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Locally advanced vulva cancer: a single centre review of anovulvectomy and a systematic review of surgical, chemotherapy and radiotherapy alternatives. Is an international collaborative RCT destined for the “too difficult to do” box?

Authors

Rachel Louise O'Donnell a,b, Leen Verleye a,c, Nithya Ratnavelu a, Khadra Galaal d, Ann Fisher a, Raj Naik a

Northern Gynaecological Oncology Centre, Queen Elizabeth Hospital, Gateshead, NE9 6SX, UK

a. Northern Institute for Cancer Research, Newcastle University, Medical School, Framlington Place, NE2 4AH, UK
b. Northern Institute for Cancer Research, Newcastle University, Medical School, Framlington Place, NE2 4HH, UK
c. Present address: Belgian Health Care Knowledge Centre (KCE), Doorbuilding, Boulevard du Jardin Botanique 55, Brussels, Belgium
d. Present address: Royal Cornwall Hospital, Truro, Cornwall, TR1 3LJ, UK

Email addresses

Rachel O'Donnell: Rachel.O'Donnell@newcastle.ac.uk
Leen Verleye: Leen.Verleye@kce.fgov.be
Nithya Ratnavelu: Nithya.Ratnavelu@ghnt.nhs.uk
Corresponding Author:

Rachel O’Donnell, Northern Gynaecological Oncology Centre, Queen Elizabeth Hospital, Sheriff Hill, Gateshead, NE9 6SX, UK

Email: Rachel.O'Donnell@newcastle.ac.uk

Tel: +44 (0)191 445 2445 / +44(0)7766312646

Fax: +44(0)191 445 6192

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Abstract

**Introduction**
Treatment of locally advanced vulva cancer (LAVC) remains challenging. Due to the lack of randomised trials many questions regarding the indications for different treatment options and their efficacy remain unanswered.

**Methods**
In this retrospective study we provide the largest published series of LAVC patients treated with anovulvectomy, reporting oncological outcomes and morbidity. Additionally, a systematic literature review was performed for all treatment options 1946 - 2015.

**Results**
In our case series, 57/70 (81%) patients were treated in the primary setting with anovulvectomy and 13 patients underwent anovulvectomy for recurrent disease. The median overall survival (OS) was 69 months (1-336) with disease specific survival of 159 months (1-336). Following anovulvectomy for primary disease, time to progression and OS were significantly higher in node negative disease (10 vs. 96 months; 19 vs. 121 months, p<0.0001). Post-surgical complications were observed in 36 (51.4%), the majority of which were Grade I/II infections. There was one perioperative death.

Review of the literature showed that chemotherapy, radiotherapy or combination treatments are alternatives to surgery. Evidence relating to all of these consisted mostly of small retrospective series, which varied considerably in terms of patient characteristics and treatment schedules. Significant patient and treatment heterogeneity prevented meta-analysis with significant biases in these studies. It was
unclear if survival or morbidity was better in any one group with a lack of data reporting complications, quality of life, and long term follow-up. However, results for chemoradiation are encouraging enough to warrant further investigation.

**Conclusions**
There remains inadequate evidence to identify an optimal treatment for LAVC. However, there is sufficient evidence to support a trial of anovulvectomy versus chemoradiation. Discussions and consensus would be needed to determine trial criteria including the primary outcome measure. Neoadjuvant chemotherapy or radiotherapy alone may be best reserved for the palliative setting or metastatic disease.

**Word Count:** 299

**Key Words:** Locally advanced vulval cancer (LAVC); anovulvectomy; colostomy; chemoradiation; exenteration
**Introduction**

Surgery forms the cornerstone of management of vulval cancer. Approximately one third of vulval cancer patients present with locally advanced vulval cancer (LAVC)[1], for which there is little consensus regarding its definition. We have defined LAVC as cancers which encroach upon or cross the borders with surrounding structures such as the urethra or anus. Interest in non-surgical alternative more conservative approaches for this subset of women stems from the recognised psychosexual sequelae and physical morbidity associated with radical surgical resection and in particular, the need for a stoma. There has been little progress made in the last 20 years in the development of guidance for treatment of LAVC and it should be acknowledged that the evidence to date for managing LAVC is entirely based on small phase II trials, uncontrolled studies or retrospective case series without matched controls. It is therefore difficult to group or compare patients owing to the significant heterogeneity in both the patient populations as well as variation in the treatment approach and the complicating factor that many patients treated by primary chemoradiation would have been considered unsuitable for surgery by numerous institutions. Modern medicine dictates the use of evidence-based medicine and in this review we collate the available evidence for surgical management as well as the alternative approaches of chemotherapy, radiotherapy and combination modalities.

In addition, we provide our institute's experience of the surgical management of locally advanced peri-anal tumours treated with anovulvectomy, which comprises the largest series from a single tertiary centre over 36 years and report the oncological outcomes and morbidity. Finally, we discuss the need and feasibility of a clinical trial to address many of the unanswered questions.
Methods

Case Series
A retrospective review of women, 1978 – 2014, with LAVC treated by anovulvectomy at the Northern Gynaecological oncology Centre, UK was conducted. Data from operative records, pathology reports, medical records, the MDT database and death certificates were accessed in conjunction with morbidity data from the prospectively collected departmental database.

The staging workup for patients with LAVC is not standardised. In our institute all patients underwent examination under anaesthesia and preoperative imaging (MRI /CT, from 1990) to define extent of local tumour, lymph node status and presence of distant metastatic disease. PET has been introduced in more recent years to evaluate metastatic disease. In primary diagnosed cases, bilateral groin node dissection (BGND) was also performed. The operative procedure is described in Supplementary Box 1. All vulval biopsies and excision specimens were reported as advised by the Royal College of Pathologists’ Standards and datasets for reporting cancers [3]. The new FIGO staging (2009) was retrospectively determined in all cases predating the revised guidelines [4]. Follow-up was to the last date seen in the outpatient clinics, or last contact by patient or GP.

Primary oncological outcomes included time to progression and overall survival (OS). Univariate associations between these endpoints and other variables were examined using Chi² or Fisher's exact test, as appropriate. Secondary outcomes focused upon treatment-related morbidity. Peri-operative and long-term side-effect frequencies were reported. For OS, patients who died at follow-up (any cause) were considered uncensored, whereas patients alive at last follow-up, or lost to follow-up
were censored. Univariate analyses for OS and PFS were generated by Kaplan–Meier survival curves and log-rank (Mantel–Cox) tests for statistical significance.

**Systematic Literature Review**

The aim of this systematic review was to assess the evidence for the impact of surgery, radiotherapy, chemotherapy, and combination chemoradiation treatments on survival in patients with histologically proven LAVC. The secondary objective was to assess associated morbidity with each of these treatment modalities including preservation of anus.

A systematic literature search was conducted in December 2015 using the PRISMA guidance [5]. MEDLINE (1946 to 2015), EMBASE (1980 to 2015), Web of Science and relevant Cochrane registers were searched. Controlled vocabularies and key words that were related to “vulva* cancer*/carcinoma*/malignan*/neoplasm*”, “anovulvectomy”, “exenteration”, “chemotherap*” and “radiotherap*/radiation” were used in a search strategy. In addition, hand searching the reference lists of previous related review articles was performed. Title/abstract screening, full-text review, data extraction, and quality assessment were performed. Data regarding the patient group, treatment modality regimen, secondary treatments and survival was extracted along with reported morbidity, where available. Articles without an available English translation and case studies of single patients were excluded. Both prospective and retrospective studies were included.

**Results**

**Case Series**

In the 36 year study period 70 patients underwent anovulvectomy for primary or recurrent LAVC. The median age of diagnosis was 69 years (30 - 91) with 68/70
(97.1%) squamous cell carcinomas, one adenocarcinoma and one adenoid cystic carcinoma. 57/70 (81.4%) patients underwent anovulvectomy as primary treatment for histologically-proven vulval cancer, 56 of which underwent BGND. One patient with a Bartholin’s gland SCC did not undergo lymphadenectomy.

Median length of follow-up for the entire cohort (primary and recurrent disease) was 39 months (0 - 336 months). 19/70 (27.1%) patients received adjuvant treatment post-operatively; 17 of whom received groin radiotherapy for groin node metastases (+/- vulva radiotherapy for close resection margin(s)); one had chemotherapy, and one had combination chemo-radiation for extra-pelvic node metastases.

**Anovulvectomy for primary treatment of LAVC**

For the primary surgery group (n=57), 12 (21.1%) had Stage II, 37 (64.9%) had Stage III and 8 (14.0%) had Stage IV, Table 1. The median tumour size was 70 mm, (20 - 200 mm) in the single largest diameter. All tumours reached near the anal margin and for one patient there was suspicion of a recto-vaginal fistula. Surgical margin, following fixation, ranged from 0 (disease at margin) to 17 mm, with a median margin of 5 mm. Complete primary closure of the vulval wound was achieved in 21 (36.8%) cases. The remaining patients had the vulval wound left partially or completely open to heal by secondary intention. No cases underwent reconstructive or plastic surgery. There was no delay in receiving adjuvant therapy in the 19 patients in whom this was indicated, due to vulval wound complications.

Of the 24 (42.1%) patients with margins less than 8 mm after fixation, 21 had tumours greater than 50 mm in their largest diameter. Two patients underwent further surgical excision and 10 received further treatment with radiotherapy. 25
(43.9%) patients had one or more positive groin nodes, of which 12 (21.1%) were bilateral.

Survival for all cases was not significantly associated with age, tumour size or resection margin. However, survival was positively associated with lymph node status and stage. As expected, prognosis was significantly worse in node positive disease in comparison to node negative disease, Figure 1, Table 1. Median time to progression in the node positive group was 10 months, in comparison to 96 months in the node negative group, log-rank, p<0.0001. Median OS was 19 months in node positive disease in comparison to 121 months in node negative disease, log-rank, p=0.0010, Figure 1.

**Anovulvectomy for locally recurrent disease**

The 13 patients who underwent anovulvectomy as treatment for recurrent vulval cancer included 4 (30.8%) patients with Stage 1 disease, 7 (53.8%) with Stage 2 and 2 (15.4%) with Stage 3 disease. All patients were managed primarily with surgical excision, four of which had undergone previous multiple surgical procedures. Twelve patients had previously undergone lymphadenectomy (1/12 node positive) and two patients had also received groin radiotherapy. The median disease free interval following primary treatment was 72 months (range 7 - 336 months). Following treatment of recurrent LAVC with anovulvectomy only one patient had complete primary closure of the vulval wound, with the remaining 12 patients having partially or completely open vulval wounds to heal by secondary intention. Following anovulvectomy, the median time to further disease recurrence was 14 months (0-76) with additional median survival following anovulvectomy of 25 months (0-156).
Morbidity

Median duration of hospitalisation after surgery was 16 days (range 1 – 90). The length of stay reduced with time reflecting developing clinical practice with a median inpatient stay of 29 days in 1990s compared with only 14 days in 2000s. 41/70 (58.6%) patients experienced one or more post-operative complications. 81.3% of which were Clavien Dindo Grade I/II and the majority of which were superficial wound breakdown or minor infective complications, which resolved following antibiotic therapy. There were 11 cases of post-operative lymphoedema and six stoma complications, with one patient requiring refashioning of the colostomy before discharge. There was one peri-operative death, caused by a myocardial infarction (MI) on post-operative day 4. A further five patients experienced treatment related complications which included two MIs, one cerebrovascular accident and three pulmonary emboli. During follow-up, five patients reported vaginal prolapse and elected to undergo prolapse surgery and there were three patients who reported symptoms resulting from the rectal stump. Of those that had died, 27 (67.5%) died of disease, and 13 died of other causes, the majority of which were secondary to advanced cardiological or respiratory co-morbid conditions.

The rate of complications observed in this series is low in comparison to similar case series treated with pelvic exenteration. In one exenteration case series, in which the indication for exenteration was primary LAVC in the majority, the authors report a mortality rate of 7%, of which intra-operative mortality accounted for 3.5% [6]. Additionally, with exenteration major complications occurred in 42.9%, with early complications including massive bleeding from the sacral plexus, adult respiratory distress syndrome, acute renal failure, ureteric injury, re-operation and pulmonary
embolus. This is further supported by several other reports in gynaecological series [7-9].

**Literature Review**

191 articles were identified from the initial search for further evaluation. A majority were review articles published in oncology journals or case series with 43 studies included in the review. There were no randomised controlled trials (RCTs) directly comparing the different treatment modalities and no case controls in the studies included. The heterogeneity of articles and differences in definitions and outcomes made this unsuitable for a meta-analysis.

**Radical Surgery (n=12 studies)**

It is largely accepted that if it is possible to resect the primary tumour with clear surgical margins without damaging the urethra or anal sphincter leading to urinary or faecal incontinence, primary surgical excision is typically the preferred treatment.

When the disease involves the anus, rectum, rectovaginal septum, proximal urethra, or bladder, in order to obtain adequate surgical margin, some form of pelvic exenteration may be required necessitating permanent colostomy and/or urinary diversion and therefore may only be appropriate in carefully selected cases. Since the 1970s pelvic exenteration has been repeatedly discussed and evaluated in small studies [10-12], with variable oncological outcomes and varying degrees of associated morbidity [13, 14], Table 2. Historically, 5-year survival after pelvic exenteration for vulval cancer has been reported around 50%, but, survival is related to lymph node status, with a poor prognosis when groin lymph nodes are found to be positive [15-18].
As alternatives to exenteration there have been several published series, including a series by Hoffman et al who described the use of radical local excision (complete anal resection without colostomy, anal resection with partial resection of the sphincter, and partial removal of the anal skin) [19]. This however resulted in faecal incontinence in 100% of the first group, 50% of the second and 11% of the third. Adams et al reported on the use of proctectomy combined with vulvectomy and BGND in a small series of five patients [20]. This was a single-step procedure, with stapling of the rectum and creation of a transverse colostomy and mucus fistula. It was not possible to comment on long-term survival as only 3/5 patients were alive and free of disease after a relatively short period of follow-up. A small series from our own institution (n=23) [21], which has been included in the case series in this review, reports the use of anovulvectomy for LAVC. This approach offers a treatment with good survival outcomes and with relatively low morbidity.

When considering all radical surgery collectively, surgery has a reported post-operative mortality rate ranging from 0% to 20%, with a mean of about 4% [1]. Psychological morbidity can also be considerable but there is a lack of robust published evidence to quantitate or assess it directly. Sexual impact of vulvectomy has not been assessed however, a systematic review and meta-analysis on quality of life after surgery for rectal cancer, found no significant differences in quality of life in rectal cancer patients with a permanent stoma when compared to non-stoma patients [22, 23]. No similar data is available for LAVC.

Overall when considering all surgical approaches, including exenteration as well as our series of anovulvectomy, surgical excision has been shown to result in good survival outcomes. The cumulative disease-free survival is reported at 46% overall and as with early stage vulval cancer, prognosis correlates well with lymph node
status [1]. This is frequently at the cost of performing a stoma but data reporting the physical and psychological consequences of this is lacking.

Reconstructive surgery

A full discussion of reconstructive surgery following radical excision of LAVC is out with the scope of this review but it should be acknowledged that reconstructive options includes skin grafting as well as the use of flaps. Skin grafting is challenging in this area as it is difficult to avoid shearing forces and infection with delayed healing or graft loss being common [24]. Contractures can also be problematic, interfering with functions such as urination and intercourse [25]. Additionally, if patients have previously received local radiotherapy, reconstructive surgery is more challenging and may be associated with higher rates of morbidity. There is a lack of evidence comparing primary/secondary closure with reconstructive surgery.

Neoadjuvant radiotherapy (n=5 studies)

Over the last 2 decades, the use of primary radiotherapy (RT) for patients with stage III-IVA vulval cancer increased from 18% in 1988 to 30% by 2008 [26]. Boronow et al first reported neoadjuvant RT followed by surgical resection as an alternative to pelvic exenteration in 1982 [27]. In this series of 48 patients, 77% received preoperative RT followed by radical vulvectomy. No residual disease was identified in 42.5% of surgical specimens and exenteration was performed in four cases. The 5-year survival rates were 75.6% for the primary cases, 62.6% for the recurrent cases, and an overall 72% for all 48 cases treated. Hacker et al published similar findings in eight patients treated with preoperative RT with satisfactory shrinkage of tumour in 87.5%, [28]. However, in the series of 16 patients, 11 of which had perianal disease, treatment by RT to the vulva, inguinal and pelvic nodes, followed by radical vulvectomy and lymphadenectomy, failed in 6 (37.5%) patients, necessitating
colostomy formation [29]. Despite macroscopic excision margins of 2 cm, 5/14 showed microscopic disease within 1 cm of the margin, three of which later developed local recurrence and a further 25% of patients developed central recurrence disease.

Although the data are limited, it appears that preoperative RT alone (45-54 Gy EBRT ± 24 Gy brachytherapy) may downsize of the tumour in 70% - 85% of patients, reducing the need for exenterative surgery. This is unavoidable in some, see Table 3. Additionally, this approach is also associated with significant morbidity. Following neoadjuvant RT, surgery and subsequent healing may be compromised by poor local blood supply and lymphatic drainage. Radiotherapy also carries risks of skin desquamation, wound cellulitis with subsequent prolonged hospitalisation, bowel and bladder toxicity and contractures. Furthermore, a temporary bowel diversion may be required for patients to be able to tolerate and complete a course of radiation therapy. Even with combined therapy, 50-70% of advanced stages may recur [30]. Further data upon short and long-term morbidity as well as survival are needed.

Based upon a reasonably good response rate from these series, further investigation of this modality appears warranted especially in groin node positive cases where radiotherapy to the groins may be given simultaneously and where the long term prospects appear to be poor with all of the treatment options.

**Neoadjuvant chemotherapy (n=5 studies)**

Different chemotherapy regimens have been used in LAVC with varying degrees of success, Table 4. All of the studies suggest that vulval cancer responds to chemotherapy to a variable extent and there is evidence that some cancers can be rendered more operable. In an EORTC Phase II study of neoadjuvant treatment with
triple combination therapy (Bleomycin, methotrexate and lomustine) complete response was seen in only 8%, and partial response in 48% [31]. The 1 year survival was only 32% and this regimen was associated with major haematological side effects and mild signs of bleomycin-related pulmonary toxicity. In another series of 21 stage IV patients, Benedetti-Panici, et al reported partial response in the size of the primary tumour in two patients and partial/complete response in the inguinal node disease in 14 patients [32]. All patients required radical vulvectomy but the therapeutic results were poor with a 3-year survival of 24%. Sixty-eight percent of the operated patients recurred 3-17 months from the end of treatment and 50% of them had a distant relapse.

Giesler et al showed no clinical response with cisplatin alone but partial clinical response following combination treatment with cisplatin and 5-FU [33]. All patients underwent radical vulvectomy following NACT and the anal sphincter and urethra were conserved in all patients receiving combination chemotherapy.

Recurrence remains a problem even after successful surgical removal of residual disease with 20/27 patients who completed treatment with NACT followed by surgery developing local/nodal recurrences in one study [34]. Toxicity of chemotherapy may also be problematic with severe haematological toxicity and gastro-intestinal toxicity all being well documented.

Overall, the role of neoadjuvant chemotherapy appears limited but may serve a role in those cases unsuitable for surgery or radiotherapy treatments, in those with distant disease or in the palliative setting in select cases.
**Concurrent chemoradiation with or without subsequent surgery (n=19 studies)**

The addition of chemotherapy concurrent with RT for LAVC was influenced by advances in the treatment of anal squamous cell carcinomas, which showed improved local control and colostomy-free survival with the addition of fluorouracil (5-FU) and mitomycin C [35, 36]. Several small studies have assessed the feasibility and activity of concomitant chemoradiation in a neoadjuvant setting followed by tailored surgery for LAVC with a variety of regimens and agents used, Table 5.

The combination of bleomycin and RT was disappointing [37, 38]. The use of RT with single-agent 5-FU or 5-FU with mitomycin C [39-46] or 5-FU with cisplatin [47-55] has demonstrated variable but promising response rates. The GOG undertook a phase II trial (GOG 101) to determine feasibility of using preoperative chemoradiation (5-FU with cisplatin) [56]. 71 patients underwent treatment with chemoradiation followed by surgical excision and BGND, which resulted in an overall response rate of 46.5%. Only 2.8% had residual unresectable disease, and among the 50 patients initially requiring exenterative surgery, only one patient necessitated exenteration and two required colostomy. At a median follow-up of 50 months, 32.9% developed recurrence and 54.9% were alive without recurrent disease. The authors concluded that toxicity was acceptable, with acute cutaneous reactions to chemoradiation and surgical wound complications being the most common adverse effects.

The subsequent GOG 205 Phase II study using a combination of weekly cisplatin with RT resulted in complete clinical response in 37/40 (92.5%) patients. Of the 34 patients who underwent biopsy, 29 had a complete pathologic response. The
authors concluded that this combination of therapy successfully yielded high, complete clinical and pathologic response rates with acceptable toxicity [57].

Despite these findings, a Cochrane review of five series concluded that the combination of chemoradiation and radical surgery is associated with significantly more morbidity than either treatment given on its own [58]. The combination of 5-FU and mitomycin C is associated with high rates of toxicity and subsequently this regimen has not been used in the newer chemoradiation studies in other cancer types. Skin and subcutaneous atrophy is common and wound breakdown occurs in 20–31% of the patients [25]. Severe complications can include bowel perforation, bowel obstruction, avascular hip necrosis, and toxic deaths. Surgical interventions after chemoradiation have high complication rates and the impact of tumour bed resection in cases of complete remission is unclear [24]. Additionally, acute toxicities may necessitate radiotherapy interruptions and dose modifications, compromising its treatment effect [59].

Collectively available studies have demonstrated that pre-operative combination chemoradiation is feasible and may reduce the need for more radical surgery. However, this is at a cost of a lower local control rate compared with primary surgery.

**Concurrent chemoradiation versus surgery (n=3 studies)**

Scarse prospective data are available on the treatment of LAVC in the curative setting with primary chemoradiation without planned surgery. A systematic review specifically comparing chemoradiation in LAVC to other treatment modalities by Shylasree et al [60] included two retrospective series [46, 61] of primary chemoradiation versus primary surgery and one RCT [62] of neoadjuvant
chemoradiation versus primary surgery in patients with operable disease. None of the studies showed a survival benefit for either treatment option and no differences in morbidity could be demonstrated. However, study populations are small and the RCT discussed has not been published as a full paper version. In addition, reporting of morbidity was incomplete and none of these studies include data on quality of life [60].

**Targeted Therapies**

There are no published trials of targeted biological agents in LAVC. There is however one ongoing Phase II study of Pazopanib (a tyrosine kinase inhibitor and vascular endothelial growth factor inhibitor) registered with the Clinical Trials Register, which includes advanced vulval cancer as well as other gynaecological malignancies[63].

**Recurrent disease**

The majority of case series and studies to date have focused upon the treatment of LAVC in the primary setting. Although some cases of recurrent disease have been included in some reports overall there is little published evidence addressing the specific needs of this group of patients.

**Discussion**

It would appear from the literature review, which includes our own institute’s experience of anovulvectomy, that there remains a strong case for surgical management of LAVC, especially in node negative cases, with good reported disease specific survival. Our study of anovulvectomy presents the outcomes from a single institution across nearly 5 decades, wherein management policies have remained relatively unchanged. We conclude that radical anovulvectomy is at least
an equivalent treatment in terms of survival with disease specific survival of 35 months (1-336). Surgery however carries with it the physical and psychological morbidity including procedure related morbidity, physical disfigurement, psychosexual sequelae and a largely unknown impact on overall quality of life. Studies from colorectal patients with stomas suggest that the impact is less than many speculate but definitive studies of this are lacking in our cohort. The morbidity reported in this case series is modest with complications occurring in 41 (58.6%) patients and we believe that the risk of surgical complications can be reduced by good surgical technique by surgeons experienced in management of advanced vulval cancer alongside high quality peri-operative care and careful patient selection. Given the location of many LAVCs, many patients present with pain and physical limitations. Therefore, surgery may also be indicated for rapid palliation of disabling symptoms.

The alternative approach of chemoradiation remains experimental but the data for this multimodal treatment, especially in the neoadjuvant setting has reported good survival, comparable to that of surgery, and has also been shown to result in a reduction in the rate of stoma formation. Stomas however may still be necessary in a proportion of patients. The extent of treatment related side effects are not well described, especially in those who still require surgical excision, but there is a suggestion that the combination of chemo, radiotherapy and surgery, albeit it a more conservative excision, may still result in significant morbidity and it is unclear if these cumulative treatment-related side effects result in more of an impact upon overall quality of life in comparison to stoma formation. Conversely, a proportion of patients who undergo upfront anovulvectomy with narrow resection margins or positive lymph
nodes will require radiotherapy and it is unclear if this treatment order results in less morbidity and better outcomes in comparison to neoadjuvant chemoradiation.

The literature for the use of chemotherapy in the treatment of LAVC is relatively clear, confirming our concerns. In comparison to radical surgery, chemotherapy has been shown to be associated with poor survival and significant treatment related toxicity. It is our view that chemotherapy is therefore best reserved for use in the palliative setting, in patients with distant disease, or where the presence of significant co-morbidities precludes chemoradiation or surgical treatments.

The ideal alternative treatment would improve both survival and quality of life, without increasing complications and morbidity but it is clear that there is no universal recommendation that can be made for all patients. Accepting that many patients affected by LAVC are largely elderly, often with significant morbidity, many may not be suitable for all treatment modalities and therefore we still need to maintain a degree of personalisation of care. Survival outcomes should be considered alongside the associated side-effect profiles of each modality enabling appropriate treatments to be selected for each individual. However, for those patients whose treatment options are not restricted there remain many unanswered questions.

Despite a number of publications from recognised institutions, uncertainty regarding optimal treatment remains and it is unlikely that additional case series will add sufficient evidence to dictate a change in current practice. LAVC however represents a relatively small proportion of any individual institutions’ caseload and it is evident that different centres have their own approach. These variations in treatment practices represents a state of clinical equipoise presenting the opportunity to
explore this dilemma and answer the question of optimal treatment in a clinical trial. To our knowledge, there are currently no plans for any randomised trials. Published series to date have supplied the baseline data necessary for such a study providing an understanding of the important clinical endpoints. It is not disputed that any RCT in this cohort of patients will have its own limitations owing to the rarity of LAVC, the complicating factors of variable tumour size, patient comorbidities and difficulties in randomisation. However, accepting that these are limitations that can be overcome through consensus we present the basis of a RCT where these factors would need to be debated.

Topics for debate include: 1) designing the control and investigational arms of an RCT. Based upon the observed good survival seen in the review of radical surgical resection, and the achievement of local disease control and symptoms, we propose radical surgery to be the standard treatment arm. In light of the promising survival outcomes achieved with chemoradiation alongside a possible reduction in the need for radical surgery including stoma formation, we recommend chemoradiation with or without additional tailored surgery for the investigational arm.

2) Sample size and feasibility. One of the greatest anxieties about an RCT in this setting is the ability to recruit adequate numbers of patients with sufficient follow-up. A primary outcome of a modest survival difference of 5-10% between the two arms, powered to 90% with significance set at p=0.05, two tailed (as uncertainty as to which treatment would provide an improved survival) would require a sample size of approximately 500 patients, which is not unrealistic in an international setting. Alternatively, an RCT powered to show equivalence in terms of survival with the primary outcome measures of quality of life and/or morbidity may provide a more
robust assessment of these very relevant aspects but would necessitate a larger sample size.

3) Outcome measures. For many clinicians and patients endpoints relating to quality of life may be considered the most important, in particular the impact of stoma formation. The challenges of selecting the methodologies for assessment of such endpoints may however be complex and although there are several validated questionnaires available for assessment of psychosexual health, anatomical disfigurement, incontinence and overall quality of life, it is not clear if they are all suitable for this study and consensus for their use would be required. Incorporation of evaluation of QALYs and cost-effectiveness of each treatment modality is also desirable but may be challenging in an international setting.

4) Inclusion, exclusion criteria and stratification. Despite the variable approaches to treatment all published studies show a clear stratification of cases in terms of survival according to lymph node status. Without prior stratification of patients by node status, sub group analysis for both survival and qualitative measures would be required. This could be compensated for in the initial sample size calculation or patients with node positive disease could be excluded from the randomisation. Owing to the poor survival universally seen in node positive disease, these patients should be considered for a more conservative approach and analysed separately from the rest of the cohort

5) Pre-treatment investigations. The question of how to clarify nodal status prior to selection of treatment modality therefore needs to be addressed and without consensus on how lymph node status should be determined radiological assessment
(CT/MRI/PETCT) or surgical sampling should be considered for inclusion in the study protocol.

6) Treatment regimens. Within the surgical treatment arm, the heterogeneous nature of the anticipated procedures performed may complicate analysis with the need for inclusion of surgical complexity scores, measures of surgical quality assurance, patient reported evaluation of disfigurement, impact upon quality of life including psychosexual issues necessary to enable holistic evaluation of the selected treatment. The optimum chemoradiation treatment schedule to be used also requires clarity with a variety of regimens described in the literature. In addition, evaluation of response to chemoradiation will also require standardisation with a need for clinical and histological confirmation of response, particularly if a secondary surgical excision is deemed unnecessary.

Accepting that there are numerous and complex issues to take into consideration, it is also clear that we are in a state of clinical equipoise with evidence that can be best described as conflicting, biased and inadequate. Due to the rarity of the condition and the lack of patient support groups in vulva cancer promoting and demanding better research in this cancer site it is not surprising that it features low in the priority list of most national and international research groups rendering it into a “Cinderella” status. So we should ask ourselves, is locally advanced vulvar cancer really in the “too difficult to do” box?

**Conclusion**

Treatment of LAVC with radical surgery, including anovulvectomy continues to be a standard of care which results in good survival outcomes and acceptable morbidity. Neoadjuvant chemotherapy or radiotherapy alone may be best reserved for the
palliative setting or metastatic disease. There is also evidence to support the alternative approach of chemoradiation as the investigational arm of a definitive RCT. Direct comparisons with the standard approach of radical surgery are required to address the uncertainty of survival outcomes, morbidity and quality of life measures between the two treatment approaches.

**Contribution to Authorship**

RN devised the study, supervised the data collection and contributed to data analyses and discussions. ROD, LV and KG collected the data. ROD and ADF performed data analyses and drafted the manuscript. All authors contributed to the discussions and approved the final manuscript.

**Conflict of interest**

The authors certify that they have no affiliations with or involvement in any organisation or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript. All authors certify that this material or similar material has not been and will not be submitted to or published in any other publication.

**Details of Ethics Approval**

This audit of clinical service provision was prospectively registered with the SafeCare & Audit Department and ethics approval was not necessary.

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Not applicable
**Table Legends**

Box 1: Operative Anovulvectomy Procedure

Table 1: Table of patient demographics, histopathological diagnoses and survival

Table 2: Radical surgery

Table 3: Neoadjuvant radiotherapy

RT = radiotherapy; BGND = bilateral groin node dissection; EBRT = external beam radiotherapy; Gy = Gray

Table 4: Neoadjuvant chemotherapy

CDDP = cisplatin; Bleo = bleomycin; MTX = methotrexate; EBRT = external beam radiotherapy; 5-FU = 5-fluorouracil.

Table 5: Concurrent chemoradiation with or without subsequent surgery

Adapted from [69]. 5-FU = Fluorouracil; MitC = Mitomycin; CDDP = Cisplatin
Tables and Figures

**Box 1 Operative Anovulvectomy Procedure**

Examination under anaesthesia is performed to assess the extension of the tumour and groin node involvement.

A catheter is inserted and the patient is in a supine position. Pre-1990 a midline laparotomy was performed to assess the abdominal and pelvic cavity for metastasis and pelvic and para-aortic lymph node involvement. If palpable lymph nodes were found, a pelvic lymph node dissection was performed. This was later omitted in patients with no radiological evidence of lymphadenopathy. A permanent sigmoid end colostomy was formed, with stapling or oversewing of the distal segment of bowel. The midline laparotomy incision was later modified to a parastomal incision.

In primary diagnosed cases, bilateral groin node dissection is performed with separate linear groin incisions [2]. Closed suction drains are placed in the groin wounds and are maintained for 5 days post-op.

The patient is moved to the lithotomy position and radical excision of the vulval tumour is performed with the limits of the excision marked at 15-20 mm from the tumour edge, aiming for margins >10 mm after fixation. The exact limits will vary depending upon the location and extent of the lesion. Up to 2 cm of the distal urethra can be excised without interfering with continence. The anterior limit of the resection is grasped with Littlewood forceps and the incision deepened to the deep fascia. The entire vulva is then removed by sharp dissection in a posterior direction. The rectum is isolated by dissecting it from its surrounding tissue and from the pubococcygeus attachment. Next, the rectum is separated from the vaginal attachment. With traction
applied to the surgical specimen, the rectum is cross-clamped, ensuring adequate margins. The rectal stump edges are oversewn for haemostasis and the stump is left open to allow drainage. The vulval defect produced is either closed primarily or left open and allowed to heal by secondary intention and a urethral catheter inserted. Interrupted deep mattress sutures reduce dead space and appose skin edges, where possible, without undue tension. The area is sutured down to the point a short distance above the urethral orifice to avoid a hood over the urethral opening. Thereafter the remainder of the vulva can be covered by opposing the lateral cut edge with the vaginal mucosa. At the end of the procedure it is usual to insert a bladder catheter which is maintained until vulval oedema has resolved.

Post-operative care focuses upon prevention of wound complications with meticulous wound care, prevention of pain, constipation, and venous thromboembolism and early mobilisation. Sutures can typically be removed after 7 days.
<table>
<thead>
<tr>
<th></th>
<th>Median (range) / n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Age</strong></td>
<td>69 (30 - 91)</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>57 (81.4)</td>
</tr>
<tr>
<td>Recurrent disease</td>
<td>13 (18.6)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
</tr>
<tr>
<td>Recurrent disease</td>
<td>13 (18.6)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>12 (17.1)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>37 (52.9)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>8 (11.4)</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>67 (95.7)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>1 SCC Barts</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>1 Adenoid Cystic Carcinoma</td>
<td></td>
</tr>
<tr>
<td><strong>Differentiation</strong></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>14 (20.0)</td>
</tr>
<tr>
<td>Moderate</td>
<td>26 (37.1)</td>
</tr>
<tr>
<td>Poor</td>
<td>30 (42.9)</td>
</tr>
<tr>
<td><strong>Time to recurrence (months)</strong></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>12.0 (0 - 122)</td>
</tr>
<tr>
<td>Recurrent disease*</td>
<td>14.2 (0 - 76)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>41.0 (6 - 96)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>14.0 (2 - 122)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>5.0 (1 – 38)</td>
</tr>
<tr>
<td><strong>Overall Survival (months)</strong></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>20.0 (1 - 336)</td>
</tr>
<tr>
<td>Recurrent disease**</td>
<td>24.0 (0 – 156)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>40.7 (12 - 121)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>18.0 (3 - 122)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>8.2 (1.5 – 77)</td>
</tr>
<tr>
<td><strong>% 1 yr Survival</strong></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>83.1</td>
</tr>
<tr>
<td>Recurrent disease**</td>
<td>91.7</td>
</tr>
<tr>
<td>Stage 2</td>
<td>100.0</td>
</tr>
<tr>
<td>Stage 3</td>
<td>84.4</td>
</tr>
<tr>
<td>Stage 4</td>
<td>37.5</td>
</tr>
<tr>
<td><strong>% 5 year Survival</strong></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>39.6</td>
</tr>
<tr>
<td>Recurrent disease**</td>
<td>25.0</td>
</tr>
<tr>
<td>Stage 2</td>
<td>66.6</td>
</tr>
<tr>
<td>Stage 3</td>
<td>50.0</td>
</tr>
<tr>
<td>Stage 4</td>
<td>12.5</td>
</tr>
<tr>
<td><strong>Time to recurrence</strong></td>
<td></td>
</tr>
<tr>
<td>Node Positive</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Node Negative</td>
<td>10.0 (1 - 73)</td>
</tr>
<tr>
<td>Node Negative</td>
<td>96.0 (6 - 122)</td>
</tr>
<tr>
<td><strong>Overall Survival</strong></td>
<td></td>
</tr>
<tr>
<td>Node Positive</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Node Negative</td>
<td>19.0 (1 - 77)</td>
</tr>
<tr>
<td>Node Negative</td>
<td>121.0 (8 - 122)</td>
</tr>
</tbody>
</table>

*Time to next recurrence following anovulvectomy; **Additional survival following anovulvectomy
<table>
<thead>
<tr>
<th>Author</th>
<th>Ref</th>
<th>Year</th>
<th>No. patients</th>
<th>Primary/recurrent disease</th>
<th>Median age</th>
<th>Positive nodes</th>
<th>Treatment</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams et al</td>
<td>[20]</td>
<td>1979</td>
<td>5</td>
<td>5 primary</td>
<td>74 (52-74)</td>
<td>-</td>
<td>Vulvectomy + proctectomy</td>
<td>-</td>
</tr>
<tr>
<td>Philips et al</td>
<td>[15]</td>
<td>1981</td>
<td>16 (vulva/vaginal)</td>
<td>10 primary 6 recurrent</td>
<td>53.5 (33-75)</td>
<td>3/9</td>
<td>Vulvectomy + exenteration</td>
<td>2 yr: 56% 5 yr: 54%</td>
</tr>
<tr>
<td>Cavanagh et al</td>
<td>[16]</td>
<td>1982</td>
<td>13</td>
<td>13 primary</td>
<td>44 (27-69)</td>
<td>-</td>
<td>Vulvectomy + anterior/posterior/ total exenteration</td>
<td>5 yr: 50%</td>
</tr>
<tr>
<td>Hoffman et al</td>
<td>[19]</td>
<td>1989</td>
<td>24</td>
<td>24 primary</td>
<td>-</td>
<td>-</td>
<td>Partial/total anal resection +/- anovulvectomy</td>
<td>-</td>
</tr>
<tr>
<td>Remmenga et al</td>
<td>[64]</td>
<td>1991</td>
<td>5</td>
<td>5 primary</td>
<td>(47-67)</td>
<td>-</td>
<td>Vulvectomy + partial anal and rectal resection</td>
<td>-</td>
</tr>
<tr>
<td>Hopkins et al</td>
<td>[17]</td>
<td>1992</td>
<td>19</td>
<td>11 primary 8 recurrent</td>
<td>50 (40-74)</td>
<td>5/14</td>
<td>Anterior/posterior/ total exenteration</td>
<td>5 yr: 60%</td>
</tr>
<tr>
<td>Barton et al</td>
<td>[65]</td>
<td>1993</td>
<td>22</td>
<td>21 primary 1 recurrent</td>
<td>62 (24-85)</td>
<td>-</td>
<td>Radical vulvectomy with plication of the external anal sphincter and puborectalis muscles</td>
<td>-</td>
</tr>
<tr>
<td>Miller et al</td>
<td>[18]</td>
<td>1995</td>
<td>21</td>
<td>8 primary 13 recurrent</td>
<td>57 (34-74)</td>
<td>3/13</td>
<td>Anterior/posterior/ total exenteration</td>
<td>-</td>
</tr>
<tr>
<td>Maggioni et al</td>
<td>[66]</td>
<td>2009</td>
<td>106 (9 vulva)</td>
<td>Recurrent</td>
<td>54 (30-79)</td>
<td>-</td>
<td>Anterior/posterior/total exenteration</td>
<td>Median OS:16% (vulval)</td>
</tr>
<tr>
<td>Forner et al</td>
<td>[67]</td>
<td>2012</td>
<td>27</td>
<td>9 primary 18 recurrent</td>
<td>66 (35-81)</td>
<td>10/27</td>
<td>Anterior/posterior/total exenteration</td>
<td>5 yr: 67%</td>
</tr>
<tr>
<td>Kaur et al</td>
<td>[68]</td>
<td>2012</td>
<td>36 (8 vulva/vagina)</td>
<td>4 primary 32 recurrent</td>
<td>57 (35-81)</td>
<td>-</td>
<td>Anterior/posterior/total exenteration</td>
<td>5 yr: 44% (57% vulval/vaginal)</td>
</tr>
<tr>
<td>O'Donnell et al</td>
<td>[69]</td>
<td>2016</td>
<td>70</td>
<td>56 primary 14 recurrent</td>
<td>69 (30-91)</td>
<td>25/56</td>
<td>Anovulvectomy +/-BGND</td>
<td>69 (1-336) months 5 yr: 39.6% (primary and recurrent cases)</td>
</tr>
</tbody>
</table>
### Table 3: Neoadjuvant radiotherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Ref</th>
<th>Year</th>
<th>No pts</th>
<th>Primary/recurrence</th>
<th>FIGO Stage</th>
<th>Primary treatment</th>
<th>Pathologic response</th>
<th>Secondary Treatment</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boronow et al</td>
<td>[27]</td>
<td>1982</td>
<td>33</td>
<td>26 primary 6 recurrent</td>
<td>II: (1) III: 20 (5) IV: 3</td>
<td>RT or brachytherapy +/- EBRT</td>
<td>-</td>
<td>Vulvectomy +/- BGND 1 exenteration</td>
<td>65% (primary); 71% (recurrent)</td>
</tr>
<tr>
<td>Hacker et al</td>
<td>[28]</td>
<td>1984</td>
<td>8</td>
<td>Primary</td>
<td></td>
<td>EBRT (1 brachytherapy)</td>
<td>No residual disease 62.5%</td>
<td>Vulvectomy</td>
<td>62.5% (FU 15mths-10yrs)</td>
</tr>
<tr>
<td>Boronow et al</td>
<td>[69]</td>
<td>1987</td>
<td>48</td>
<td>37 primary</td>
<td>III: 20 IV: 4 Other: 3</td>
<td>RT or brachytherapy +/- EBRT</td>
<td>No residual disease 42.5%</td>
<td>Radical vulvectomy, 4 exenterations</td>
<td>5 yr 75.6%</td>
</tr>
<tr>
<td>Rotmensch et al</td>
<td>[29]</td>
<td>1990</td>
<td>16</td>
<td>Primary</td>
<td>III: 13 IV: 3</td>
<td>400 rad vulva, 4500 rad groins</td>
<td>12/16 regressed with RT; 62.5% preservation viscera</td>
<td>Radical vulvectomy</td>
<td>5 yr 45%</td>
</tr>
<tr>
<td>Pohar et al</td>
<td>[70]</td>
<td>1995</td>
<td>34</td>
<td>21 primary 13 recurrent</td>
<td>I: 2 II: 8 III/IV: 12</td>
<td>60 Gy (53-88 Gy) brachytherapy</td>
<td>-</td>
<td>Nil</td>
<td>5 yr 29%</td>
</tr>
</tbody>
</table>

*RT = radiotherapy; BGND = bilateral groin node dissection; EBRT = external beam radiotherapy; Gy = Gray*
<table>
<thead>
<tr>
<th>Author</th>
<th>Ref</th>
<th>Year</th>
<th>Retrospective /prospective</th>
<th>Primary /recurrence</th>
<th>Primary treatment</th>
<th>No. of cycles</th>
<th>Response</th>
<th>Secondary Treatment</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benedetti-Panici et al</td>
<td>[32]</td>
<td>1993</td>
<td>Prospective</td>
<td>21</td>
<td>CDDP, bleo, MTX</td>
<td>2-3</td>
<td>90% operability (79% radical surgery), 33% pathologic downstaging</td>
<td>79% radical surgery Progressive disease - EBRT</td>
<td>24 % 3 yr survival</td>
</tr>
<tr>
<td>Wagenaar et al</td>
<td>[31]</td>
<td>2001</td>
<td>Phase II prospective</td>
<td>12 primary, 13 recurrent</td>
<td>Bleo, MTX, lomustine</td>
<td>3</td>
<td>2 complete, 12 partial (overall 56%)</td>
<td></td>
<td>12% at 8 months. Median survival 7.8 months. 1-yr survival 32%</td>
</tr>
<tr>
<td>Geisler et al</td>
<td>[33]</td>
<td>2006</td>
<td>Prospective</td>
<td>13</td>
<td>10 pts: CDDP, 5-FU; 3 pts cis only</td>
<td>2-4</td>
<td>(CDDP + 5-FU): 9/10 partial, 1/10 complete. No measurable response (CDDP alone).</td>
<td>Radical vulvectomy +BGND</td>
<td>CDDP + 5-FU: mean survival 79 months; CDDP only: mean 9 months</td>
</tr>
<tr>
<td>Domingues et al</td>
<td>[71]</td>
<td>2010</td>
<td>Retrospective</td>
<td>25</td>
<td>10 pts Bleo (A); 5 pts paclitaxel (B); 10 pts 5-FU and CDDP (C)</td>
<td>3</td>
<td>(A) 60%; (B) 40%; (C) 20%</td>
<td>Radical vulvectomy 2/5 radical vulvectomy (C) 2/10 radical vulvectomy</td>
<td>70% 1 yr survival; 30% 5 yr survival; 60% / 20%; 10% 1 yr survival.</td>
</tr>
<tr>
<td>Aragona et al</td>
<td>[73]</td>
<td>2012</td>
<td>Prospective</td>
<td>35</td>
<td>12 pts CDDP + 5-FU; 6pts CDDP + paclitaxel, 6 pts CDDP + paclitaxel + 5-FU, 6 pts vincristine + bleo + CDDP; 5 pts bleo alone.</td>
<td>3</td>
<td>71.4% partial 5.7% stable</td>
<td>8 pts no surgery; 14 pts radical vulvectomy; 13 pts WLE: 2 pts posterior exenteration, vulvectomy, BGND</td>
<td>5 yr relapse free survival 89.5%. Mean relapse free OS 129.5 months (excluding pts who did not complete therapy) Local recurrence in 20 patients</td>
</tr>
</tbody>
</table>

CDDP = cisplatin; Bleo = bleomycin; MTX = methotrexate; EBRT = external beam radiotherapy; 5-FU = 5-fluorouracil.
Table 5: Concurrent chemoradiation with or without subsequent surgery

<table>
<thead>
<tr>
<th>Author</th>
<th>Ref</th>
<th>Year</th>
<th>No pts</th>
<th>Chemotherapy</th>
<th>Total radiation Dose (Gy)</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levin et al</td>
<td>[40]</td>
<td>1986</td>
<td>6</td>
<td>5-FU, MitC</td>
<td>20-25</td>
<td>OR = 100%</td>
</tr>
<tr>
<td>Thomas et al</td>
<td>[41]</td>
<td>1989</td>
<td>24</td>
<td>5-FU +/- MitC</td>
<td>36-64</td>
<td>cCR = 58%</td>
</tr>
<tr>
<td>Berek et al</td>
<td>[49]</td>
<td>1991</td>
<td>12</td>
<td>CDDP + 5-FU</td>
<td>44-54</td>
<td>cCR = 67%, OR = 91.7%</td>
</tr>
<tr>
<td>Russell et al</td>
<td>[50]</td>
<td>1992</td>
<td>25</td>
<td>5-FU + CDDP (n=11)</td>
<td>34-72</td>
<td>cCR = 80%, pCR = 40%</td>
</tr>
<tr>
<td>Koh et al</td>
<td>[42]</td>
<td>1993</td>
<td>20</td>
<td>5-FU + CDDP (n=5) or + MitC (n=1)</td>
<td>40-54</td>
<td>cCR = 50%, cPR = 40%</td>
</tr>
<tr>
<td>Sebag-Montefiore et al</td>
<td>[39]</td>
<td>1994</td>
<td>32</td>
<td>5-FU, MitC</td>
<td>45-50</td>
<td>cCR = 47%, OR = 81%</td>
</tr>
<tr>
<td>Eifel et al</td>
<td>[51]</td>
<td>1995</td>
<td>12</td>
<td>5-FU + CDDP</td>
<td>40-50</td>
<td>OR = 91%, pCR = 33%</td>
</tr>
<tr>
<td>Wahlen et al</td>
<td>[43]</td>
<td>1995</td>
<td>19</td>
<td>5-FU, MitC</td>
<td>45-50</td>
<td>cCR = 53%, cPR = 37%</td>
</tr>
<tr>
<td>Landoni et al</td>
<td>[45]</td>
<td>1996</td>
<td>58</td>
<td>5-FU, MitC</td>
<td>54</td>
<td>pCR = 31%</td>
</tr>
<tr>
<td>Lupi et al</td>
<td>[44]</td>
<td>1996</td>
<td>31</td>
<td>5-FU, MitC</td>
<td>54</td>
<td>OR = 94%</td>
</tr>
<tr>
<td>Cunningham et al</td>
<td>[52]</td>
<td>1997</td>
<td>14</td>
<td>5-FU + CDDP</td>
<td>45-65</td>
<td>cCR = 64%, OR = 92%</td>
</tr>
<tr>
<td>Leiserowitz et al</td>
<td>[53]</td>
<td>1997</td>
<td>23</td>
<td>5-FU (n=6), or 5-FU + CDDP (n=17)</td>
<td>54 (36-62.5)</td>
<td>7/9 no residual tumour at resection cCR = 14/23</td>
</tr>
<tr>
<td>Moore et al</td>
<td>[47]</td>
<td>1998</td>
<td>71</td>
<td>CDDP + 5-FU</td>
<td>47.6</td>
<td>cCR = 47%</td>
</tr>
<tr>
<td>Han et al</td>
<td>[48]</td>
<td>2000</td>
<td>54</td>
<td>5-FU + Mit C (n=14) or 5-FU + CDDP (n=6)</td>
<td>45 + 6-17 to gross disease</td>
<td>cCR = 54%</td>
</tr>
<tr>
<td>Akl et al</td>
<td>[54]</td>
<td>2000</td>
<td>12</td>
<td>5-FU + Mit C</td>
<td>30-36</td>
<td>ccR = 100%</td>
</tr>
<tr>
<td>Mulayim et al</td>
<td>[46]</td>
<td>2004</td>
<td>17</td>
<td>5-FU + Mit C or Mit C alone</td>
<td>32.4 (16.2-48)</td>
<td>cCR = 85.7% (combined) cCR = 0% (MitC alone)</td>
</tr>
<tr>
<td>Gerszten et al</td>
<td>[55]</td>
<td>2005</td>
<td>18</td>
<td>CDDP + 5-FU</td>
<td>44.6</td>
<td>cCR = 72%, OR = 100%</td>
</tr>
<tr>
<td>Gaffney et al (GOG 101 Phase II)</td>
<td>[56]</td>
<td>2009</td>
<td>71</td>
<td>5-FU + CDDP</td>
<td>47.5</td>
<td>OR = 46.5%</td>
</tr>
<tr>
<td>Moore et al (GOG 205 Phase II)</td>
<td>[57]</td>
<td>2010</td>
<td>40</td>
<td>CDDP</td>
<td>57.6</td>
<td>cCR = 69%</td>
</tr>
</tbody>
</table>

Adapted from [72]. 5-FU = Fluorouracil; MitC = Mitomycin; CDDP = Cisplatin
**Figure**

Kaplan–Meier survival curves for time to progression and OS in patients with all stages of vulval cancer treated with primary ano-vulvectomy with lymph node (LN) positive versus LN negative disease. A: median time to progression was shorter in the LN positive group (10 months versus 96 months, log-rank, p<0.0001). B: median OS was 19 months in LN positive disease compared with 121 months in LN negative disease (log-rank, p<0.0001). C/D: a trend is seen in both time to progression and OS according to degree of LN involvement.

A  
**Time to progression by Lymph Node Status**

B  
**Overall Survival by Lymph Node Status**

C  
**Time to progression by Lymph Node Status**

D  
**Overall survival by Lymph Node Status**

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References


