CHEMORADIATION

IN

ADVANCED

VULVAL

CARCINOMA

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DECLARATION

I declare that this thesis is all my own work.

Dr LJ Rogers

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3. ABSTRACT

Vulval carcinoma is uncommon, affecting approximately 2 per 100 000 women annually. The treatment of choice is radical vulvectomy and inguinal lymph node dissection.

'Advanced' vulval carcinomas involve midline structures (such as clitoris, urethra or anus) and/or adjacent pelvic organs or bone, and adequate excision may require urinary diversion, colostomy or pelvic exenteration. Less morbid and less mutilating therapeutic alternatives have been investigated, particularly chemoradiation, which has shown significant success in the management of anal carcinomas.

Primary chemoradiation has been used, instead of primary radical surgery, to treat advanced vulval carcinomas at Groote Schuur Hospital (GSH) since 1982.

Aims

1) To assess the survival of women with advanced vulval carcinoma treated with primary chemoradiation.
2) To examine the role of surgery after treatment with primary chemoradiation.

Objectives

1) To describe the demographic characteristics of women with advanced vulval carcinoma.
2) To examine the complications and morbidity of chemoradiation.
3) To determine prognostic factors for survival in women with advanced vulval carcinoma.

Methods

In this retrospective study, data was transcribed from patient case records onto a standardized proforma. The data was computerised and analysed.

Results

Between 1982 and 2001, 50 women with advanced vulval carcinomas were treated with chemoradiation at GSH. Fourteen (28%) women who had a complete response to chemoradiation had significantly improved survival compared to the 29 (58%) who had a partial response ($p = 0.000218$). Partial responders who had surgery had significantly better survival than those who did not ($p = 0.0064$). Other prognostic factors for survival were performance status and tumour stage.

Conclusions

Just under a third of the women treated with primary chemoradiation had a

complete response. Survival was improved in women who responded partially but had residual disease surgically excised. Performance status, age and tumour stage were also associated with survival.

4. INTRODUCTION

Vulval carcinoma is an uncommon tumour, accounting for only 3 – 5% of all gynaecological malignancies[1], and affecting 0,5 – 2 per 100 000 women annually[2]. It is predominantly a disease of older women, with a peak incidence in the seventh decade; though with the increased incidence of Human Papilloma Virus (HPV)-related Vulval Intra-epithelial Neoplasia (VIN usual type) that has accompanied the HIV pandemic, a second peak incidence in younger women in their forties has developed.

Vulval cancer is difficult to treat, both due to the physical, psychological and sexual morbidity of the radical surgery which may be necessary in order to gain improved local control and cure rates, and because of the likelihood of co-morbid disease in older patients.

The treatment of choice for vulval carcinoma is modified radical vulvectomy and inguinal lymph node dissection. This was described by Taussig[3], in the 1940's, and Way[4], and resulted in substantially better survival rates than those obtained previously[1]: the mortality rate dropped from over 80% to 40%, though at the expense of high operative mortality and morbidity[5]. The overall uncorrected 5-year survival rate following this procedure is currently quoted as 65% (range 46 – 75%)[1]; with better outlooks for those patients

whose inguinal lymph nodes are not yet involved with tumour.

The most common complication of this radical surgery is wound breakdown (85% of patients), with 30 – 70% of women experiencing chronic lymphoedema, and 15 - 20% suffering from genital prolapse and vaginal strictures[1]. The original radical vulvectomy and en bloc bilateral inguinal groin node dissections through 'butterfly' incisions has been modified over the years to less extensive vulval surgery, separate groin incisions with preservation of the skin bridge, and less radical groin node surgery, in order to decrease morbidity.

Thomas et al state that "the role of radiation therapy in the management of vulvar cancer has not been explored in a systematic fashion"[1], and reports of poor survival rates and severe complications, such as skin necrosis, caused this modality to fall into disrepute. However, several reports of pre-operative irradiation being used to debulk lesions that would have otherwise have required pelvic exenteration, suggested that radiotherapy could be used to reduce the extent of subsequent surgery or even eradicate disease in some patients if a high enough dose of radiation was used[6,7,8]. This was despite concerns of increasing the incidence of complications such as fistula formation and lymphoedema, when the combination of surgery and

radiotherapy were used.

Advanced vulval cancers include both those tumours which involve the urethra, bladder, anus, rectum or pelvic bone; and those for which adequate surgical excision requires sacrifice of one of the central structures (clitoris, urethra and anal sphincter) or even a total pelvic exenterative procedure.

Alternative forms of therapy have been sought to alleviate the morbidity of this radical surgery, and it was observed that concomitant radiotherapy and chemotherapy with 5-fluorouracil (5FU), resulted in long-term local control and cure of anal carcinomas, and rapid regression of squamous carcinomas of the oesophagus, head, neck and cervix[5]. This lead to investigation of the use of chemoradiation as the primary therapy of vulval carcinoma, particularly in the radical treatment of advanced tumours.

The Groote Schuur Hospital (GSH) Departments of Gynaecological Oncology and Radiation Oncology have been using chemoradiation in the management of advanced vulval carcinoma since 1982. This thesis aims to examine the role of chemoradiation in the management of advanced vulval carcinoma, with reference to both the outcomes of patients treated at Groote Schuur Hospital, and a critical review of the literature. It is based on a retrospective study of the outcomes of women with advanced vulval

carcinoma who were treated with primary chemoradiation at Groote Schuur Hospital (GSH) between January 1982 and January 2001.

Aims of the study:

1) To assess the survival of women with advanced vulval carcinoma treated with primary chemoradiation.
2) To examine the role of surgery after treatment with primary chemoradiation.

Objectives of the study:

1) To describe the demographic characteristics of women with advanced vulval carcinoma.
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5. REVIEW OF THE LITERATURE

Radical vulvectomy and inguinal lymphadenectomy is the accepted treatment for vulval carcinoma; however, for those patients with irresectable tumours, a variety of other treatments have been attempted.

5.1 Pre-operative radiotherapy

Boronow[6] and Hacker et al[7] first suggested the use of pre-operative radiotherapy to shrink irresectable vulval tumours, in order to reduce the extent of the surgery required (as an alternative to exenteration).

5.2 Radiotherapy combined with chemotherapy

Iversen first attempted to render tumours operable by using radiotherapy combined with chemotherapy (bleomycin), though conceded that in most cases, the regime was suitable for palliation only[9].

5.3 The Nigro regime for squamous carcinomas of the anal canal

The use of preoperative chemotherapy (5FU and mitomycin-C) and radiotherapy in the treatment of squamous carcinomas of the anal canal was begun by Nigro's group in 1972[10]. Evidence suggested that 5-fluorouracil (5FU), administered by continuous intravenous infusion during radiotherapy,

acted as a radiation sensitizer, thereby enhancing cell kill[11]. By 1975 it had become apparent that chemoradiation was so effective, producing local control rates of 90 – 95%, that abdomino-perineal resections were no longer routinely performed[10, 12].

5.4 Chemoradiation for vulval carcinomas

In a series of 54 women with locally advanced primary and recurrent vulval cancers, Han et al showed that overall survival was significantly better in patients treated with chemoradiation than with radiotherapy alone ($p = 0.04$). There was also a statistically significant improvement in disease-specific ($p = 0.03$) and relapse-free ($p = 0.01$) survival[13].

In a review of Concomitant 5-Fluorouracil, Mitomycin-C, and Radiotherapy for Advanced Gynecologic Malignancies in 1988, Evans et al stated that "The treatment of vulval cancers has recently changed from a surgical approach to a combined approach using radiotherapy for advanced stages." They concluded that the combination of chemotherapy and radiotherapy seemed "tolerable and promising", though admitted that patient numbers were small, and follow-up short[14].

In the same year, Thomas et al published an article examining the role of

radiation and concurrent 5FU, with or without mitomycin-C, in 33 patients with vulval carcinoma, treated between June 1984 and February 1988[8]. Of the 33, only 9 patients received primary chemoradiation, and of these 6 had initial complete responses. Three subsequently developed vulval relapses. Seven of the 9 were disease free after chemoradiation alone, or with the addition of a local excision of residual or recurrent disease, at the time of reporting (median duration of follow-up was 16 months).

It is notable that doses of radiation to the vulva ranged from 44 to 60 Gy; and Thomas et al state that patients should be treated with doses of at least 55 Gy in order to increase local control rates. Regarding complications, they state it is important to keep the daily radiation fraction size to the vulva at 175 cGy or less, in order to minimize the development of vulval fibrosis, necrosis and atrophy. They found that the moist desquamation which all patients suffered as a result of vulval irradiation, healed rapidly within 10 to 14 days[8].

Berek et al conducted a phase II trial of concurrent cisplatin and 5FU chemotherapy and radiotherapy for the primary treatment of 12 patients with stage 3 and 4 vulval cancer. Complete tumour responses were seen in 8 of 12 (67%) women, partial responses in 3 women, and one woman had persistent

disease. Radical vulvectomy or excision was then performed in 3 patients, and exenteration in one patient. With a median follow-up of 37 months, 10 patients were alive and disease-free, and two patients died at 12 and 15 months respectively. There were no treatment-related deaths, and no Grade 4 toxicity. They stated that their data supports the use of chemoradiation as an alternative treatment strategy to primary radical surgery in women with advanced vulval squamous carcinoma[15].

Russell et al reported the use of chemoradiation in the treatment of 25 women with locally advanced or recurrent vulval cancer. Of the 18 previously untreated patients, the majority of whom were stage 3 or 4a, a complete clinical response was obtained in 16 (89%). They concluded that initial management with chemoradiation may offer some patients with locally advanced vulval cancer an alternative to exenterative surgery, and may even offer the potential of cure to some women with irresectable or inoperable disease[16].

Koh et al reported the use of chemoradiation in 20 women with locally advanced vulval cancer. They concluded that there was a suggestion that better local control was obtained in patients who received radiation doses more than, or equal to, 50 Gy[17].

Wahlen et al reviewed the outcomes of 19 women treated with combination therapy in order to evaluate the role of combined chemotherapy and radiotherapy, with or without local excision, as primary therapy for advanced vulval cancer. Fifteen patients had stage 3 disease, and four had stage 2 disease. Two patients with positive ipsilateral inguinal nodes had these nodes removed before treatment. Median follow-up was 34 months: complete responses were seen in 10 patients (53%), partial responses in 7 (37%), no response in one woman, and one woman progressed during treatment. Chemoradiation resulted in a local control rate of 74% (14/19). All five treatment failures occurred within 6 months of treatment, and four of these patients were salvaged by radical vulvectomy and/or exenteration[18].

Cunningham et al treated 14 patients with stage 3 and 4 vulval carcinomas with chemoradiation, and achieved a 92% response rate. Nine patients (64%) had complete responses. With a mean follow-up of 36.5 months, only one of these patients recurred, though all the patients who had partial responses died, with a mean survival of 15.7 months. Surgical excision of the primary site was not performed in those who had a complete response, and they concluded that surgery is not necessary in those who show a complete response to chemoradiation[19].

Lupi et al published a pilot study of the use of preoperative chemoradiation in locally advanced vulval carcinoma: 31 patients were treated, with a staggering 65% post-operative morbidity rate, and a mortality rate of 13,8%. They concluded, unsurprisingly, that the combined approach might offer new perspectives for the treatment of advanced vulval cancer, if treatment-related morbidity could be decreased[20].

Gerszten et al reported the use of twice daily radiation, delivered concurrently with chemotherapy, to treat advanced and "critically located" vulval carcinomas. Inguinal nodes were included in the treatment field even if they were clinically negative. Resection of the tumour bed and inguinal dissection were planned for 4-6 weeks post-treatment. A retrospective review of the outcomes of eighteen patients showed there were complete responses in 13 patients, of whom 12 had no evidence of disease at 25 months. Five patients responded partially, and two of these had local recurrences[21].

5.5 The Cochrane Database Systematic Review

A recent Cochrane Database systematic review of neoadjuvant chemoradiation for advanced primary vulval cancer concluded that patients with inoperable primary tumours or lymph nodes only benefit from

chemoradiation if an operation can subsequently be performed, but that the complications of neoadjuvant therapy might outweigh the complications of exenterative surgery. They state that "with the current knowledge neoadjuvant therapy is not justified in patients with tumours that can be adequately treated with radical vulvectomy and bilateral groin node dissection alone"[22].

This Cochrane review found that no randomized controlled trials were available, and only five studies met their inclusion criteria ("Studies of curative treatment of patients with advanced, primary squamous cell carcinoma of the vulva… Treatment included concurrent radiotherapy and chemotherapy, followed by surgery."): Montana 2000[23], Moore 1998[24], Landoni 1996[25], Eifel 1995[26], and Scheistroen 1993[27].

Chemotherapy was given fairly uniformly in these studies, with three studies using concomitant cisplatin and 5FU, one using 5FU and mitomycin-C, and one using bleomycin (this study achieved a significantly lower operability rate of only 20%). Chemoradiation schedules varied between the studies, as did the radiotherapy dose fractionation techniques, fields and target definitions. Skin complications were observed in most of the patients; other common side-effects of treatment were wound breakdown and infection, and

lymphoedema and lymphocysts. Sixty-three – 92% of tumours were rendered operable in the four studies that utilized 5FU and cisplatin or mitomycin-C. Periods of follow-up ranged from between 5 and 125 months, and 26 – 63% of patients were found to be alive and well. Twenty-seven – 85% of patients died due to treatment-related causes or disease[22].

5.6 Historic progression

The rationale behind these studies and the historic progression is easy to follow: the search for alternative treatments to radical surgery, and particularly exenteration, for inoperable vulval tumours, lead to investigation of the role of neoadjuvant radiotherapy, and then chemoradiation, with the use of certain chemotherapies as radiosensitisers. The success of the Nigro regime to treat squamous carcinoma of the anus was used as an example.

The high doses of RT required, and resulting morbidity, have lead to chemoradiation for advanced vulval cancer falling into disfavour recently, despite its effectiveness. Elderly women with co-morbid diseases cope poorly with chemoradiation; and increasingly, younger women are presenting with multifocal VIN and vulval carcinomas, and their physical, sexual and psychological morbidity following treatment is a significant concern.

Advanced vulval cancer is a rare condition, so numbers of patients in the studies mentioned above are small, and the studies themselves are inhomogenous. No randomized controlled trials are available, and these are unlikely to be performed.

It is clear that while neoadjuvant chemoradiation can reduce tumour size and improve operability, the results of respective studies vary considerably, and no quality of life measurements were available.

Future studies should perhaps focus on the role of neoadjuvant **chemotherapy** for advanced vulval cancer, in order to further establish its efficacy and tolerability.

5.7 Neoadjuvant chemotherapy for advanced vulval cancer

In 1993, Benedetti-Panici et al reported the results of a pilot study using cisplatin, bleomycin and methotrexate to treat 21 patients with FIGO stage 4a vulval carcinomas, prior to surgery. They achieved local control in 12 of 21 (57%) of the patients, and the 3 year corrected survival rate was 24%[28]. This study does not suggest any benefit of neoadjuvant chemotherapy over chemoradiation.

The EORTC have reported on the use of bleomycin, methotrexate and the

nitrosurea CCNU in 25 patients with locally advanced primary and recurrent vulval carcinomas. Some of the patients went on to have radical surgery followed by radiotherapy. There was significant haematological toxicity, with two treatment-related deaths. The overall response rate was 56%, with a median survival of 7-8 months[29].

Between 1997 and 2003, Geisler at al treated fourteen patients with advanced vulval cancer involving the anal sphincter and/or urethra, with 3-4 cycles of neoadjuvant chemotherapy (cisplatin and 5FU), in order to try to avoid primary pelvic exenteration. They planned to perform radical vulvectomy and groin lymph node dissection after 3 cycles of chemotherapy. Lesion size was documented by measurement and photography prior to and following chemotherapy[30].

The median age of their patients was 63 years (range 39-88). Thirteen patients received a median of 3 cycles (range 2-4): ten received cisplatin and 5FU, while three received cisplatin alone. Median time from diagnosis to surgery was 77 days (range 54-143). All except one of the patients who received cisplatin and 5FU went on to have surgery (they all demonstrated at least a partial response), while the patients receiving cisplatin alone had no measurable response. Two patients had no residual invasive cancer on the

final pathology specimen[30].

All of the patients who received cisplatin and 5FU were disease-free at the time this paper was written in 2005, while two of the three who received cisplatin alone had progressive disease[30].

From these studies, there appears to be a range of responsiveness to the various chemotherapy combinations, though haematological toxicity remains a serious concern with all of them. There is as yet no evidence to show the efficacy or otherwise of substituting a potentially less toxic drug, such as carboplatin, for cisplatin, and using this alone, or in combination with 5FU.

5.8 EGFR Inhibitors

There is, however, a case report in the recent literature describing the first experience of the use of Erlotinib (Tarceva) in two elderly patients with locally advanced vulval cancer[31]. Erlotinib is an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, and evidence exists to show that primary and metastatic vulval cancers have increased expression of the epidermal growth factor receptor[32,33].

These patients were not offered surgery due to having multiple co-morbidities and advanced tumours, and one of them had had disease

progression on standard chemotherapy with 5FU and cisplatin. Within two weeks of starting treatment with Erlotinib, one patient had complete resolution of her 9.9cm vulval tumour and its necrotic lymph node metastases, and the other had a 50% reduction in size of her 5cm tumour. These patients subsequently passed away as a result of their other medical problems[31].

Erlotinib is well-tolerated, with diarrhoea, rash and fatigue as its major side-effects. Due to the biological plausibility of using an EGFR inhibitor to treat vulval cancer, and the responses seen in this case report, the authors have initiated a phase II trial to explore the role of Erlotinib in the treatment of locally advanced or metastatic vulval cancer[31].

Thus other treatments (such as EGFR inhibitors) besides the traditional combinations of radical surgery, chemotherapy and radiotherapy, may become the cornerstones of the treatment of locally advanced vulval cancer in the future.

6. METHODS

At Groote Schuur Hospital, all women with a diagnosis of a gynaecological malignancy are referred to a Combined Assessment Clinic (CAC), where they are seen, assessed and counselled by a team consisting of both gynaecological oncologists and clinical oncologists. Once they are registered as a cancer patient with a radiotherapy (RT) folder number, they become part of a database which is divided into vulval, cervical, endometrial, ovarian and gestational trophoblastic neoplasia patients.

The database provided a list of all women treated with primary chemoradiation for advanced vulval cancer. These files were retrieved and a standardized proforma (Appendix 1) was created to assist with data capturing.

Demographic data, details of the tumour (size, position, involvement of adjacent structures), details of treatment and follow-up information was transcribed from the case notes onto the proformas. Standard therapy consisted of a split course of concomitant chemotherapy and radiotherapy.

Chemotherapy consisted of mitomycin-C (10mg/m^2) given as a bolus injection on day one of each of the radiotherapy courses. 5-Fluorouracil (5FU), at a dose of 1000mg/m^2, was then given as a continuous infusion

over 24 hours on days 1 to 4 inclusive. The infusion was begun 30 minutes after the bolus of mitomycin-C had been injected.

Radiotherapy was given via a pair of antero-posterior parallel opposed portals to include the whole pelvis, vulva and inguinal lymph nodes. Patients were treated with 10 fractions of 2,5 Gy mid-plane dose to complete the first course, and then allowed to rest for two weeks to allow the resultant wet desquamation of the vulva to settle. Fractions were given on five days of the week using a telecobalt machine.

The second course of radiotherapy comprised 10 fractions of 2 Gy to make up a total of 45 Gy. Regression of the tumour was assessed after the first course to decide whether the patient required a second course of chemoradiation, or surgery.

The data was computerised and analysed as follows: descriptive statistics were generated and survival analyses, including generation of Kaplan-Meier curves, logrank tests and calculation of hazard ratios, were performed using the R survival package (http://www.r-project.org/).

7. RESULTS

Between January 1982 and January 2001, 50 women with advanced vulval carcinoma were treated with concomitant chemotherapy and radiotherapy at Groote Schuur Hospital.

7.1 Patient Profile

Patients ranged in age from 30 to 82 years, with a median age of 56.5 years. Parity ranged from 0 to 13, with a median of 3. Patients were drawn from a wide geographical area: 26 were from out of Cape Town and 11 from the Eastern Cape. Thirty-one of the women were of mixed race or coloured, 16 women were black, and three women were white. Their WHO performance status is documented in Table 1.

Table 1: WHO performance status

WHO performance status	**Number of patients**
No symptoms = 0	38
Symptomatic but not bedridden = 1	11
Bedridden but <50% time in bed = 2	1

7.2 Disease Profile

The commonest associated vulval condition was vulval intraepithelial neoplasia (VIN) in 14 (28%) patients. Five (10%) patients had vulval warts, and one suffered from lichen sclerosus.

Figure 1: Massive Condylomata Accuminata

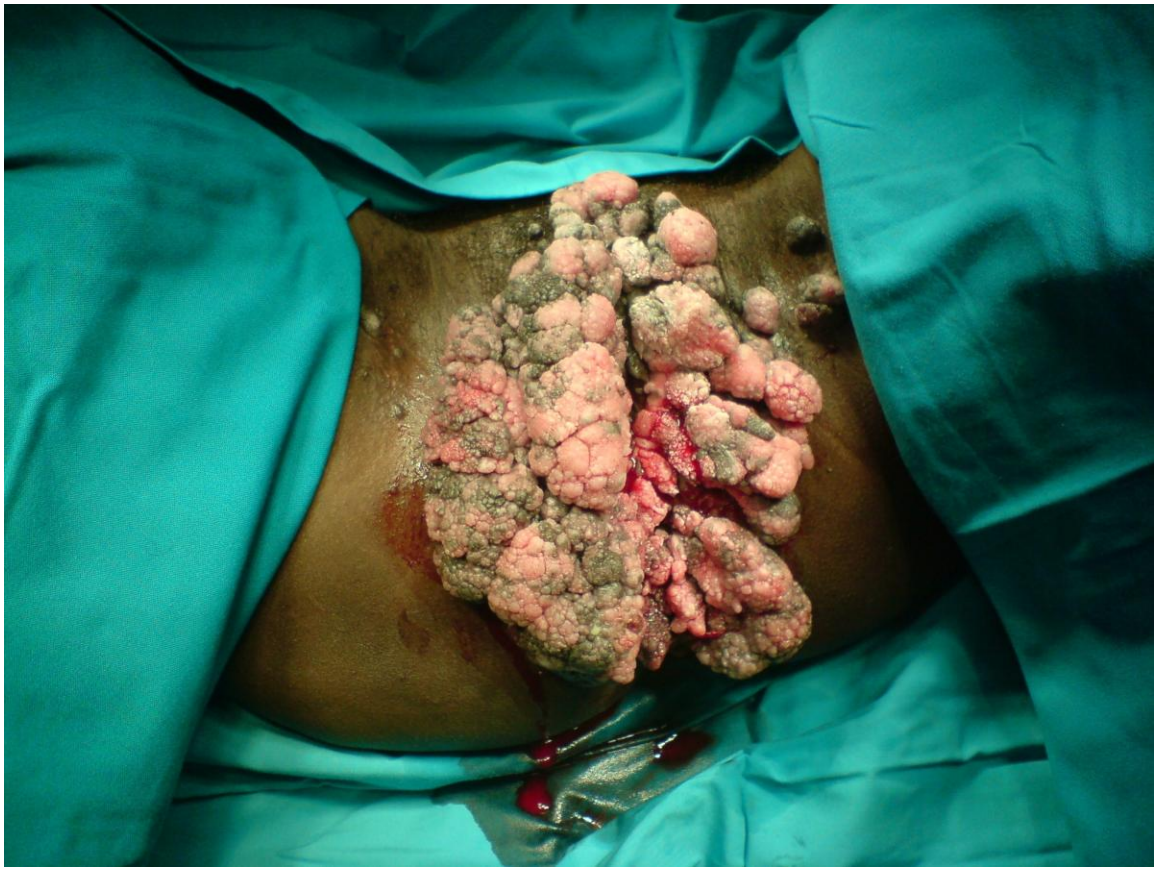
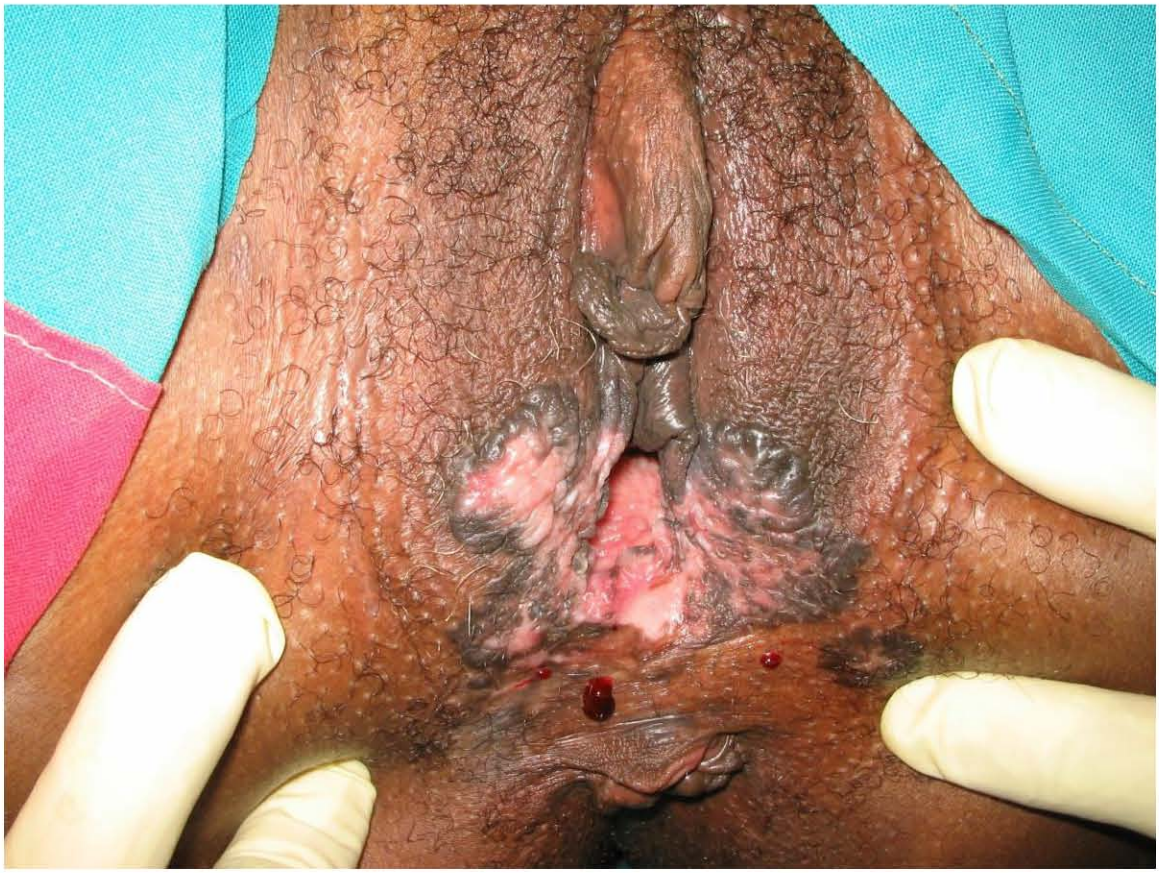


Figure 2: Usual type VIN



All of the tumours were squamous cell carcinomas, and the majority were staged as FIGO stage 3 (60%) or 4a (32%). Two were stage 4b and two were stage 2. Inguinal lymph nodes were unilaterally involved in 9 patients (18%) and bilaterally involved in 16 patients (32%), as determined by fine needle aspiration or clinical palpation (Table 4).

Twenty-nine of the tumours were considered irresectable without loss of either urethra, anus or both, or because they were fixed to the pelvic bone. All of the tumours were larger than 3.1cm in diameter, with the mean tumour diameter being 8.4cm (Table 2). The vast majority (n = 41 or 82%) of the tumours were centralized, with 23 situated posteriorly, and 18 anteriorly. Table 3 shows the anatomical sites to which the tumours extended, and Table 4 shows the status of the groin lymph nodes as determined by fine needle aspiration (n = 20) or clinical palpation (n = 5). Nodes were considered 'negative' in 25 cases when no nodes were palpated in the inguinal regions.

Table 2: Tumour size

Size (cm)	**3.1-4**	**4.1-5**	**5.1-6**	**6.1-7**	**7.1-8**	**8.1-9**	**9.1-10**	**>10**
Number	3	2	7	7	9	5	4	13

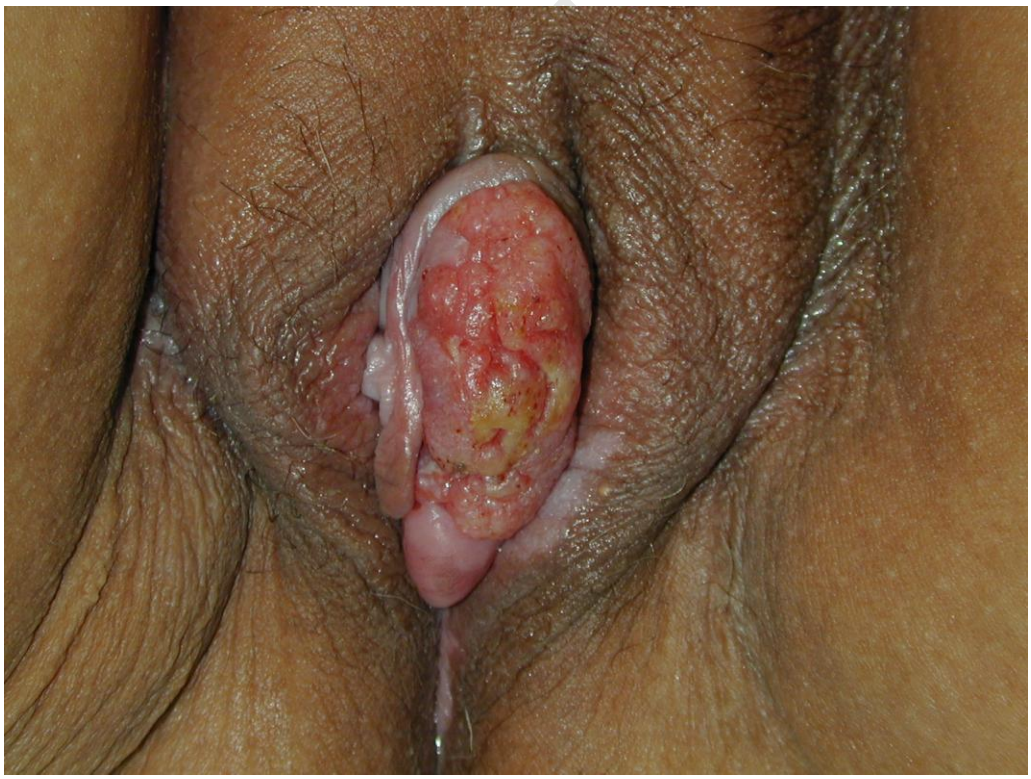
Table 3: Sites of extension of disease

Site of extension	**Number of patients**
Vagina only	17
Anus only	5
Urethra only	4
Bone only	2
Vagina and urethra	8
Vagina and anus	4
Vagina and rectum	1
Vagina and bone	1
Anus and urethra	1
Anus, vagina and urethra	2
Bone, vagina and urethra	2
Nil	3

Table 4: Groin node status

Node status	**Number of patients**
Bilateral fine needle aspiration biopsy (FNAB) +	14
Unilateral FNAB +	6
Bilateral, not FNAB	2
Unilateral, not FNAB	3
Negative	25

Figure 3: Anterior vulval carcinoma involving the clitoris and urethra



7.3 Association with other cancers

Three women had previously undergone treatment for cervical carcinomas: of these, one had a hysterectomy for a microinvasive cervical cancer 9 years before developing a vulval carcinoma, and one had received radiotherapy for a stage 2b cervical cancer 29 years earlier. Another woman had had an endometrial carcinoma 16 years before developing a vulval cancer.

At the time their vulval cancers were diagnosed, two women were also found to have early cervical carcinomas (stage 1a and stage 1b2), and another woman was found to have a laryngeal cancer. Subsequent to receiving treatment for her vulval cancer, one further woman developed both a T1N0 breast carcinoma, and a lung cancer, and subsequently died from the latter 10 years after her vulval cancer was diagnosed.

7.4 Association with immunosuppression

At the time most of these patients were treated, it was not yet our policy, as it is currently, to test all women undergoing treatment for a gynaecological malignancies for the human immunodeficiency virus (HIV) after appropriate counselling. HIV testing has become routine due to the high prevalence of this disease in South Africa, with a national antenatal HIV prevalence of 24.8%[34], and the influence of a positive test and a low CD4 count on patients' ability to withstand treatment with chemotherapy and radiotherapy. Only 14 of the women treated with chemoradiation for advanced vulval cancers were confirmed to be HIV negative, and one was suffering from severe malnutrition at the time of presentation. The other 35 patients' immune status was unknown.

7.5 Treatment

Details of the chemotherapy and radiation regimen used are given under Methods. There were many variations on the planned treatment regimen, with 18 patients receiving only one course of treatment. Some patients had their treatment completed at other centres, such as in the Eastern Cape, and received differing doses of radiotherapy. Three received additional radiation boosts to the perineum or inguinal lymph nodes. Deviations from the planned chemotherapy regimen were fewer: one patient received one cycle of cisplatin and bleomycin prior to one cycle of 5FU and mitomycin-C; and another had two cycles of cisplatin and bleomycin in addition to 5FU and mitomycin-C.

Ultimately 33 patients (70%) completed the chemoradiation treatment regimen planned for them. Six women died during the course of their treatment (of which three deaths were treatment-related); five had their treatment discontinued or interrupted due to complications of therapy (combinations of haematological, GIT and skin complications); and four patients defaulted from their treatment.

7.5.1 **Surgery** (Table 5)

Two patients had bilateral groin node dissections (BGND) prior to receiving chemoradiation: all nodes were negative. Two patients required defunctioning colostomies after chemoradiation, and a further thirteen patients had vulval and/ or groin surgery after chemoradiation. One woman had vulval biopsies only, which showed no residual disease; five had local excisions only, and one had a local excision and unilateral groin lymphadenectomy. Four women underwent 'simple vulvectomies', and one had a 'simple vulvectomy' and BGND. Only one woman underwent a radical vulvectomy and BGND.

Table 5: Surgery performed post-chemoradiation

Operation	**Number of patients**
Vulval biopsies	1
Vulval local excision	6
Simple vulvectomy	5
Radical vulvectomy	1
Inguinal node dissection only	2
Bilateral inguinal node dissection	4
Unilateral inguinal node dissection	1
Defunctioning colostomy	2

7.6 Outcomes

There was a complete response (CR), defined as no clinical evidence of disease after the completion of treatment, following chemoradiation in 14 patients (28%). Ten patients who showed a complete response received two full courses of treatment. Four patients only received one complete course.

A partial response (PR), defined as some degree of tumour regression but active disease still present after completion of treatment, was recorded in 29 patients (58%).

In 7 patients there was no change (NC) despite treatment, though no patients developed progressive disease while on treatment (Table 6).

Table 6: Response to treatment

Response	**Number of patients**
Complete	14 (28%)
Partial	29 (58%)
No change	7 (14%)
Progressive disease	0

Table 7: Comparison between complete responders and partial responders

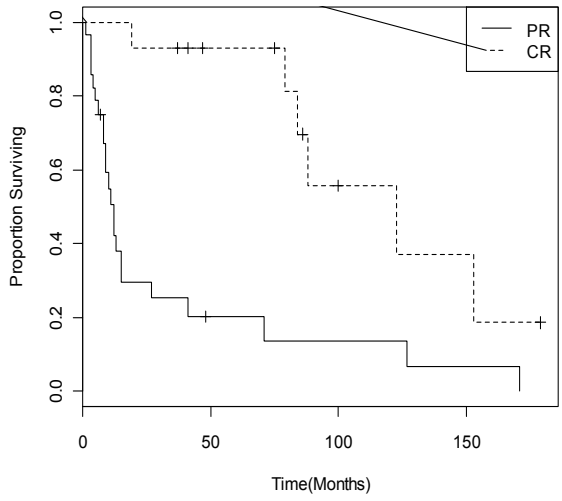
	Complete responders (n = 14)	Partial responders (n = 29)
Median age	55.5 years	60 years
Median parity	3	2.5
From: Cape Town Eastern Cape Rural Cape Other	6 2 6 0	12 8 7 1
Ethnic group: Coloured Black White	12 1 1	13 13 2
WHO performance status	0 = 12 1 = 2 2 = 0	0 = 21 1 = 6 2 = 1
Associated vulval condition	VIN = 4 warts = 1	VIN = 8 Warts = 4 Lichen Sclerosus = 1
FIGO stage	3 = 12 4a = 2	2 = 2 3 = 15 4a = 11
Median tumour diameter	7cm	7.1 – 8cm
Groin lymph node status	Clinically negative = 7 Unilaterally positive = 4 Bilaterally positive = 3	Clinically negative = 15 Unilaterally positive = 4 Bilaterally positive = 9

Table 7 shows a comparison between women who had a complete response to treatment, and those who had a partial response. Of patients who showed a complete response, five have subsequently died of unrelated causes, two

have been lost to follow-up, and 6 were alive with no evidence of disease at 36 months. One patient developed a local recurrence and lung metastases 23 months after treatment and died four months later. Figure 4 shows a Kaplan-Meier curve illustrating the difference in survival between complete and partial responders.

Figure 4: A significant difference in survival between complete and partial responders

The hazard ratio between the PR and CR groups is 4.97 (95% confidence interval 1.97 to 12.6, p-value of logrank test is 0.000218) which indicates that there is a significant difference in survival between the two groups.

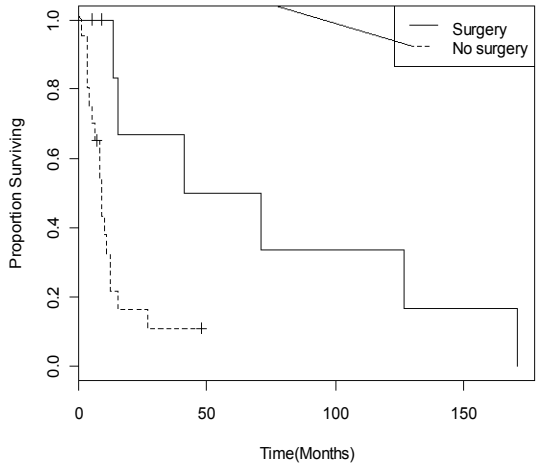


The group that showed a partial response to treatment can be divided into two subgroups: those who underwent surgery after chemoradiation and those who did not. Seven patients who showed a partial response underwent vulval surgery. One of these women died of disease at 41 months. Two were lost to follow-up at 5 and 9 months with evidence of active disease. The other four women have all died of unrelated causes. One woman was offered surgery, but declined; and a further two women underwent defunctioning colostomies.

Eighteen patients who had a partial response to treatment were not offered surgery. Three of those patients were lost to follow-up. All the others have died, with an average survival time of 7,8 months. The longest survivor from this group lived for 34 months, and the next longest lived for only 15 months. Patients who had progressive disease despite treatment survived for an average of only five months. Figure 5 shows the difference in survival between those patients with a partial response who underwent surgery, and those who did not.

Figure 5: A significant difference in survival between partial responders who had surgery, and those who did not

The hazard ratio between the Surgery and No surgery groups is 0.2 (95% confidence interval 0.0567 to 0.708, p-value of logrank test is 0.0064), which indicates that there is a significant difference in survival between the two groups.



7.6.1 Complications of Treatment

Three patients died from complications of their treatment. One died from pancytopaenia, presumably caused by chemotherapy; one died during therapy of unknown causes (no postmortem was done); and one woman was severely malnourished prior to commencing treatment, and died during treatment. Table 8 shows the total number of treatment complications documented.

Table 8: Treatment complications

Complications	**Number of patients**
Skin (wet desquamation)	11
Haematologic	2
Haematologic and Skin	2
Haematologic and GIT	1
Skin and GIT	1
Mouth Ulcers	1
Death	3
Nil	29

The mean follow-up period was 37.14 months (range 0 – 179 months). Twenty-two of the women developed recurrences during this time, and the sites of first recurrence are shown in table 9.

Table 9: Sites of first recurrence

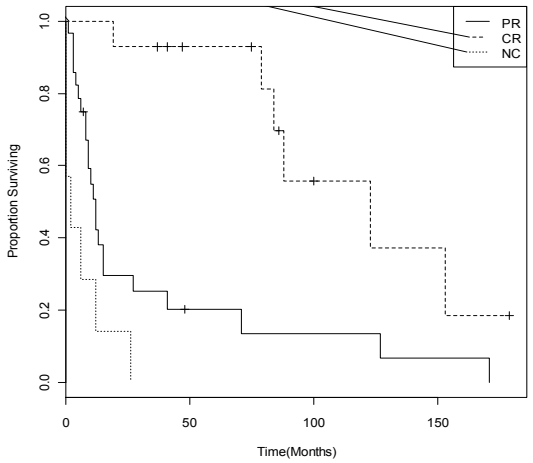
Site of recurrence	**Number of patients**
Local only	9
Groin only	3
Local and groin	8
Local and distant	1
Local, groin and distant	1

Table 10 shows the follow-up status of the patients, and Figure 6 shows survival curves for the whole group :

Table 10: Current follow-up status of patients

Status	**Number of patients**
Dead of disease	22
Dead due to treatment	3
Dead due to other causes	11
Alive and clear of disease	6
Alive with disease	0
Lost to follow up	8

Figure 6: Survival curves for the whole group

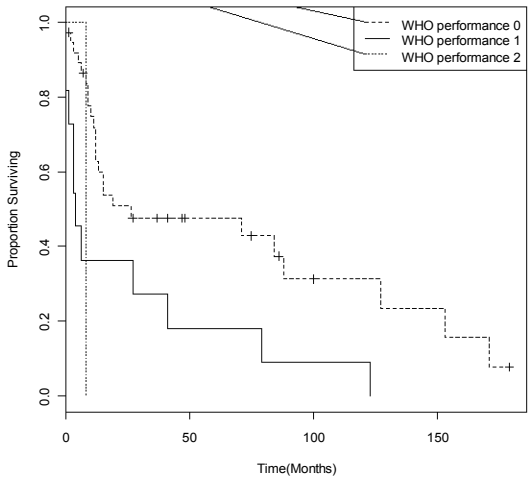


Fifteen women were known to be alive and free of disease five years after treatment, giving a disease-free and overall survival rate of 30% at five years for the whole group. Seven of these women have subsequently died of unrelated causes (three of these were partial responders who underwent adjuvant surgery), one died of cancer at 123 months, and one was lost to follow-up at 100 months.

It is notable that of the six surviving women, all demonstrated a complete response to chemoradiation, all had a good performance status (WHO = 0), and four of them were aged less than 60 years. Five of the six presented with stage 3 disease, while one had stage 4a disease. Four of the six had clinically negative nodes. Five of six completed their treatment, with one not completing her treatment course due to haematologic and gastrointestinal complications. The only surgery that this group of women underwent after chemoradiation was biopsies or local excisions, all of which proved them to be free of disease. Figure 7 illustrates that women with a better WHO performance status had a significantly better survival.

Figure 7: Women with a better WHO performance status had a significantly better survival

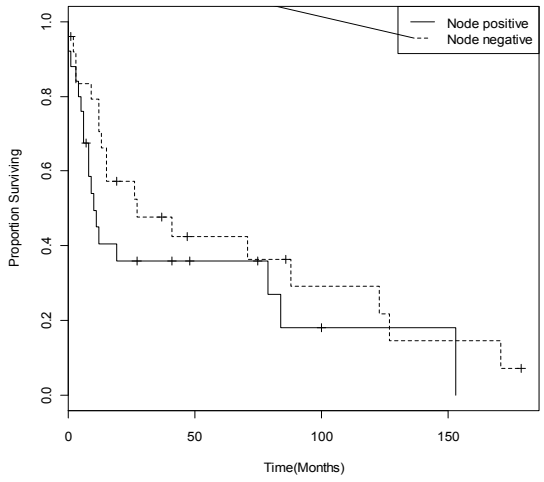
There is a significant difference in survival among the patients of three WHO performance status (p-value of logrank test is 0.011).



Surprisingly, there was not a significant difference in survival between women with positive groin nodes, and those with negative groin nodes, as shown in Figure 8.

Figure 8: No significant difference in survival between women with positive groin nodes and those with negative groin nodes

There is no significant difference in survival between the node positive and negative patients (p-value of logrank test is 0.213).



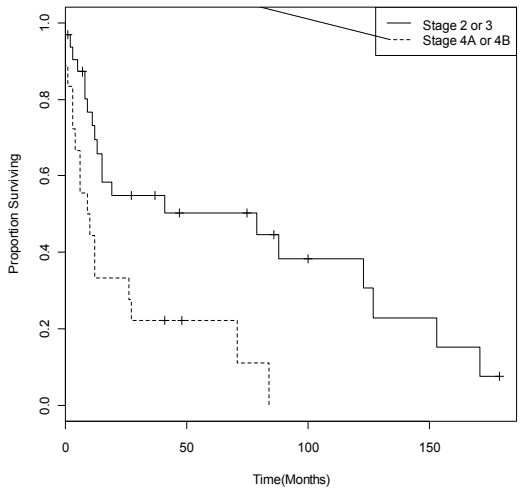
The lack of significant difference in survival could be accounted for by the fact that only 6 women underwent groin node dissections, and 20 were proven to have involved groin nodes by fine needle aspiration biopsy. Therefore the node status of half of the patients was only evaluated

clinically, so groin node micrometastases could have been missed in this group, which potentially would have affected their survival.

There was, however, a significant difference in survival between patients with stage 2 or 3, and stage 4a or 4b disease, with those patients with stage 2 or 3 disease doing better than those with stage 4 disease, as shown in Figure 9.

Figure 9: Women with an earlier tumour stage had significantly better survival

There is a significant difference in survival between the patients of stage 2 or 3 and those of stage 4A or 4B (p-value of logrank test is 0.00349).



It is therefore clear that those patients who had a complete response to chemoradiation had the best outcomes, while partial responders who had surgery did better than partial responders who did not have surgery. Other predictors of survival were good WHO performance status and earlier stage of disease. It was surprising that there was not a significant difference in survival between patients with positive groin nodes and those whose groin nodes were negative; though as chemoradiation was the primary form of therapy, this may have been because this was an effective way of sterilizing any groin lymph node metastases.

8. DISCUSSION

The Groote Schuur Hospital series is one of the largest series of patients treated with primary chemoradiation for advanced vulval carcinoma. Our patient characteristics are markedly different from those of patients in the developed world, who are likely to be predominantly elderly women with lichen sclerosus and differentiated VIN as their precursor lesions.

8.1 Reasons for late presentation

However one similarity all women with vulval lesions share is a tendency to present late – though the reasons for this may differ, depending on the age of the patient and their education and socio-economic status. Younger women tend to present earlier due to vulval symptoms, while in more elderly women there is often a delay both in presentation and in referral. Patient embarrassment, and deficiencies in education of both patients and medical professionals accounts for some of these delays. In developing countries, lack of easy access to medical care probably is the main factor leading to the late presentation of women with vulval cancers.

8.2 Survival

One of the aims of our study was to assess the survival of women with advanced vulval cancer who were treated with primary chemoradiation. Our results are disappointing, both when looked at in isolation, and when compared with the results achieved at other institutions. For example, Thomas et al report complete response rates of 66% in patients receiving primary chemoradiation, and 53% in patients being treated for recurrent disease[8]. At Groote Schuur, the corresponding response rates are 28% and 20% respectively. Long term survival is also poor in the Groote Schuur group, with only 15 (30%) patients living for longer than five years. This is similar to the 15 – 30% five year survival for stage 4 disease which is quoted by FIGO, and not nearly as good as their 50 - 75% five year survival for stage 3 disease.

A sub-group analysis of the women who were alive and free of disease after five years shows that important prognostic factors for survival in advanced vulval cancer include good performance status, earlier tumour stage, and a complete response to chemoradiation when it is offered as the primary modality of treatment. Adjuvant surgery improves the survival of partial responders to chemoradiation.

Possible reasons for the poor results produced at Groote Schuur, as compared to those of Thomas and others, include the very late presentation of those patients being treated at Groote Schuur. In the Groote Schuur group, the average diameter of the vulval lesions was 8,4cm, while the average size in the group treated by Thomas et al was 5,1cm. Women presenting at Groote Schuur did so only after symptoms had been present for an average of 7 months. Late presentation is characteristic of this disease, not only due to possible lack of access to health care, but also because women are embarrassed and delay seeking help.

The standard radiation dose given at GSH was 45Gy. This dose is probably inadequate, given the large average size of the tumours in this patient population. Thomas advises radiation doses of 55 to 65Gy in order to increase local control[8]. This advice is echoed by Koh et al, who found a correlation between radiation doses of greater than 50Gy, and overall local control[18]. They suggest that optimal radiation dose, when combined with chemotherapy, should be at least 54-55Gy[18]. Scheistroen and Trope, who also report disappointing results (25% complete response rate and 8 months median survival for patients with primary lesions), irradiated their patients with a maximum of 45Gy (30-45Gy), and conclude that increasing the radiation dose might have improved their results[17].

8.3 Complications and morbidity of chemoradiation

The obvious problem with increasing the radiation dose, is a corresponding increase in treatment morbidity, particularly skin and GIT complications. The thin, vascular vulval skin is known to tolerate radiation extremely poorly. A description of the complications and morbidity of chemoradiation was one of the objectives of our study. Studies reporting morbidity following treatment for vulval cancer are few and far between, and have only really been published in the last 20 years or so, coinciding with the increased emphasis on quality-of-life issues in cancer care.

It stands to reason that the larger or more advanced the vulval tumour at presentation, the more modalities of treatment which may be required to achieve local control and cure, and therefore the greater the treatment-related morbidity can be expected to be. Radiotherapy has two phases of toxicity: acute toxicity, which occurs within three months of completion of treatment, and which is characterised by inflammation, and dry and moist desquamation; and delayed toxicity, which is characterised by scarring and fibrosis. When chemotherapy is used in combination with radiotherapy, this may lead to an increased rate of toxicity than radiation alone; and if this results in an increase in treatment interruptions, this may cause treatment to be less effective. Also, older patients and those with co-morbid diseases are

more likely to be intolerant of concomitant chemotherapy and radiotherapy, and to suffer treatment-related side-effects[35].

Many articles describe the skin desquamation that occurs during radiotherapy as 'inevitable', yet only 11 of the Groote Schuur patients are reported to have suffered from it. The fact that 29 of our patients had no acute complications of their treatment at all, lends support to the hypothesis that the doses of radiation given were possibly inadequate. We have no long-term follow-up data on more chronic complications such a lymphoedema, which is likely to be more of a problem in patients who have been treated with both radiotherapy and surgery.

We also have no quality-of-life assessments, or assessments of psychological and psychosexual morbidity in our patients. Until recently, this has been a neglected area, though quality-of-life and psycho-sexual issues are gaining prominence in studies of the management of cancer. An early report on this subject found that more than 50% of women with vulval cancer and their partners experienced psychosexual problems. These are partly due to changes in anatomy, a lack of adequate counselling and advice were found to be significant contributing factors[36].

Other factors that have been found to be associated with sexual dysfunction

after treatment are increased age, poor performance status, a history of depression and pre-treatment psychosexual problems[37]. It is anticipated that the increased incidence of VIN and vulval cancer in younger women will lead to challenges in terms of the prevention and treatment of the psychosexual difficulties associated with vulval cancer therapies[35].

8.4 The role of subsequent surgery

Surgery was performed in 7 of the patients who had a partial response to chemoradiation. The results of the patients who had surgery are good: the mean survival time in that group is 85 months, with 3 of 5 patients (2 were lost to follow-up) surviving for longer than 5 years – a 60% 5 year survival.

Although this small group makes up only 14% of the total, their results are so much better than those for the whole group, that they strongly suggest that surgery is an important part of the treatment regime if there is a partial response to chemoradiation. Koh's findings are not as convincing: 7 patients in his series underwent surgery after a partial response to chemoradiation. Average survival time in this group was 22.7 months, with only 2 patients being free of disease at 3 years. None had survived longer than 37 months at the time of reporting[18].

Carcinoma of the vulva is traditionally quoted as being a disease of elderly women, and certainly in first world countries where there is a high incidence of lichen sclerosus and differentiated VIN, this is the case. These women tend to respond very poorly to chemoradiation, and have a high incidence of treatment related morbidity and mortality. However, this series shows that in populations where the prevalence of usual type VIN is high, the incidence of vulval carcinoma in younger women is rising, with the mean age of the women treated for advanced vulval carcinoma at GSH being only 54 years.

Maximising long term survival in such a young group of women is obviously important, and it appears that surgery is a vital part of the treatment regime in order to achieve this. However, in the South African context, where the majority of women live in poor socio-economic conditions, often in informal settlements, where they may not have running water in their homes; and where a vast sector of the population is infected with HIV; extensive vulval surgery, particularly after radiotherapy to the vulva, with the prolonged hospitalization and lengthy healing process required, may be neither practical, nor appropriate.

Fortunately, despite the high prevalence of HIV-related HPV disease, particularly cervical cancer and its precursors and vulval condylomata

accuminata, vulval cancer remains extremely rare in South Africa. Advanced vulval cancer is even rarer, estimated to make up 30 - 40% of all vulval cancers[38]. The reasons for this are two-fold: firstly, until the recent widespread use of anti-retroviral therapy, women infected with HIV probably died of other causes before they had time to develop a vulval carcinoma; and secondly, usual type VIN is far less likely to undergo malignant change than differentiated VIN (Eva et al – personal communication and unpublished data).

This is in contrast to HIV positive women with cervical intraepithelial neoplasia (CIN), who are known to be more likely to develop cervical cancer, and far more quickly, than their HIV negative counterparts[39].

8.5 The future: the roles of anti-retrovirals, HPV vaccines and neoadjuvant chemotherapy

As to what influence the role-out of highly active anti-retroviral therapy (HAART) in South Africa will have on the incidence of squamous carcinoma of the vulva, one might speculate that it may cause the incidence to increase, due to increased longevity of HIV-infected women. Anti-retrovirals have not been shown to be effective in reversing HPV-induced cancers, as they have for other HIV-associated malignancies such as

Kaposi's sarcoma and Non-Hodgkin's lymphoma, which are also caused by viruses[39]. Any effect is therefore likely to be indirect, following an improvement in host immune responses.

It is estimated that about 40% of vulval cancers have a strong aetiological association with infection with high risk types of HPV, particularly HPV 16[40]. Would HPV vaccines have an impact on the prevalence of vulval carcinoma? Two prophylactic HPV vaccines are now available: Gardasil™ and Cervarix™. These are expected to play an important role in decreasing the incidence of HPV related disease worldwide, though in order to have a significant impact on disease burden, they must be available in developing countries. The high cost of the vaccines and competition for limited resources from other areas of healthcare, as well as the logistics of delivering the vaccine in countries with poor infrastructure, and social stigma, will impact on them becoming widely available in the developing world.

Several studies have attempted to estimate the impact of the prophylactic HPV vaccines on the prevention of VIN and vulval cancer:
Hampl et al assessed prevalence and types of HPV in order to estimate the possible effect of HPV vaccines on the prevention of lower genital

tract disease. They found that HPV DNA was detected in 92% of VIN samples and 60% of vulval carcinoma samples; and that high-risk HPV types 16 or 18 were detected in 76% of VIN samples and 42% of vulval carcinoma samples[41].

Women with HPV-positive samples were younger than those with HPV-negative samples (46 years compared with 55 years for VIN, and 51 years compared with 61 years for vulval cancer). Seventy-seven percent of vulval carcinomas in women less than 56 years were HPV-positive, whereas only 41% of cancers in women older than 56 years were HPV-positive[41].

They conclude that widely-implemented prophylactic HPV vaccination could prevent about two-thirds of VIN and about half of vulval carcinomas in younger women[41].

Joura et al analysed the results of 3 trials which had randomised 18174 women to receive either quadrivalent HPV6/11/16/18 L1 virus-like-particle vaccine or placebo. The mean follow-up time was 3 years. The vaccine was found to be 100% effective in preventing VIN or VaIN associated with HPV16 and HPV18 in women who were HPV16 and HPV18 naïve, and 71% effective in women who could have been infected prior to vaccination. They conclude that with time, vaccination could

result in decreased rates of HPV-related vulval and vaginal cancers[42].

Garland et al have reported a randomised, placebo-controlled, double-blind trial involving 5455 women who had no virologic evidence of HPV 6, 11, 16 or 18. 2723 women were assigned to receive a quadrivalent HPV vaccine, and 2732 to receive placebo, and were followed up for an average of three years. Vaccine efficacy was found to be 100% for each of the coprimary end points of incidence of genital warts, VIN and VaIN, or cancer, and the incidence of CIN, adenocarcinoma in situ, or cancer associated with HPV type 6, 11, 16, and 18. In addition, vaccination reduced the rate of any vulval or vaginal perianal lesions regardless of the causal HPV type by 34%, and the rate of cervical lesions regardless of the HPV type by 20% [43].

But vaccines are for the future prevention of HPV-related vulval cancers. Current trials of neoadjuvant chemotherapy, and other therapeutic agents such as the EGFR inhibitors, are possible alternatives to radiotherapy and chemoradiation in the management of advanced vulval carcinomas – used either as an adjunct to surgery, or on their own.

The aims of therapy for advanced vulval cancers are to increase locoregional control and survival, while minimising treatment-related morbidity and

mortality. Though these tumours are rare, the management dilemmas and the treatment-associated morbidity they represent for each individual woman are substantial.

9. CONCLUSION

Chemoradiation has not been as successful a treatment for advanced vulval carcinoma at GSH, as was initially hoped. Considering that women who had a complete response to chemoradiation, and those who had surgery after a partial response to chemoradiation, had significantly improved survival, it is possible that our results could have been improved by increasing the radiation dose to a minimum of 55Gy, and by offering surgery to more of the partial responders; though both of these could also have increased the treatment-related morbidity and mortality suffered by the patients.

The other factor which influenced the prognosis of our patients is the fact that they presented with extremely large tumours and advanced disease, and improvements in education and health-care provision in South Africa are required in order to enable women to seek appropriate help earlier for vulval symptoms.

10. RECOMMENDATIONS

1) The prevention of vulval cancer by education of the general public and health care workers, and provision of an affordable HPV vaccine.
2) The prevention of advanced cancers by education of both the general public and health professionals, and increased access to health care.
3) Funding for trials of the use of less toxic cytotoxic agents, such as carboplatin, as part of chemoradiation regimens and as neoadjuvant therapy (prior to surgery) for locally advanced vulval cancer.
4) Funding for trials of the use of other drugs such as EGFR inhibitors - the results of ongoing trials are awaited.
5) SURGERY: the recent Cochrane systematic review proclaims surgery to be the most important part of any treatment strategy, and this is supported by the results of this study. However, appropriateness of the use of widespread radical vulval surgery after radiotherapy in a developing world setting has yet to be evaluated.
6) Increased emphasis on psychological support for patients and their relatives.

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12. APPENDIX 1

VULVAL CHEMORADIATION PROFORMA

1) Name _____ 2) Hospital number

3) Age at diagnosis (yrs) 4) Gravidity 5) Parity 6) Race: B W C

7) Origin: a) Cape Town b) Eastern Cape c) Rural Cape d) Other

8) Performance status (WHO):
   a) 0 = No symptoms
   b) 1 = symptomatic but not bedridden
   c) 2 = < 50% time in bed
   d) 3 = >50% time in bed
   e) 4 = bedridden

9) Previous cancer: a) yes ( ) b) no

10) Concurrent cancer: a) yes ( ) b) no

11) Associated vulval conditions:
   a) nil b) LS c) VIN d) Paget's e) Vulval warts

12) Immunosuppression:
   a) HIV b) Renal transplant c) Steroids d) nil

13) Pap smear result:
   a) inadequate b) benign c) ASCUS d) LSIL e) HSIL f) AGUS
   g) malignant h) nil

14) Histology: a) squamous cell ca b) other

15) FIGO stage at diagnosis:
   a) 1A b) 1B c) 2 d) 3 e) 4A f) 4B g)unknown

16) TNM classification:
   a) T = 1,2,3,4 b) N = 0,1,2 c) M = 0,1 d) unknown

17) Size of tumour (cm):
a) < = 1 b) 1,1 – 2 c) 2,1 – 3 d) 3,1 – 4 e) 4,1 – 5
f) 5,1 – 6 g) 6,1 – 7 h) 7,1 – 8 i) 8,1 – 9
j) 9,1 – 10 k) > 10

18) Site of tumour:
a) central anterior
b) central posterior
c) labia minora
d) labia majora

19) Sites of extension of disease:
a) vagina b) anus c) rectum d) urethra e) bladder
f) bone g) nil

20) Groin nodes:
a) clinically negative
b) unilaterally clinically positive \ not FNAB-proven
c) bilateral clinically positive \ not FNAB-proven
d) unilateral FNAB-positive
e) bilateral FNAB-positive
f) not stated

TREATMENT

21) Chemotherapy:
a) MFU 1 cycle b) MFU 2 cycles

22) Radiotherapy:
a) 1 split course b) 2 split courses c) continuous d) RT boosts

23) Treatment completed:
a) yes
b) no - Why? - Complications – absconded – died

24) Complications:
a) wet desquamation skin b) haematologic c) uncontrollable emesis
d) died e) other

25) Response to chemoradiation:
a) complete response (CR)
b) partial response (PR)
c) no change (NC)
d) progressive disease (PD)
e) not stated

SURGERY

26) Surgery performed:
a)yes b) no

27) Type of surgery:
a) local excision b) simple vulvectomy c) radical vulvectomy
d) other

28) Node dissection:
a) unilateral b) bilateral c) not performed

29) Residual disease:
a) yes b) no
If yes – completely excised
- incompletely excised (+ margins)

30) Further treatment:
a) none b) radiotherapy c) surgery d) chemotherapy

OUTCOME

31) Follow-up from 1st treatment (months):

32) Recurrence:
a) yes b) no
If yes – local, groin, distant, local + groin, local + distant,
local + groin + distant

33) Current status:

a) alive – no disease
b) alive – disease
c) dead – cancer
d) dead – other causes
e) dead – treatment complications
f) lost to follow-up

34) Overall survival (from date 1st treatment):

35) Disease-free survival: