Retrospective cohort study of neoadjuvant chemotherapy followed by tailored surgery in locally advanced sphincter-threatening vulval cancer: an alternative to exenteration?

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Objective: To determine the feasibility and overall survival (OS) outcome of utilizing neoadjuvant chemotherapy (NACT) followed by wide local excision (WLE) in women with sphincter-threatening locally advanced squamous cell carcinoma (SCC) of the vulva. Methods: The electronic chemotherapy prescribing system was used to identify patients from the West of Scotland Cancer Network (WoSCAN) who received NACT over a 5 year period, January 2012 to December 2016 inclusive. Baseline characteristics and treatment details were collected. Association of treatment type and other variables with OS were analysed using Cox proportional hazards model. Results: 57 patients with newly diagnosed SCC of the vulva were identified; recurrences were excluded. 25 patients proceeded to WLE following NACT. No permanent stomas were required. 4% of patients had a complete response with NACT alone, not undergoing surgery, and remained disease free at the study end. OS was 39.3 months (95% Confidence Interval (CI) 32.5 – Not reached (NR)) for the entire cohort and 40.1 months (95% CI 39.3 – NR) in the surgical group following median follow up of 27 months. Local recurrence was the predominant cause of failure. Conclusions: NACT followed by WLE is effective in a subgroup of patients with locally advanced vulval cancer and can minimize the extent of surgery necessary, but close monitoring is required to identify and manage relapse early.

Keywords
Vulval cancer, Neoadjuvant chemotherapy, Surgery, Radiotherapy, Wide local excision, Real-world

1. Introduction

Squamous cell carcinoma of the vulva accounts for less than 5% of all gynaecological cancers, but the incidence is increasing [1, 2]. Vulval cancer largely remains a disease of the elderly but rates are steadily rising in younger women, most likely as a result of high-risk human papilloma virus (HPV) infection.

Disease management is predominantly surgical; evolving paradigms promote less aggressive surgery in International Federation of Obstetrics & Gynaecology (FIGO) Stage 1 or 2 disease with a wide local excision (WLE) favoured as opposed to radical vulvectomy [3]. More recently, the introduction of sentinel node techniques [4] can spare some women from the morbidity of bilateral groin node dissection (BGND). However, 30–40% of cases present with locally advanced disease (FIGO Stage 3 or 4). There is no clear terminology that differentiates “operable” from “inoperable” vulval cancer. The latter may encompass a medically unfit patient, unresectable disease (bony infiltration and/or fixed nodes), and situations where the tumour is encroaching on urethra and/or anus so is technically resectable but exenterative surgery is required in order to achieve clear margins. As a result of the significant physical and psychological burden of such an approach alternative types of management such as (chemo)radiotherapy are often considered more desirable.

Our centre serves approximately half of the population of Scotland, and a significant proportion of our patients are socioeconomically deprived, often with associated multiple comorbidities. Late presentation of bulky tumours (≥5 cm) is not uncommon and the efficacy of (chemo)radiotherapy on advanced disease is uncertain. Primary exenterative surgery is frequently precluded by concerns over peri-operative morbidity and mortality. Neoadjuvant treatment is not a new concept in locally advanced vulval cancer; both pre-operative
radiotherapy and chemoradiotherapy (CRT) have previously been explored [5–7], but toxicity is a significant deterrent [5–7]. There is a small but growing body of work that supports neoadjuvant chemotherapy (NACT) in locally advanced disease [8–16]. Within our institution we offer NACT with the objective of downstaging tumour adjacent to urethra and/or anus such that a radical WLE can be performed, sparing bladder and/or bowel stoma thereby minimising morbidity. To that end, we investigated the role of NACT, as part of the Cancer Medicines Outcome Programme (CMOP). CMOP is a Scottish Government funded programme which aims to better understand treatment outcomes of systemic anticancer therapy (SACT) in the Scottish population [17]. Here, we present the results of NACT in women with sphincter-threatening vulval cancer.

2. Methods

2.1 Patients and methods

The study was a retrospective observational analysis, and the population comprised all patients who commenced NACT within the West of Scotland Cancer Network (WoSCAN) between January 2012 and December 2016. Patients were identified from the chemotherapy electronic prescribing and administration system (CEPAS). Case notes were then reviewed to identify patients who received chemotherapy with neoadjuvant intent. Only primary squamous cell carcinoma of the vulva was included; recurrences or alternative pathology were excluded. Routine magnetic resonance imaging (MRI) was not mandatory at diagnosis. Patients were followed up until death, or the end of the study period (February 28, 2018), whichever occurred first.

2.2 Data sources

Data were collected from information gathered within CEPAS; ARIA, a radiotherapy management system; Clinical Portal, an electronic application providing socio-demographic information and details with regards to treatment outcomes; and the Acute, Cancer, Deaths and Mental Health (ACaDMe) datamart [18] to obtain death records. Data were entered on a Microsoft Access database and anonymised. Statistical analysis was performed using R software, version 3.3.3 (R Foundation, Vienna, Austria) [19].

2.3 Statistical analysis

Median OS, 3-year survival and corresponding 95% Confidence Intervals (CI) were estimated using the Kaplan–Meier (KM) method. For OS and relapse, February 28, 2018, served as censor date for those still alive at study end.

Cox proportional-hazard models were used to estimate unadjusted hazard ratios (HR) for survival, for the following clinical variables: primary treatment (surgery versus (chemo)radiotherapy versus none); age; baseline performance status (0 versus 1–3); grade of pathology (1 versus 2 versus 3); baseline albumin and haemoglobin (lower than normal range versus within normal range); baseline platelets (higher than normal range versus within normal range); neutrophil lymphocyte ratio (NLR) (<5 versus ≥5) [20]; Charlson comorbidity index score (0 versus ≥1) [21]; body mass index (normal/underweight (<25 versus overweight (≥25) versus unknown); and Scottish Index of Multiple Deprivation (SIMD) [22]. Adjusted models were then created including age and the significant variables from the univariable analyses (p < 0.1). A spline was used to model the non-linear effect of age.

3. Results

3.1 Baseline characteristics and NACT regimen

57 patients were included within the analysis; median age was 65 years (interquartile range (IQR) 55–72). Tumour size ranged from 2–15 cm (median 5 cm, IQR 4–7) and 8/57 (14%) had clinically palpable inguinal lymphadenopathy documented. Charlson Comorbidity Index score of ≥1 was documented in 40% of women indicating the presence of medical comorbidities, and 67% of patients were from the most deprived quintile areas (SIMD 1/2) [22]. Cisplatin and capecitabine delivered 3-weekly was the most frequently prescribed NACT regimen (80%). Carboplatin delivered 3-weekly or mitomycin delivered 6-weekly was substituted for cisplatin if there were concerns over performance status and/or ability to cope with the fluid load required for cisplatin pre-hydration. Intravenous 5-fluorouracil was permitted as an alternative to oral capecitabine if in-patient treatment was preferred. Table 1 shows the baseline summary of patient and disease related factors that may influence choice and/or outcome of treatment along with the NACT regimen prescribed.

3.2 Management post NACT

Following NACT, 45 (78.9%) patients received definitive treatment; 25 (43.9%) proceeded to surgery, and 20 (35%) had (chemo)radiotherapy. Of the 46 women who received NACT comprising cisplatin and capecitabine, 23 (50%) proceeded to surgery and 16 (34.8%) had (chemo)radiotherapy. Conversely, five of the 11 (45.5%) women who were administered a NACT regimen other than cisplatin and capecitabine did not receive any definitive therapy. Within the residual group of 12 women, 9 (75%) were managed palliatively with a small number (n < 5) going on to receive further SACT. One patient died following the first cycle of NACT. The remaining 4% of patients (n < 5) had a complete clinical response and mapping biopsies of the vulva confirmed complete pathological response. Surgical resection was deemed unnecessary and they were closely monitored.

3.3 Surgery

The surgical cohort consisted of 25 patients; median age was 63 years (IQR 55–68) and median tumour size was 5 cm (IQR 4–7). Seven (28%) of these patients had palpable groin lymphadenopathy on clinical examination or radiologically suspicious nodes on diagnostic imaging with MRI at presentation. Biopsy of inguinal nodes was not performed, as the intention was to proceed to WLE and BGND regardless. All 25 patients had WLE, and 19 (76%) had BGND. Reasons for
Table 1. Baseline Characteristics & Neoadjuvant chemotherapy details.

| Characteristic                        | Measure         | Result                      |
|---------------------------------------|-----------------|-----------------------------|
| Age (years)                           | Median (IQR)    | 65 (55–72)                  |
|                                       | Range           | 33–88                       |
| ECOG performance status               | 0 n (%)         | 32 (56)                     |
|                                       | 1–2 n (%)       | 11 (19)                     |
|                                       | Not available n (%) | 14 (25)                  |
| Pathology                             | Squamous n (%)  | 57 (100)                    |
| Tumour size (cm)                      | Median (IQR)    | 5.0 (4–7)                   |
|                                       | Range           | 2–15                        |
| Baseline BMIa                         | Median (IQR)    | 28.1 (25–31)                |
| Haemoglobin (g/L)b                    | Median (IQR)    | 134.5 (120–144)             |
| Platelets (×10⁹/L)b                    | Median (IQR)    | 302.5 (253–351)             |
| Albumin (g/L)                         | Median (IQR)    | 37.5 (35–41)                |
| Neutrophil lymphocyte ratio (NLR)b     | ≥5 n (%)        | 11 (19)                     |
| Charlson comorbidity index score      | ≥1 n (%)        | 23 (40)                     |
| Scottish Index of Multiple Deprivation (SIMD 2012) | 1 n (%) | 26 (46) |
|                                       | 2 n (%)         | 12 (21)                     |
|                                       | 3 n (%)         | 8 (14)                      |
|                                       | 4 n (%)         | 5 (9)                       |
|                                       | 5 n (%)         | 6 (10)                      |
| NACT regimen                          | Cisplatin/Capcitabine n (%) | 46 (80.7)              |
|                                       | Platinum± Capcitabine/5-fluorouracil n (%) | 6 (10.5)             |
|                                       | Mitomycin/Capcitabine n (%) | 5 (8.8)                  |
| No. of cycles                         | Median (IQR)    | 3 (2–4)                     |
|                                       | Range           | 1–6                         |
| Dosage information for Cisplatin/Capcitabine NACT regimen (n = 46) | Cisplatin ≥70 mg/m² n (%) | 34 (73.9) |
|                                       | Cisplatin <70 mg/m² n (%) | 12 (26.1)                |
|                                       | Capcitabine ≥825 mg/m² n (%) | 39 (84.8)             |
|                                       | Capcitabine <825 mg/m² n (%) | 7 (15.2)                  |

a n = 33, results not available for 24 patients; b n = 56; results not available for 1 patient; c Platinum – either carboplatin or cisplatin (other than those who received cisplatin and capcitabine); d Dose of medicine is at first cycle.

Abbreviations: IQR, Interquartile range; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; NACT, neoadjuvant chemotherapy.

not performing nodal dissection included comorbidity; previous hernia repair; and patient choice. NACT resulted in complete pathological response at the primary site in 10/25 (40%) cases. R0 resection was achieved in 12/25 (48%) patients; a margin of <8 mm was documented in 11/12. R1 resection was attained in the remaining surgical patients. Further surgery was not performed as this would have entailed sphincter dysfunction or stoma formation. Inguinal lymph nodes were positive in 7/25 (28%), negative in 12/25 (48%), and status was unknown in 6/25 (24%).

Most surgical procedures (n = 17, 68%) were performed with plastic surgery support. Twelve patients required a reconstructive flap, and the remaining five required either skin graft or assistance with primary closure. There was a single peri-operative death but cause of mortality was unclear. Otherwise, morbidity was acceptable with seven cases of dehiscence, infection, lymphocyst, or lymphoedema.

3.4 Adjuvant (chemo)radiotherapy following surgery

Adjuvant external beam (chemo)radiotherapy to the inguinal/pelvic nodes (4500–5000 cGy) was delivered to women (n < 5) with ≥2 positive inguinal nodes at BGND (or ≥1 node with extracapsular spread (ECS)). Vulval irradiation was recommended for women with an R1 margin (n < 5) but did not proceed due to deterioration in performance status and/or patient choice.

3.5 Survival outcome

After median follow up of 27 months (IQR 14.4–36.6), 26 patients had died and the median OS was 39.3 months (95% CI 32.5 – Not reached (NR)). The estimated 3-year OS was 57.6% (95% CI 45.1–73.5). Following stratification according to treatment type, median OS was comparable for both surgery (n = 25) and (chemo)radiotherapy groups (n = 20); 40.1 months (95% CI 39.3–NR) and 38.1 months (95% CI 17.6–NR), respectively. Kaplan-Meier plots are shown in Fig. 1. Estimated 3-year OS was 73.3% (95% CI 54.8–98.1) and 52.5% (95% CI 33.9–81.4) in the surgery and
(chemo)radiotherapy arms, respectively. Patients who received no subsequent definitive treatment (n = 12) had poorer survival than those who proceeded to surgery, unadjusted HR 4.18 (95% CI 1.54–11.35). Of note, the no definitive treatment subgroup contained the patients who had a complete clinical response and remained disease free at the study end.

Applying univariable Cox proportional hazard models, the following factors had a significant influence on survival: NACT regimen; age; performance status; baseline haemoglobin and albumin; baseline NLR; and definitive therapy following NACT. Using multivariable analysis, the factors that remained independently associated with poorer survival were: age (non-linear p value 0.005), NACT regimen other than cisplatin/capecitabine (HR 3.48 (95% CI 1.08–11.28)), and NLR ≥5 (HR 4.34 (95% CI 1.05–17.96)) (Table 2). Supplementary Fig. 1 shows the spline used to model the non-linear effect of age.
3.6 Relapse

At the time of data censoring, 15 potential relapses were recorded in the surgical cohort. Of these, one was excluded as death occurred as a result of synchronous malignancy. Another patient died suddenly within 30 days of surgery, but had clear margins and to the best of our knowledge was disease free. Overall, there were 13 confirmed relapses; 12 patients with loco-regional disease (11/12 locoregional only and 9/12 vulva only). All of the women who developed nodal and/or distant metastases had at least one positive inguinal node at BGND and 75% had ECS. 23% were successfully salvaged (with further WLE or radical radiotherapy).

### Table 2. Univariable and multivariable survival analysis.

| Characteristic                                      | No. patients | No. deaths | Univariable HR (95% CI) | p value | Multivariable Adjusted HR (95% CI) | p value |
|-----------------------------------------------------|--------------|------------|-------------------------|---------|------------------------------------|---------|
| Definitive therapy following NACT                  |              |            |                         |         |                                    |         |
| Surgery                                             | 25           | 8          | 1.00                    | 0.02    | 1.00                               | 0.02    |
| (Chem)radiotherapy                                  | 20           | 10         | 1.72 (0.68–4.36)        | 0.26    | 0.70 (0.21–2.39)                   | 0.57    |
| None                                                | 12           | 8          | 4.18 (1.54–11.35)       | 0.006   | 2.78 (0.67–11.56)                  | 0.16    |
| Age                                                 | 57           | 26         | 1.028 (1.00–1.06)       | 0.09°   | 0.09                               | 0.005°  |
| ECOG Performance Status                             |              |            |                         |         |                                    |         |
| 0                                                   | 32           | 12         | 1.00                    | 0.09    | 1.00                               | 0.09    |
| 1–3                                                 | 11           | 6          | 2.41 (0.88–6.57)        | 0.09    | 1.95 (0.55–6.95)                   | 0.30    |
| Unknown                                             | 14           | 8          | 2.4 (0.96–6.02)         | 0.06    | 1.39 (0.36–5.37)                   | 0.67    |
| Grade of pathology\(^e\)                           |              |            |                         |         |                                    |         |
| Grade 1                                             | 12           | \(b\)     | 1.00                    | 0.63    |                                    |         |
| Grade 2                                             | 32           | 15         | 1.51 (0.5–4.56)         | 0.46    |                                    |         |
| Grade 3                                             | 13           | 7          | 1.79 (0.51–6.24)        | 0.36    |                                    |         |
| NACT regimen                                        |              |            |                         |         |                                    |         |
| Cisplatin/Capeptabine                               | 46           | 18         | 1.00                    | 0.04    | 1.00                               | 0.04    |
| Other                                               | 11           | 8          | 2.56 (1.1–5.95)         | 0.03    | 3.48 (1.08–11.28)                  | 0.04    |
| Baseline Haemoglobin (g/L)\(^c\)                    |              |            |                         |         |                                    |         |
| <115 g/L (<lower limit normal)                      | 12           | 10         | 1.00                    | 0.005   | 1.00                               | 0.005   |
| 115 g/L–165 g/L (normal range)                      | 44           | 15         | 0.29 (0.13–0.65)        | 0.003   | 0.88 (0.22–3.59)                   | 0.86    |
| Baseline Platelets (×10\(^9\)/L)\(^c\)              |              |            |                         |         |                                    |         |
| 150–400 × 10\(^9\)/L (normal range)                 | 47           | 19         | 1.00                    | 0.16    |                                    |         |
| >400 × 10\(^9\)/L (>upper limit normal)             | 9            | 6          | 2.04 (0.81–5.15)        | 0.13    |                                    |         |
| Baseline Albmin (g/L)\(^c\)                         |              |            |                         |         |                                    |         |
| <35 g/L (<lower limit normal)                       | 13           | 10         | 1.00                    | 0.003   | 1.00                               | 0.003   |
| 35–50 g/L (normal range)                            | 43           | 15         | 0.26 (0.11–0.6)         | 0.002   | 0.49 (0.23–1.92)                   | 0.30    |
| Neutrophil Lymphocyte Ratio\(^c\)                   |              |            |                         |         |                                    |         |
| <5                                                  | 45           | 16         | 1.00                    | <0.001  | 1.00                               | <0.001  |
| ≥5                                                  | 11           | 9          | 6.08 (2.52–14.68)       | <0.001  | 4.34 (1.05–17.96)                  | 0.04    |
| Body Mass Index (BMI)\(^d\)                         |              |            |                         |         |                                    |         |
| <25                                                 | 7            | \(b\)     | 1.00                    | 0.01    |                                    |         |
| ≥25                                                 | 26           | 8          | 2.03 (0.25–16.33)       | 0.50    |                                    |         |
| Unknown                                             | 24           | 17         | 5.76 (0.76–43.82)       | 0.09    |                                    |         |
| Charlson comorbidity index score                     |              |            |                         |         |                                    |         |
| 0                                                   | 34           | 16         | 1.00                    | 0.74    |                                    |         |
| ≥1                                                  | 23           | 10         | 0.87 (0.39–1.93)        | 0.74    |                                    |         |
| Scottish Index of Multiple Deprivation (SIMD) 2012   |              |            |                         |         |                                    |         |
| 1                                                   | 26           | 14         | 1.00                    | 0.36    |                                    |         |
| 2                                                   | 12           | 6          | 1.00 (0.38–2.63)        | 0.99    |                                    |         |
| 3                                                   | 8            | \(b\)     | 0.93 (0.3–2.87)         | 0.91    |                                    |         |
| 4                                                   | 5            | \(b\)     | 0.31 (0.04–2.38)        | 0.26    |                                    |         |
| 5                                                   | 6            | \(b\)     | 0.25 (0.03–1.89)        | 0.17    |                                    |         |

Abbreviations: HR, hazard ratio; CI, confidence interval; LLN, lower limit normal.
°non-linear p value for age; \(^b\)Numbers <5 not reported; \(^c\)n = 56, 1 patient with no data available; \(^d\)variable not included in multivariable model due to extent of unknown data; \(^e\)Grade of pathology 1–3 corresponding to well differentiated, moderately differentiated and poorly differentiated respectively; Bold indicates \(p < 0.1\).
There were 11 cases of disease progression or relapse in the time observed within the (chemo)radiotherapy group; none were successfully salvaged.

In order to identify clinicopathological factors that may predict recurrence in the surgical group, we compared the relapsed patients with those who did not develop a relapse during the study period (Table 3). Patients who relapsed were older, had a larger median tumour size at diagnosis, and the majority were peri-urethral in distribution. Conversely, the relapse free group is characterised by absence of lymphovascular space invasion (LVSI), perineural invasion (PNI), extracapsular spread (ECS), and the closest surgical margin \( \geq 2 \text{ mm} \).

### 4. Discussion

#### 4.1 Summary of main results

Overall, WLE following NACT was achievable in 45\% of women presenting with sphincter-threatening disease and considered unnecessary in 4\% (complete pathological response). There were no permanent stomas in this population. Median OS was 39.3 months and the 3-year estimated OS was 57.6\%. Loco-regional relapse was the main cause of treatment failure; the majority of recurrences developed in the vulva as opposed to nodal basins and arose within the surgical bed. In an attempt to predict those most likely to recur, we have descriptively compared the clinical and pathological factors. It is difficult to draw definitive conclusions in view of the small patient numbers but a higher number of recurrences were documented in women with peri-urethral tumour, residual disease \( \geq 10 \text{ mm} \), closest surgical margin \( < 2 \text{ mm} \), \( \geq 1 \) node, and ECS. Positive nodes and/or ECS were a precursor of nodal and/or distant recurrence.

#### 4.2 Results in the context of published literature

The proportion of women proceeding to surgery compares favourably with Durrant et al. [8], Wagenaar et al. [10], Domingues et al. [12], and Han et al. [14], who reported operability rates (OR) of 20–60\%. However, this cohort falls short of the 78–100% operability as evidenced by other groups [9, 11, 13, 15, 16, 23]. All of the available series to date comprise heterogeneous patient groups and utilize a variety of NACT regimens. It is unclear whether choice of chemotherapy and/or dose intensity is pivotal. With the exception of a disappointing response rate of 20\% in a subgroup of 10 patients treated by Domingues et al. [12], cisplatin and 5-fluourouracil appears to be a potent doublet. Replacing cisplatin with a less toxic alternative, carboplatin or mitomycin C, may result in suboptimal outcomes. Fewer patients proceeded to definitive therapy and multivariable analysis indicated that selection of a non-cisplatin/capecitabine regimen increased the HR in our cohort. We acknowledge that the numbers are small and there may be confounding factors such as age. Elderly patients (\( \geq 70 \) years) were more likely to be offered carboplatin or mitomycin C and/or a dose reduction due to frailty and/or impaired renal function. It may explain why age is a poor prognostic factor, but operability was not based exclusively on tumour response. Intriguingly, attenuated survival was also observed in the youngest women.

In addition to variance over NACT regimen, the definition of operability and procedure(s) performed is not consistent across the literature. For example, in the majority of studies the aim was radical vulvectomy and not WLE. Moreover, the rate of pelvic exenteration was up to 19\% [9]. The focus in the prospective non-randomised trial conducted by Aragona et al. [13] is organ preservation, so we can assume that all of these patients had sphincter-threatening disease rather than (or in addition to) fixed or ulcerating nodes. The response rate was dramatic with 91\% achieving a partial response, defined as \( \geq 50\% \) clinical reduction. Of the 27 patients who proceeded to surgery, 14 had radical vulvectomy and 13 had WLE. More aggressive surgery may explain the impressive local control rate and remarkable OS (92\% at 5 years) [13]. The authors believe that proximity of vulval malignancy to a sphincter complex is more important than size.

### Table 3. Utilising clinicopathological factors to predict relapse in patients who underwent surgery (n = 23) following neoadjuvant chemotherapy.

| Characteristic                  | Patients with relapse in time observed | Patients with no relapse in time observed |
|--------------------------------|----------------------------------------|------------------------------------------|
| Number of patients             | 13                                     | 10                                       |
| Mean age (years)               | 63                                     | 58                                       |
| Median tumour size (cm)        | 5 cm                                   | 4 cm                                     |
| Median number NACT cycles      | 4 (range 2–6)                           | 3 (range 2–5)                            |
| BGND                           | 11/13 (84.6%)                          | 7/10 (70%)                              |
| Site                           | 9/13 (peri-urethral) (69.2%)            | 8/10 (peri-anal) (80%)                   |
| Residual disease \( < 10 \text{ mm} \) | 6/13 (46.2%)                           | 8/10 (80%)                              |
| Surgical margin \( < 2 \text{ mm} \) | 5/13 (38.5%)                           | 0/10 (0%)                               |
| Absence of LVSI               | 12/13 (92.3%)                          | 10/10 (100%)                            |
| Absence of PNI                | 11/13 (84.6%)                          | 10/10 (100%)                            |
| Absence of positive nodes      | 8/13 (61.5%)                           | 9/10 (90%)                              |
| Absence of ECS                | 10/13 (76.9%)                          | 10/10 (100%)                            |

Abbreviations: NACT, neoadjuvant chemotherapy; BGND, bilateral groin node dissection; LVSI, lymphovascular space invasion; PNI, perineural invasion; ECS, extracapsular spread; A-RT, adjuvant radiotherapy.
We propose that specific sphincter encroachment may be just as crucial. Accordingly, the majority of relapses in our cohort occurred in women with peri-urethral disease. A recent analysis of over 300 surgical patients from the Netherlands indicated that women with peri-clitoral tumours had poorer disease free survival than their counterparts with perineal tumours [24]. There may be surgical/anatomical reasons for this but tumour biology, notably HPV, appears to be fundamental [25, 26].

The role of radiotherapy or more commonly CRT in the neoadjuvant setting is becoming increasingly controversial. Previously, a Cochrane analysis advised that pre-operative CRT was not recommended in locally advanced vulval cancer, providing radical vulvectomy and BGND was technically feasible, as toxicity was significantly more pronounced with multimodality therapy [27]. However, if primary surgery is not an option then (chemo)radiotherapy has traditionally been an accepted means of down-staging disease. A recent pooled re-analysis of published data comparing NACT and neoadjuvant CRT with definitive CRT in FIGO stage III/IVA vulval cancer [28] indicated equivalent 5-year OS outcomes of approximately 70% for both neoadjuvant approaches, in contrast to 43% for definitive CRT. NACT alone would have the advantage of sparing patients from the long-term morbidity of radiotherapy. However, it is unclear whether radiotherapy can routinely be safely omitted in the context of less extensive surgery as most of the procedures included in the analysis consisted of radical vulvectomy rather than WLE. NACT may down-stage the groin as well as the primary site of disease in which case one has to question whether adjuvant external beam irradiation to the inguinal and pelvic nodal basins should be standard protocol. As there were few cases of nodal relapse in our series, we do not believe this to be advantageous. The rate of vulval recurrence, however, suggests that a tri-modality approach is advisable to sterilize the primary site if a radical vulvectomy is not performed, especially as a complete pathological response or a margin of ≥8 mm was achieved in <50% of cases. This is clearly not required for all women as there is a disease free cohort who received only NACT and WLE (or remarkably, NACT alone). The ethos at our centre is to reserve radiotherapy for inoperable recurrence but, moving forward, adjuvant radiation to the vulva will be strongly considered, especially if the margin obtained is <2 mm and/or disease is located at the urethra, in accordance with the risk factors associated with local failure in this study. Recent data indicates that the traditional 8mm clearance may be unnecessary and aiming for 2 mm may be sufficient [29], but this has not yet been proven in more advanced disease.

Finally, OS for those patients who proceeded to definitive (chemo)radiotherapy rather than surgery was comparable to previous reports, suggesting that NACT is not detrimental from a radiobiological perspective even if surgery is not performed. However, we accept that there was no control arm who received chemo(radiotherapy) without upfront NACT. Our results (3-year OS 52.5%) reconcile with a review of the National Cancer Database reporting 5-year OS of 27.4% (radiotherapy alone) and 49% (CRT) in locally advanced vulval cancer [28, 30], although enhanced outcomes may be achieved with dose escalated intensity modulated radiotherapy [31].

4.3 Strengths and weaknesses

The major strength of this study is the relatively large number of participants treated at a single institution, all of whom had sphincter-threatening disease. There was reasonable concordance in NACT regimen prescribed, but drug and/or dose modifications were deemed necessary on clinical grounds in 45.6% of patients. In addition, the surgical procedure performed varied considerably as is the nature with a tailored patient-centred approach. Detailed description of FIGO stage was not always recorded as patients were deemed “resectable” or “non-resectable” and therefore this information was not included. Similarly, MRI imaging was not implemented consistently at diagnosis so the incidence of locoregional node involvement might have been underestimated, but would not have altered management (unless there were involved pelvic nodes). HPV and p16 immunohistochemistry testing at diagnosis was not routinely performed at the time of this study, and HPV/p16 status was therefore unavailable for the cohort. Finally, quality of life data was not available but would have helped to enrich our findings.

4.4 Implications for practice and future research

Ultimately, it would be helpful to identify patients most likely to respond to NACT. HPV may prove to be a useful predictive tool following future research (it has already been shown to prognosticate outcome in surgery and radiotherapy) [25, 26] but there may be additional or alternative targets that mediate response. An international randomised trial of NACT in vulval cancer might not be achievable, but Aragona et al. [13] demonstrate that a multi-centre prospective series is feasible. The next step would be an integrated tissue bank platform with which to perform molecular testing and identify potential biomarkers; the recently opened RaNGO (Rare Neoplasms of Gynaecological Origin) UK tissue registration study [32], may be a valuable contribution. Radiotherapy and/or more radical surgery could then be offered to women unlikely to respond, sparing them the toxicity of potentially ineffective SACT. An alternative, more direct means of delivering SACT, is electrochemotherapy; a promising tool in the palliative setting [33] that has recently demonstrated some efficacy as a neoadjuvant therapy prior to surgery [34], although the precise role of this procedure in large primary tumours has yet to be determined. Increasing interest in checkpoint inhibitors has led to speculation over the use of immunotherapy in vulval cancer, especially in the HPV-derived subtype. As the evidence is currently very limited [35], it is unclear if the combination of this treatment modality and/or targeted agents [36] will improve outcomes in locally advanced vulval cancer, and, if so, what the optimal
sequencing of treatments would be. Lastly, the potential role of NLR also warrants further scrutiny, as this was significant on multivariable analysis and is a simple test to perform at diagnosis.

5. Conclusions

In conclusion, NACT resulted in an operability rate of over 40% in women with sphincter-threatening squamous cell carcinoma of the vulva, and may be curative alone in a minority of cases. Although we did not achieve the striking survival outcomes reported by other groups, we included elderly women, often with comorbidities and/or very bulky disease, and took a conservative approach; we did not perform either radical vulvectomy or exenteration, and radiotherapy was used sparingly. Also, a small number of women with a complete clinical and pathological response were excluded from the surgical group as they did not undergo a definitive procedure and this is likely to skew the survival analysis. For the first time, we have shown that tumour localization might influence outcome of NACT. WLE following NACT is an option in order to preserve sphincter function, especially in the context of peri-anal disease, but local relapse rates are high and careful follow up is imperative as there may be opportunity for salvage treatment.

Author contributions

KBai, KG, NR, JL, CC, JP, KK, TM, MB, NS, KBur, JT, RL, SS, RH, AS conceptualised and designed the study. KBai, KG and CC performed the data analysis. CC and TM assisted with data management, and KK and JP provided additional statistical support. KBai, KG, JL, KK, MB contributed to the interpretation of the results. KG wrote the manuscript. KBai, KG, NR, JL, MB, JP, KK, TM, NS, RL critically revised the text. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Public Benefit and Privacy Panel for Health and Social Care (1819-0055). Due to the nature of this clinical effectiveness study, additional ethical approval was not required.

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Conflict of interest

KBai, JL, CC, TM, MB, KK, JP all report grants from Scottish Government, during the conduct of this study. KBai reports other from attendance at the 2019–2021 PM Clinical Leadership in Pharmacy (CLIP) Scotland programme which is sponsored/funded by Daichi Sankyo UK Ltd, GlaxoSmithKline Plc and Napp Pharmaceuticals Ltd, outside the submitted work. RL reports other from Intuitive sponsored visit to IRCAD robotic facility in Strasbourg, outside the submitted work. All other authors declare no competing interests.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://ejgo.imrpress.com/EN/10.31083/j.ejgo4205139.

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