated	110 (29.4)	95 (34.1)	15 (15.8)	<0.001[2]
Moderately differentiated	173 (46.3)	128 (45.9)	45 (47.4)	
Poorly or undifferentiated	91 (24.3)	56 (20.1)	35 (36.8)	
Missing	115	101	14	
ECOG performance status, *n*	*391*	*297*	*94*	
0–1	330 (84.4)	255 (85.9)	75 (79.8)	0.16[2]
2–4	61 (15.6)	42 (14.1)	19 (20.2)	
Missing	98	83	15	
Primary treatment	*489*	*380*	*109*	
Surgery, *n*	449 (91.8)	349 (91.8)	100 (91.7)	<0.001[2]
Surgery solely	338 (69.1)	283 (74.5)	55 (50.4)	
Surgery + (chemo) radiotherapy	111 (22.7)	66 (17.4)	45 (41.3)	
Definitive (chemo) radiotherapy	32 (6.5)	26 (6.8)	6 (5.5)	
Other[5]	8 (1.6)	5 (1.3)	3 (2.8)	
Missing	0	0	0	
Extent of vulvar surgery, *n*	*442*	*342*	*100*	
Wide excision	276 (61.9)	214 (61.8)	62 (62.0)	0.011[2]
Partial vulvectomy	104 (23.3)	89 (25.7)	15 (15.0)	
Complete vulvectomy	56 (12.6)	35 (10.1)	21 (21.0)	
Exenteration	10 (2.2)	8 (2.3)	2 (2.0)	
Missing	7	7	0	
Surgical groin staging in presumed stage IB-II	*257*	*206*	*51*	
Yes	196 (76.3)	160 (77.7)	36 (70.6)	0.29[2]
No	61 (23.7)	46 (22.3)	15 (29.4)	
Missing	0	0	0	
Type of surgical groin staging, *n*	*314*	*235*	*79*	
IFL, uni- or bilateral	176 (56.1)	129 (54.9)	47 (59.5)	0.57[2]
LN sampling	28 (8.9)	19 (8.1)	9 (11.4)	
SNB, uni- or bilateral	96 (30.6)	76 (32.3)	20 (25.3)	
Unilateral SNB, contralateral IFL	14 (4.5)	11 (4.7)	3 (3.8)	
Missing	0	0	0	
Tumor free margins in pathology report, *n*	*442*	*342*	*100*	
0 mm	35 (9.5)	26 (9.2)	9 (10.6)	0.46[2]
<5 mm	122 (33.2)	90 (32.1)	32 (36.4)	
≥5 mm	246 (66.8)	190 (67.9)	56 (63.6)	
Median (min-max), *mm*	7 (0–40)	7 (0–40)	6 (0−20)	0.56[1]
Missing	74	62	12	
LN metastases in groins, *n*	*314*	*235*	*79*	
None	225 (76.5)	187 (84.6)	38 (52.1)	<0.001[2]
One LN	39 (13.3)	18 (8.1)	21 (28.8)	
More than one LN	30 (10.2)	16 (7.2)	14 (19.2)	
Missing	20	14	6	
Site of 1st recurrence		*NA*	*109*	
Isolated vulvar			61 (61)	
Groins, +/− vulvar			30 (30)	
Distant, +/− locoregional			9 (9)	
Missing			9	

Table 1 (*continued*)

Characteristics	Study population	Recurrence-free	First recurrence	*P*-value
	$n = 489$	$n = 380$	n = 109	
	N (%)	N (%)	N (%)	
Time to recurrence, months, median (min-max)				
Isolated vulvar	26.1 (2.5–66.3)			
Groins, +/− vulvar	9.0 (2.0–52.4)			
Distant, +/− locoregional	6.5 (2.8–65.8)			

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IFL, Inguinofemoral lymphadenectomy; SNB, Sentinel node biopsy; LN, lymph node; RFS, recurrence-free survival; OS, overall survival.

[1] Wilcoxon rank sum test.
[2] Pearson's chi squared test.
[3] FIGO stage according to the 2009 classification.
[4] Tumor size assessed clinically.
[5] Neoadjuvant chemotherapy followed by chemoradiation, primary chemotherapy.

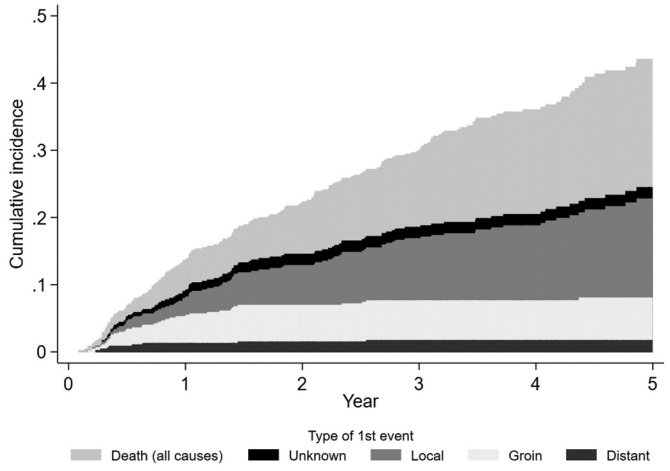

Fig. 2. Cumulative incidence rates for competing first events in the study population ($n = 480$). The 2-year cumulative incidence rate for all recurrences was 14.5%; 5.9% for local recurrences, 5.5% for groin recurrences (with or without vulvar recurrences) and 1.5% for distant recurrences (with or without locoregional recurrences). The corresponding figures for 5-year cumulative incidence rates were 24.4%; 14.7%, 6.3% and 1.7%, respectively. The competing event of death comprises any cause of death.

competing event. As depicted, the incidence of local vulvar recurrence is steadily rising over time, without reaching a plateau, whereas both groin and distant recurrences occur early in the course of disease with almost no further increase over time. This is also illustrated by the shorter median time to recurrence for groin and distant recurrences (9.0 and 6.5 months, respectively) compared with local recurrences (26.1 months, Table 1) and by the different 2-year and 5-year CIR for local, groin and distant recurrences (Fig. 2). The CIR for of local recurrences rises sharply from 5.9% at 2 years to 14.7% at 5 years, while the rate of groin recurrences hardly changes (5.5% at 2 years and 6.3% at 5 years).

Of the 257 women in presumed stages IB-II VSCC with primary surgical treatment, 61 (23.7%) did not undergo SGS. Women without surgical groin staging were significantly older, had poorer performance status and smaller pathological tumor margins compared with surgically staged women (Table 2). Of the 196 women who underwent SGS, 12.8% received adjuvant (chemo)radiotherapy, in 2 cases including the groins, whereas 11.5% of the women without SGS received adjuvant (chemo)radiotherapy, in 3 cases including the groins. Recurrent disease was more common among the women not undergoing SGS compared with those surgically staged, but the difference was not significant.

Table 2
Characteristics of all primary surgically treated women with FIGO stages IB-II ($n = 257$) in relation to surgical groin staging[1].

Characteristics	With SGS $n = 196$ N (%)	Without SGS $n = 61$ N (%)	*P*-value
Age at diagnosis, years			
Median (IQR)	70 (72,88)	82 (60,78)	<0.001[2]
FIGO stage[4]			
IB	163 (83.2)	47 (77.0)	0.28[3]
II	33 (16.8)	14 (23.0)	
Tumor size[5], mm			
Median	20	30	0.22[2]
Histological grade			
Well differentiated	51 (30.7)	8 (18.2)	0.16[3]
Moderately differentiated	86 (51.8)	24 (54.5)	
Poorly or undifferentiated	29 (17.5)	12 (27.3)	
ECOG performance status			
0–1	143 (87.7)	28 (62.2)	<0.001[3]
2–4	20 (12.3)	17 (37.8)	
Primary treatment			
Surgery solely	171 (87.2)	54 (88.5)	0.79[3]
Surgery + (chemo)radiotherapy	25 (12.8)	7 (11.5)	
(Chemo)radiotherapy to the vulva only	19 (9.7)	4 (6.6)	
(Chemo)radiotherapy to the vulva and the groins	2 (1.0)	3 (4.9)	
Tumor free margins in pathology report, mm			
Median	8	5	<0.001[2]
Recurrences			
No	160 (81.6)	46 (75.4)	0.29[3]
Yes	36 (18.4)	15 (24.6)	
Site of 1st recurrence			
Isolated vulvar	23 (64.0)	6 (40.0)	0.12[3]
Isolated groins	10 (27.8)	6 (40.0)	
Groins with vulvar	1 (2.8)	0	
Distant with or without locoregional	1 (2.8)	0	
Unknown localization	1 (2.8)	3 (20.0)	

Abbreviations: SGS, surgical groin staging; IQR, Interquartile range; ECOG, Eastern Cooperative Oncology Group.

[1] Inguinofemoral lymphadenectomy, sentinel node biopsy, lymph node sampling.
[2] Wilcoxon rank sum test.
[3] Pearson's chi squared test.
[4] FIGO stage according to the 2009 classification.
[5] Tumor size assessed clinically.

Isolated groin recurrences occurred in stage IB and stage II disease in women without SGS in 9.8% (6 out of 61 women) and in women with SGS in 5.1% (10 out of 196 women). In node-negative women, the isolated groin recurrence rate was 7.0% (5 out of 71 women) after a SNB and 4.9% (5 out of 102 women) after an IFL (supplementary Table S2). Women with groin recurrences after IFL had in median 4 lymph nodes per groin retrieved, compared with 7 lymph nodes in women without a groin recurrence.

3.1. Survival outcome

The 5-year RFS and OS were 56.5% (95% CI, 51.1–61.5) and 67.0% (95% CI, 62.1–71.4), respectively, for the study population (Table 3A). For surgically treated women with FIGO stages IB VSCC, the 2-year and 5-year median RFS and OS were 88.9% and 81.3% vs 92.6% and 79.0%. The relatively few surgically treated patients in stage II showed similar survival rates (Table 3A).

The median 2-year and 4-year OS post recurrence is shown in Table 3B. Among the 109 women with recurrent VSCC, 2-year and 4-year median OS post recurrence was 38.5% (95% CI, 28.9–48.0) and 26.8% (95% CI, 16.7–37.9) respectively. Median 4-year OS was 37.4% for women with isolated vulvar recurrence and 10.3% for those with groin recurrence. No woman with distant recurrence survived 2-years post recurrence.

Table 3A
Recurrence-free and overall survival of women with no evidence of disease at completion of primary treatment of vulvar squamous cell carcinoma ($n = 480$), and of women with surgically staged FIGO IB-II.

Cohorts	Median recurrence-free survival[1]		Median overall survival[2]	
	2-year % (95% CI)	5-year % (95% CI)	2-year % (95% CI)	5-year % (95% CI)
Study population, *n = 480*	77.9 (73.9–81.4)	56.5 (51.1–61.5)	86.3 (83.0–89.1)	67.0 (62.1–71.4)
FIGO stages IB-II[3] with surgical groin staging, *n = 196*	88.7 (83.3–92.5)	78.7 (70.3–85.0)	93.4 (88.9–96.1)	79.1 (72.4–84.3)
FIGO IB, *n = 163*	88.9 (82.8–93.0)	81.3 (72.6–87.5)	92.6 (87.4–95.8)	79.0 (71.6–84.6)
FIGO II, *n = 33*	87.9 (70.9–95.3)	68.5 (43.0–84.4)	97.0 (80.4–99.6)	80.4 (61.1–90.8)

[1] Recurrence-free survival was calculated from the last day of primary treatment.
[2] Overall survival was calculated from date of diagnosis of primary tumor.
[3] FIGO stage according to the 2009 classification.

Table 3B
Post-recurrence overall survival of women with a first recurrence of vulvar squamous cell carcinoma.

	Median post-recurrence overall survival[1]	
	2-year % (95% CI)	4-year % (95% CI)
Recurrence, *n = 109*	38.5 (28.9–48.0)	26.8 (16.7–37.9)
Isolated vulvar	57.8 (43.5–69.7)	37.4 (18.9–56.0)
Groins, +/− vulvar recurrence	17.2 (6.3–32.7)	10.3 (2.6–24.3)
Distant, +/− locoregional recurrence	0	0

[1] Post-recurrence overall survival was calculated from date of diagnosis of recurrence.

Estimates of hazard ratios for survival in surgically treated women with stages IB-II VSCC showed a statistically significant association between SGS and recurrence-free and overall survival (Table 4). Women in whom SGS was omitted had poorer RFS (HR 2.5, 95% CI, 1.7–3.8) and OS (HR 3.2, 2.1–5.1) compared with women who had SGS. The association remained significant after adjustment for age, FIGO-stage, tumor size, resection margins and performance status.

4. Discussion

In this nationwide population-based cohort of women with vulvar squamous cell carcinoma we found an overall recurrence rate of 22.3% with predominantly isolated vulvar recurrences which steadily increased over time. The cumulative incidence rate for local recurrences was low and median time to diagnosis exceeded 2 years but for those affected prognoses was poor with less than 40% surviving four years. Surgical groin staging was omitted in nearly one fourth of primary surgically treated women with presumed FIGO stages IB-II. Omitting SGS was associated with poorer recurrence-free and overall survival compared with women who underwent SGS.

In line with other reports, the cumulative incidence of isolated vulvar recurrence increased with time, but the rate was lower in our study compared with those of others. A recent systematic review including twenty-two studies estimated a local recurrence rate of 4% annually without plateauing [22]. In the AGO-CaRE-1 sub study including patients with VSCC FIGO stage ≥ IB, all SGS, the 2-year local recurrence rate was 12.6%, i.e., twice as high as in our study [17]. In GROINSS V–I, the 5-year local recurrence rate was 27.2% [15]. We can only speculate about possible explanations for the discrepancies observed since risk factors for local recurrence are equivocal and information on biological factors are by large missing. In the systematic review previously described a meta-analysis on prognostic factors for local recurrence could not be performed due to the very heterogenous studies [22]. In contrast to the study by Woelber et al. and the GROINSS V–I study, however, we also included patients with FIGO stage IA disease and had a lower rate of women with lymph node metastases (23.5% in our cohort versus 35.8% in the AGO-cohort).

The poor overall survival post local recurrence that we observed in our study is concerning. The 5-year OS post isolated local recurrence was 66.9% in the AGO-CaRE-1 study [17]. However, the 1249 patients included were treated at 29 Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) cancer centers while we present data from an unselected nationwide cohort without centralized treatment. In addition, the mean age was lower compared with our study and all had SGS which indicates relatively fit patients. Biological factors may also have contributed. An increased incidence and change in tumor biological characteristics of VSCC have been observed from 1974 to 2013 in Germany which possibly may have influenced prognosis [27,28]. Comparisons with other studies are difficult to make due to differences in reported outcome measures. In contrast, our study population consists of an unselected cohort of women treated during a time where

Table 4
Estimates of hazard ratios (Cox regression) for recurrence-free and overall survival in women with FIGO stages IB-II treated with primary surgery in relation to surgical groin staging ($n = 257$).

Endpoint	SGS	Crude		Adjusted[1]		Adjusted[2]	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
RFS	Yes	1		1		1	
	No	2.5 (1.7–3.8)	<0.001	2.1 (1.4–3.2)	0.001	1.9 (1.0–3.5)	0.04
	Number of women	252		252		172	
OS	Yes	1		1		1	
	No	3.2 (2.1–5.1)	<0.001	2.7 (1.7–4.3)	<0.001	2.0 (1.1–3.8)	0.04
	Number of women	257		257		174	

Abbreviations: SGS, surgical groin staging; HR, Hazard Ratio; 95% CI, 95% Confidence Interval; RFS, recurrence-free survival; OS, overall survival.
[1] Adjusted for FIGO (IB versus II), age at diagnosis (>70 years versus <71 years).
[2] Adjusted for FIGO (IB versus II), age at diagnosis (>70 years versus <71 years), tumor size (as continuous variable), resection margin (as continuous variable), ECOG performance status (0–1 versus 2–4).

centralization for vulvar cancer in Sweden had not yet been implemented. We have previously reported the results on primary treatment and relative survival in VSCC [23]. We found an excellent prognosis for stage I VSCC except for women at least 80 years old who had a 5-fold increased risk for excess mortality. It is plausible that some of these women were undertreated for isolated vulvar recurrent disease.

In our cohort, the rate of isolated groin recurrences in node-negative women after SNB was higher than reported from other cohorts [4,29]. In 2015, Covens et al. conducted a meta-analysis and calculated an isolated groin recurrence rate of 2.8% after SNB and 1.4% after IFL, thus, considerably lower than in our cohort [19]. Our results, especially regarding IFL, where the median node count was only four lymph nodes per groin for women with a groin recurrence, underscore the importance of centralization, both when using the sentinel technique, and in IFL, as emphasized by other authors [11,12,21].

For the 61 women without any surgical treatment of the groins, the groin recurrence rate was almost 10%, hence, a substantial proportion of these women were probably misclassified as being diagnosed at early stage, but instead had occult stage III disease. Primary therapy without treatment of the groins is not consistent with current international and Swedish guidelines but already in 1996, van der Velden et al. showed in their population-based cohort of 131 Dutch women that SGS was omitted in 80% of the cases from non-specialized hospitals [30]. In 2015, Gien et al. described a large Canadian cohort where 32% of the women were treated without SGS, but without a significant difference in OS between women with or without groin dissection [13,31]. However, they included both node-positive and node-negative women in their multivariate model which makes further conclusions difficult, as their expected groin recurrence rate differs substantially. Besides, they even included women with tumors invading less than 1 mm, in general not regarded as being in risk for groin metastases and collected their cohort before the introduction of the sentinel node technique, nowadays a common treatment in early-stage disease. In our study, we compared women without SGS exclusively with node-negative women in stage IB-II disease, as both groups were considered to have early-stage disease, and 36.2% of them were treated by sentinel node biopsy (supplementary Table S2). In regression analysis, omitted SGS was significantly associated with worse RFS and OS which further stresses the importance of proper primary surgery, including SGS.

To our knowledge, this is the largest population-based study on recurrence and post-recurrence survival in VSCC. The study covered over 90% of the Swedish population minimizing selection bias. A high degree of concordance was found between variables in the SQRGC and re-abstracted data from medical charts except for tumor size, pathological tumor-free margins and ECOG performance status. There were few missing data except for histological grade and performance status. Further strength is the linkage between SQRGC to other official databases which permanently ascertains the vital status for registered patients.

A limitation is the lack of central pathological review which would have provided information on e.g., prognostic factors such as pathological tumor size, p16 and perineural invasion. Despite efforts to add details from individual medical charts, some data remained missing, and in nine women we could not retrieve any information about their recurrences, except the date of recurrence. Furthermore, certain variables (performance status, clinical tumor size, histological grading) showed a low accuracy when assessing the validity of the registry. We lack information on secondary treatment making interpretation of survival results difficult. In addition, although our cohort is comparatively large, the number of patients in some subgroups were small. Our findings are derived from a specific nationwide cohort and generalization to other countries should be done with caution.

Death from other causes was found a strong competitive factor and made interpretation of some data difficult.

5. Conclusions

In this unselected nationwide study, we found that one out of five vulvar cancer patients recurred, and an isolated local recurrence was the commonest event. For those affected, prognosis was poorer than expected which raises concerns about undertreatment. The higher-than-expected rate of groin recurrences, particularly after SNB and IFL, combined with a lower lymph node harvest in recurrent women, stresses the importance of surgical proficiency when treating vulvar cancer. SGS is a crucial part of primary surgical treatment and associated with better RFS and OS. To safeguard high quality management and treatment of a rare disease, especially when affecting elderly women with comorbidities, national guidelines and centralization including multidisciplinary management and treatment are important. In Sweden, these measures have recently been undertaken.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.03.013.

Declaration of Competing Interest

EÅL: Honoraria, Roche. Advisory boards, Clovis Oncology; Astra Zeneca; Tesaro; Genmab.

All other authors have no conflicts of interest to declare.

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