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Pelvic exenteration for vulvar cancer: Postoperative morbidity and oncologic outcome – A single center retrospective analysis

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ABSTRACT

Background: Pelvic exenteration may be the only curative treatment for some patients with primary advanced or recurrent vulvar cancer but is associated with high morbidity. This study evaluated the clinical outcome of patients treated at a centralized service in Norway.

Methodology: This retrospective study included patients treated with pelvic exenteration for primary locally advanced or recurrent vulvar cancer between 1996 and 2019 at Oslo University Hospital, Norway. Complications were coded according to the contracted Accordion classification. Relapse free survival (RFS), cancer specific survival (CSS) and overall survival (OS) were estimated with the Kaplan Meier method.

Results: The 30 patients were followed for a median of 4.94 years (95%CI: 3.37-NR). Exenteration due to primary vulvar cancer was carried out in 16 (53%) patients, 14 (47%) had recurrent vulvar cancer. Free histopathological margins were achieved in 28 (93%) patients. The 90 days morbidity for grade 3 complications was 63%, predominantly wound/surgical flap infections, 7% had no complications. 90 days mortality was 3%. Five-year RFS was 26% (95% CI 8–48%), OS was 50% (95%CI: 29–69%) and CSS was 64% (95% CI 43–79%). There was no significant difference in survival between patients with primary vs recurrent disease. The 3-year CSS for patients with negative lymph nodes and positive lymph nodes was 70% (95% CI 47–84%) and 30% (95% CI 1–72%), respectively.

Conclusions: Acceptable oncologic outcomes after pelvic exenteration for primary and recurrent vulvar cancer can be achieved if surgery is centralized. Careful patient selection is imperative due to significant postoperative morbidity and considerable risk of relapse.

1. Introduction

Vulvar cancer is a rare disease and accounts for 4% [1] of all gynecological cancers. The incidence is increasing, with the age-standardized incidence rate for women of all ages, increasing over a 20-year period by 14% and by 38% in women <60 years of age [2]. This has been suggested to be due to an increase in HPV-associated VIN(1, 2). Still, the age-specific incidence rate increases with age with a peak incidence after 75 years [3]. In Norway there are approximately 80 new cases annually, giving an incidence rate of 4.66/100 000 per year [3].

Patients with early-stage disease will often be treated with wide local incision alone or modified radical vulvectomy with unilateral/bilateral sentinel lymph node biopsies or inguinofemoral lymphadenectomy. However, 30% present with locally advanced disease that has spread to regional organs and/or lymph nodes [3]. For these patients' ultraradical procedures such as pelvic exenteration may be necessary to obtain free surgical margins. For recurrent vulvar cancer, especially after primary chemoradiation, pelvic exenterative surgery is the only option offering a chance of curation in selected patients with disease extending to the pelvic organs, but without distant metastases.

There is a considerable amount of literature on outcomes after pelvic exenteration in a mixed population of women with gynecological cancer, but only very few, small retrospective case series

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have specifically addressed outcomes after pelvic exenteration in patients with vulvar cancer [4–7]. The number of patients included ranged from 19 to 27(4–7) with median age ranging from 50 to 66 years. Five-year survival rates of 50–66.7% [7] have been reported. Lymph node status [4,5], as well as resection margins have been reported as factors associated with survival [4]. Complications were not reported in all studies, and studies differed in how complications were categorized and presented. The mortality rate for women undergoing pelvic exenteration for vulvar cancer has been 0% in the most recent publications [4–7], but in larger reports on exenterative surgery encompassing all gynecological malignancies mortality rate ranged from 1,3% to 3% [8–11].

The Norwegian guidelines for treatment of vulvar cancer recommend to refer patients to a specialized gynecological oncology department. For patients with primary advanced vulvar cancer or recurrent vulvar cancer treatable by pelvic exenterative surgery, the Department of gynecological oncology at Oslo University Hospital (OUH) serves as a national centralized treatment center. We aimed to evaluate the postoperative morbidity and oncologic outcome of patients treated with exenterative surgery for vulvar cancer in Norway.

2. Materials and methods

2.1. Ethics and approvals

This was study approved as a quality assurance study by the Regional Committee for Medical and Health Research Ethics (ID 123729) and the local data protection office at Oslo University Hospital. Because of the nature of the study, the need to obtain written informed consent was waivered.

2.2. Design and study population

This is a single-center retrospective study. The study included all patients treated with pelvic exenteration for primary or recurrent vulva cancer at The Department of gynecological oncology at Oslo University Hospital (OUH) between March 1996 and December 2019. All patients were individually discussed in a multidisciplinary team with radiologists, radiation oncologists and gynecologic oncologists. For patients with primary advanced vulvar cancer, exenteration was decided if chemoradiotherapy was not likely to achieve a curative potential, the patient was considered to tolerate extensive surgery and if there was a high chance to achieve free margins. Another consideration was the indication for stoma creation prior to chemoradiation.

The patients were identified in our institution's electronic medical records.

2.3. Baseline clinical data and outcome assessment

Baseline demographic characteristics as well as data on FIGO stage at diagnosis, histology, treatment preceding pelvic exenteration and surgical details, complications and oncological outcomes were collected from the patients' electronic records.

For the calculation of 90 days postoperative morbidity, complications were coded according to the contracted Accordion classification [12]. Because of the ultraradical nature of exenterative surgery, Grade 1 complications [12] were expected as part of the treatment and not recorded as complications.

In addition to utilizing the contracted Accordion classification, complications were grouped according to which surgical procedure they were related to and subdivided into Infection/abscess, in need of surgical revision, cardiovascular, other surgical complications and other medical complications.

Patients received standard postoperative follow-up at our department. After discharge, standard follow-up at the outpatient clinic or local hospital was carried out, according to standard of care [13].

Date for recurrence was based on histological reports confirming recurrence where available, or on imaging or clinical evaluation when these showed clear evidence of recurrence. The electronic patient records are linked to Statistics Norway, where individual survival data is recorded.

2.4. Statistical analysis

Patient characteristics were summarized with frequencies and percentages for categories (continuous variables were categorized).

Median follow up time was calculated with the inverse Kaplan Meier method. Time-to-event data was analyzed with the Kaplan-Meier method. Relapse-free survival (RFS) was defined as time from exenterative surgery to relapse or death from any cause. Cancer-specific survival (CSS) was defined as time from exenterative surgery to death caused by vulvar cancer, and overall survival (OS) was defined as time to death of any cause [14]. Patients who had not experienced an event at the time of last follow-up 24th of May 2021, were censored at that time point. For the whole cohort we calculated 5-year RFS, OS and CSS. We compared 5-year CSS between patients with primary advanced vulvar cancer and recurrent vulvar cancer. To compare patients with positive lymph nodes with patients with negative lymph nodes we utilized 3-year CSS, because median CSS and 5-year CSS were not reached in both groups.

We studied the association between age, lymph node status, resection margin and lymphovascular space invasion and survival using Cox regression analysis calculating hazard ratios with 95% confidence intervals. Two-sided p-values of <0.05 were considered statistically significant.

Statistical analysis was carried out utilizing STATA statistical software (V 16.1).

3. Results

3.1. Baseline characteristics and surgical results

We included 30 patients who underwent pelvic exenteration with a median age of 66 years (33–80 years) (Table 1) between March 1996 and December 2019.

Out of the 30 patients, 16 patients (53%) were treated for primary advanced vulvar cancer and 14 patients (47%) had recurrent vulvar cancer. All patients had squamous cell carcinoma of the vulva. Of the 14 patients with recurrent vulvar cancer, two patients had undergone radiochemotherapy, five surgery alone, and seven had previously received surgery and radiotherapy with/without concomitant chemotherapy.

Regarding the exenterative surgery, eight patients (27%) were treated with total pelvic exenteration, six patients (20%) underwent anterior pelvic exenteration, six (20%) and ten (33%) patients underwent posterior and modified posterior exenteration, respectively. All procedures were infra-levator pelvic exenterations. For patients who underwent modified posterior exenteration, deep perineal dissection and rectosigmoid anastomosis was performed.

Lymphadenectomy was performed in 18 patients. The majority ($n = 13$) of these patients had primary advanced vulvar cancer, five had recurrent vulvar cancer. In three patients with primary advanced vulvar cancer, lymphadenectomy was not performed. One of these patients had previously undergone inguinal radiation in conjunction with an anal cancer, one patient rather underwent adjuvant radiotherapy to bilateral inguinal nodes due to advanced age, no reason was stated for the third patient. Regarding the five

Table 1
Baseline and surgical characteristics.

Patient characteristic		Unit/No of patients
Age at exenteration (years)	Median (range)	66 years (33–80 years)
	30–49 years	3
	50–69 years	13
	70–89 years	14
Preoperative BMI (kg/m^2)	Mean	26.1 (16.9–38.3)
	Underweight (BMI <18.5)	1
	Normal weight (BMI 18.5–24.9)	15
	Overweight (BMI 25.0–29.9)	7
	Obese (BMI >29.9)	7
FIGO staging at time of diagnosis	I	6
	II	10
	III	10
	IV	4
Preoperative Hb (g/dL)	Mean	12.9 (9.6–15.1)
	Anemia (Hb < 11.7 g/dL)	2
Preoperative albumin (g/L)	Mean	42.0 (31–51)
	Hypoalbuminemia (Albumin >36 g/L)	2
Length of stay	Median (range)	28 days (14–70 days)
Surgical characteristic		
Procedure	Type	No of patients
Urinary diversion	None	16
	Bricker	13
	Kock	1
Colostomy	None	5
	Yes	25
Surgical flap	None[a]	6
	VRAM/SKRAM	21
	Other (gracilis/pudendal)	2
	Unknown	1
Neovagina	No	28
	Yes	2
Lymphadenectomy	No	12
	Yes	18
Histopathological results		
Lymphovascular/vascular infiltration	No	21
	Yes	9
Positive lymph nodes	No	25
	Yes	5
Resection margin	Negative	28
	Positive	2

[a] The use of musculocutaneous flaps may be underestimated due to under recording in the early years.

patients with recurrent vulvar cancer receiving lymphadenectomy, these patients had previous sentinel lymph node resection, unilateral lymphadenectomy, or other suspect lymph nodes (iliacal or rectal lymph nodes) removed during exenterative surgery. One patient had suspicious inguinal lymph nodes removed in previous irradiated area. In the total cohort, five patients had positive lymph nodes on histopathological examination, all located in either or both inguinal areas. Of these five, four had primary advanced vulvar cancer and one had recurrent vulvar cancer. Four of these patients received adjuvant radiotherapy, one with concomitant cisplatin. One patient received no adjuvant treatment, because the patient only had one of 17 positive lymph nodes without perinodal infiltration. This patient had primary advanced vulvar cancer and remains free from recurrence.

The vast majority of patients (n = 28, 93%) were operated with free surgical margins.

3.2. Postoperative morbidity

Within the first 90 days postoperatively, 2 (7%) patients had no recorded complications. Of the remaining 28 patients, 24 patients (80%) had at least one grade 2 complication and 19 patients (63%) had at least one grade 3 complication. Infections related to surgical wounds/flap were the most common complications, also among patients with grade 3 complications. One (3%) patient died during the 90 days postoperative period. This patient was discharged after surgery in good clinical condition, but died after 64 days due to an infection of unknown origin, recorded as a Grade 4 complication. A more detailed overview of complications is listed in Table 2.

3.3. Survival outcomes

During median follow-up time of 4.94 years (95%CI: 3.37-NR), 15 (50%) patients relapsed. A total of 17 patients died, 11 due to cancer, 6 due to other causes. Three patients relapsed but were free from disease or died of other causes at end of follow-up. Examining these cases further, one patient had a vulvar recurrence treated with vulvectomy and remained recurrence free the remaining 6 years of follow-up, 1 patient treated with posterior exenteration had a paraurethral recurrence treated with vulvectomy and chemoradiation and remained free from recurrence through end of follow-up (7 years after exenterative surgery). The third patient developed a vulvar and paraurethral recurrence after posterior exenteration and was treated by chemoradiation followed by anterior exenteration. She remained free from recurrence of vulvar cancer but died due to breast cancer 5 years later.

Table 2
List of complications by Accordion Grade and relation to procedure.

Grade	Association with procedure	Detailed	N
Grade 2			
	Colostomy	None	–
	Urinary conduit	Urinary infection	5
	Surgical wound	Infection	10
		Abscess	1
	Surgical flap	Infection	1
	Neovagina	None	–
	Other	Pneumonia	4
		Erysipelas	1
		Blood transfusion	9
		Urinary infection[a]	5
		Total parenteral nutrition	5
		Fungal infection groin	1
		Oral candidiasis	2
		Pulmonary embolus	1
		Atrial fibrillation	1
		Nasogastric tube (retention)	1
		Infection of unknown origin	1
Grade 3			
	Colostomy	None	–
	Urinary conduit	Blocking/Expansion	1
		Leakage	1
	Surgical wound	Bleeding	2
		Revision (necrosis)	5
		Infection	1
	Surgical flap	Abscess	2
		Revision (infection or necrosis)	5
	Neovagina	Removal (displaced)	1
	Other	Incontinence (suprapubic cath)	1
		Bowel obstruction (ileus)	3
		Abdominal/pelvic abscess	4
		Pleural effusion	2
Grade 4			**1**
	Death	Infection of unknown origin	1

[a] Intact urinary bladder** Note that more than one Grade 2/3 complication can occur in the same patient.

Of patients treated for primary advanced vulvar cancer seven (44%) relapsed. Four had central/pelvic recurrence, one had recurrence in pelvic lymph nodes alone, one recurred with only distant metastasis and one had synchronous central/pelvic and distant metastases. In the group of patients treated for recurrent vulvar cancer eight (57%) patients relapsed. Central/pelvic recurrence alone was found in six patients, one recurred with only distant metastasis and one had recurrence in pelvic lymph nodes in addition to distant metastasis.

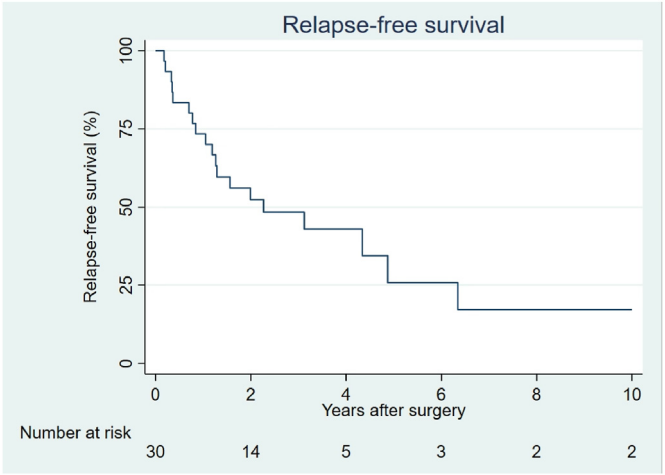

Fig. 1a. Relapse-free survival of the whole cohort.

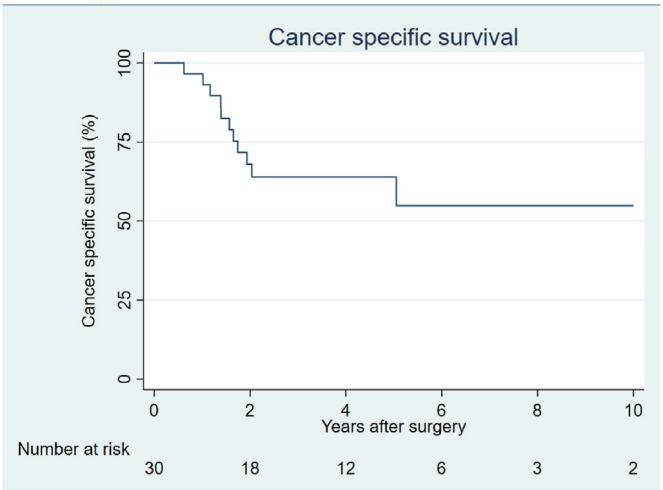

Fig. 1b. Cancer specific survival in the whole cohort.

Median relapse-free survival for the whole cohort was 2.27 years (95% CI 1.90–4.87 years) (Fig. 1a). The 5-year relapse-free survival was 26% (95% CI 8–48%). Median cancer-specific survival was not reached (Fig. 1b), but 5-year cancer-specific survival was 64% (95% CI 43–79%). Median overall survival was 5.05 years (95% CI 1.74–8.99 years), and 5-year overall survival was 50% (95% CI 29%–69%).

There was no difference between median relapse-free survival for patients with primary advanced disease and recurrent disease (3.12 years (95% CI 0.93-NR) compared to 1.56 years (95% CI 0.36–6.35 years), respectively), (Fig. 1c). 5-year cancer-specific survival was 66% (95% CI 37–85%) and 62% (95% CI 31–82%) for patients with primary and recurrent disease, respectively (Fig. 1d).

For patients with histologically confirmed metastases to the lymph nodes median CSS was 2.04 years (95% CI 1,17-NR), for patients with negative lymph nodes, median CSS was not reached. The 3-year CSS was 70% (95% CI 47%–84%) for patients with negative lymph nodes (N = 25) and 30% (95% CI 1–72) for patients with positive lymph nodes (N = 5). (Fig. 1e). Log-rank test for CSS across these groups gives a P-value of 0.219.

In univariate- and multivariate-analyses, none of the assessed clinic-pathologic variables were significantly associated with relapse-free - or overall survival (Table 3).

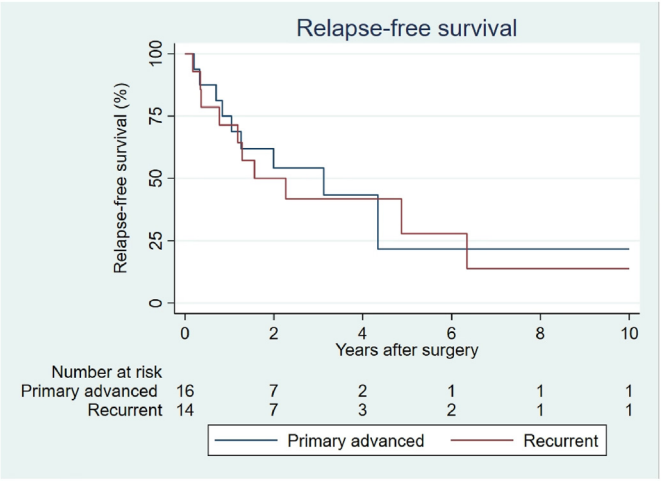

Fig. 1c. Relapse-free survival in patients with primary advanced vs recurrent disease.

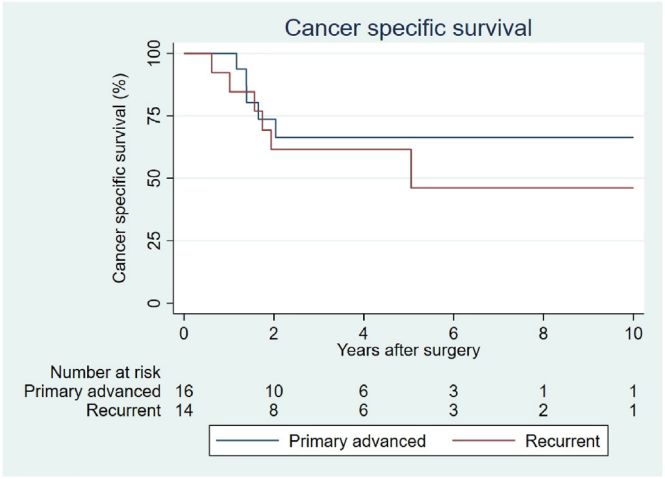

Fig. 1d. Cancer specific survival in patients with primary advanced vs recurrent disease.

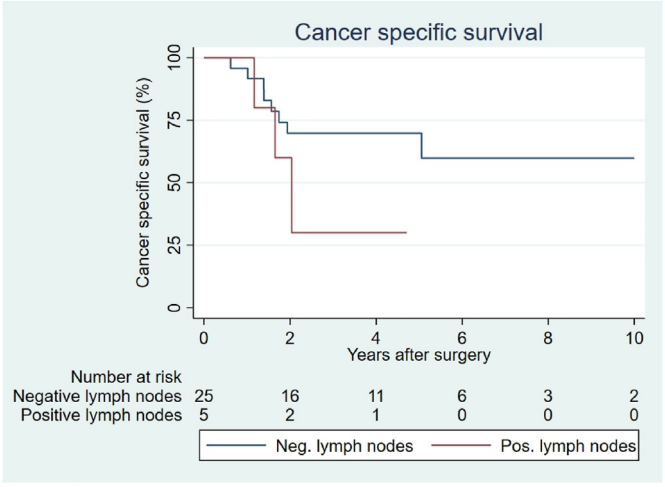

Fig. 1e. Cancer specific survival in patients with positive lymph nodes vs negative lymph nodes.

4. Discussion

4.1. Main findings

In this to date largest series of patients with vulvar cancer undergoing pelvic exenteration, 26% of the patients remained free from relapse or death at 5 years, with a 5-year disease specific survival of 64% and 5-year overall survival of 50%. No clinical parameter was clearly associated with survival in our series. In both primary advanced vulvar cancer and recurrent vulvar cancer, cancer-specific survival was above 60%. Five years cancer-specific survival for patients without lymph node metastases was 70%. Sixty-one percent of the patients had at least one grade 3 complication; the majority were related to infections in the surgical wound/flap.

Due to the rarity of this procedure in vulva cancer and the limited sample size of all published series, it is difficult to compare the point estimates of survival between the studies. We report numerically lower overall survival at 5 years (50%) compared to the 60–70% in other reports [4–7], but confidence intervals overlap. We did not find differences in survival between patients with primary vs recurrent disease in contrast to other reports finding lower overall survival in patients with recurrence [4–7].

Of the 11 deaths in our study, 6 were due to other cause and the patients in our study were slightly older at the time of exenteration than in other reports (66 years compared to 50 years and 57 years [4–6]). This may have contributed to the numerically lower overall survival in our study. The reported disease specific survival 64% in the whole cohort confirmed the curative potential of this procedure and is considered a more appropriate outcome measure when comparing such small cohorts of patients.

Due to the heterogeneity in reporting of complications, it is difficult to make comparisons across studies. One study did report minor complications in 44% and complications requiring surgical intervention in 22% [4]. Another utilized the Clavien-Dindo classification and reporting 42,1% Grade 3 complications within 30 days of surgery [7]. Others report serious complications in 52% [5] or simply in descriptive terms without classifying the severity [6]. The fact that 61% of the patients in our study experienced grade 3 complications underlines the importance of constant quality assurance of the surgical program as well as careful patient

Table 3
Univariate analysis of clinical variables and relapse free- and overall survival.

Variable	Relapse-free survival			Overall Survival		
	HR	P > l z l	95% CI	HR	P > l z l	95% CI
Age by group						
30–49 years	1.0	–	–	1.0	–	–
50–69 years	0.557	0.494	0.112–2.880	0.896	0.921	0.102–7.871
70–89 years	1.511	0.596	0.329–6.940	1.520	0.696	0.186–12.404
Primary advanced disease	1.0	–	–	1.0	–	–
Recurrent disease	1.017	0.971	0.418–2.470	1.199	0.712	0.457–3.142
Free resection margin	1.0	–	–	1.0	–	–
Resection margin, not-free	1.014	0.986	0.229–4.485	1.429	0.644	0.314–6.506
Negative LVSI	1.0	–	–	1.0	–	–
Positive LVSI	1.519	0.378	0.600–3.846	1.313	0.595	0.481–3.588
Negative LN	1.0	–	–	1.0	–	–
Positive LN	1.155	0.823	0.327–4.078	1.859	0.355	0.499–6.920

selection and counselling. Reporting complications in the 90 days following surgery, compared to 30 days [7] may partly explain why our morbidity is higher. Even though patients were operated over a long time span, this surgery is performed by a team of two surgeons and complications rates were quite stable throughout the inclusion period with a trend towards less grade 3 complications in 2018/2019 (data not shown).

4.2. Clinical implications

Our study confirms that careful evaluation of a surgical service is necessary to identify areas for improvement. Wound complications remain amongst the most common and serious causes of morbidity in patients undergoing surgery for vulvar cancer [15]. Flaps and grafts are a feasible solution to reduce tension, avoid wound breakdown and infection. Optimizing glucose control, administration of antibiotic prophylaxis and preoperative patient preparation including smoking cessation are validated effective measures to reduce risk of infection. Protocols for enhanced recovery after surgery cover most of these aspects and the implementation in patients undergoing pelvic exenteration seems feasible [16]. Specific data on patients with vulvar cancer is so far lacking. The implementation of an ERAS protocol for patients undergoing laparotomy at our department in 2018 may also have affected this cohort with a trend towards decreasing complication rates, but specific evidence on patients with exenteration is pending.

The rarity of the disease require centralization of the service to achieve adequate quality such as shown for ovarian cancer surgery [17]. Increased awareness regarding patient selection is warranted and in addition to surgical resectability, age, comorbidities and frailty should be given thorough consideration. Collecting and analyzing prospective data including standardized reporting of complications will allow systematic evaluation of the surgical techniques over time.

We confirm that a considerable proportion of patients were spared from cancer-specific death, both in the primary advanced and in the recurrent setting. The results published so far warrant the careful evaluation of other treatment options in patients with advanced or recurrent vulvar cancer. A Cochrane review [18] identified only three studies comparing chemoradiation (primary or neoadjuvant and surgery) in patients with primary locally advanced vulvar cancer (Stage III/IV) [19–21], reported no significant difference in survival and treatment emergent adverse effects, but the quality of the evidence is too low to draw conclusions. There are further two phase II GOG studies assessing response to chemoradion in locally advanced vulvar cancer. In those series, not all of the patients would have been candidates for pelvic exenteration [22,23], so direct comparisons with our series is difficult. Despite promising response rates of up to 64% with complete pathological remission in 50% of the patients, overall survival did not exceed 60% with very short follow up of 24.8 months [22]. Abdulrahman et al. retrospectively compared their group treated with exenterative surgery for primary advanced vulvar cancer (n = 14) with a group receiving primary radiotherapy (n = 12), with 5-year survival of 69.3% and 0%, respectively [7], underlining the role of pelvic exenteration in locally advanced disease even though the report lacks some details on stage and treatment intention in the radiotherapy group. There is evidence from observational studies that neoadjuvant treatment increased resectability [24], allowing for less radical surgery and a higher chance to preserve continence. However, the only randomized controlled study to date [20] has only been published in abstract form and neoadjuvant chemoradiation did not offer any survival advantages but was associated with a higher rate of complications, particularly wound break downs. More recently, neoadjuvant chemotherapy has been evaluated as an option to reduce local tumor burden. Response rate of 60–90% [25–28] have been reported with varying survival rates due to the heterogeneity of patients included. Studies may indicate that fewer patients require complex procedures such as resection of the urethra and colostomy [25] but studies are small, mostly of retrospective design and chemotherapy regimens are highly heterogenous. Further, quality of life was not reported in any of the studies and the reporting of adverse events was incomplete. There are to date no comparative studies in patients with recurrent disease. In patients who have previously undergone radiation, surgery may indeed be the only option of salvage and we here confirm the curative potential of exenterative surgery also in patients with recurrent disease. The more recent discussion on the impact of the size of resection margins will also play a role when tailoring the extent of resection in patients with locally advanced disease [29]. In some patients, less extensive surgery may be sufficient with comparable oncological outcome. The high risk for serious complications and of dying of other causes but also the unknown impact on quality of life in survivors warrant further research on better selection criteria prior to offering patients exenterative surgery.

4.3. Strengths and limitations

This is the first study reporting on postoperative morbidity according to a standardized classification system. It is also the largest series to date of patients undergoing exenterative surgery for vulvar cancer. Complete follow-up including cause of death was available for our patients allowing us to calculate more appropriate outcome measures such as disease specific survival.

Still the number of patients is not sufficient to achieve statistically significant results with regards to factors affecting survival outcomes. Harmonized reporting would be necessary for pooling of data from retrospective series.

5. Conclusions

With a disease specific survival of 64%, pelvic exenterative surgery remains a valid treatment option for carefully selected patients with locally advanced or recurrent vulvar cancer. However, complication rates remain high and patients are at high risk of dying of other causes. So far alternative treatment strategies such as radiochemotherapy or neoadjuvant strategies have not shown superior survival outcomes and prospective, sufficiently large, powered studies are lacking due to the rarity of the disease. Comparative data on long-term health related quality of life will also be necessary to evaluate these strategies. Harmonized protocols and reporting, as well as international collaborative initiatives, will be necessary to improve the standard of care for patients with locally advanced vulvar cancer who are candidates for pelvic exenteration.

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CRediT authorship contribution statement

H. Valstad: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Funding acquisition. **B. Eyjolfsdottir:** Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Y. Wang:** Methodology, Writing – original draft, Writing – review & editing. **G.B. Kristensen:** Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing. **T. Skeie-Jensen:**

Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing. **K. Lindemann:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors have no conflicts of interest.

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