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Treatment and outcomes of late stage vulva cancer at Pretoria Academic Hospital Complex, South Africa.

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Background
Vulva cancer has been regarded as a rare disease in elderly women, diagnosed at a mean age of 70 years. Over the past few decades however, vulva cancer has shown an increasing incidence with a concurrent decreasing mean age.[1] The increased incidence of human papilloma virus (HPV) is believed to be linked with the increasing incidence in younger women.[1,2]

Two independent pathways of vulvar carcinogenesis exist. The first type involves oncogenic human papillomavirus infection that causes vulva epithelial neoplasm (VIN).[3] The second type of vulva cancer involves vulva non-neoplastic epithelial disorders (VNED), usually occurring in older women, and leading to cellular atypia and cancer. It is related to chronic vulva inflammation, lichen sclerosis and hyperplasia.[3]

The treatment of late stage vulva cancer presents several challenges for the treating gynecologic oncologist, and patients diagnosed with late stage diseases have poor survival rates.[2] Locoregional late stage vulvar cancer is considered when the disease is beyond surgical resection with standard radical vulvectomy, irrespective of groin lymph node status without distant metastasis.[3-6] Locally advanced vulva cancer with affected adjacent structures, usually warrants radical vulvectomy with bilateral inguinofemoral lymphadenectomy and partial or complete resection of the urethra, vagina or anus. Local fascio-cutaneous skin flaps can be applied for minor defects, while regional myo-cutaneous skin flaps are frequently needed to cover large defects.[3-6]

Pelvic exenteration has the potential to offer high cure rates in late stage vulvar cancer. The high morbidity and peri-operative mortality rates are probably the reason why it is not widely offered as primary treatment for late stage vulvar cancer.[7]

For patients who are not considered for primary surgical procedures, treatment options include neo-adjuvant chemotherapy or neo-adjuvant chemoradiotherapy and primary chemo- radiotherapy.[3-6] There is however a lack of guidelines on the optimal sequencing of these treatment options. Neoadjuvant chemotherapy alone has been investigated as a potential option of down staging advanced vulvar cancer to allow for less extensive surgery with different chemotherapy regimens; this option demonstrated varying degrees of success.[8] The EORTC trial of patients who received a lower dose of methotrexate, demonstrated an overall response rate of 55 percent.[8] Benedetti-Panici et al in their study of 21 patients treated for locally advanced vulvar cancer also demonstrated encouraging response rates with a combination of cisplatin, bleomycin, and methotrexate with 33% of patients showing pathological down staging.[9]

Neo-adjuvant chemoradiation provides a promising option. A Gynecologic Oncology Group phase II trial involving 71 patients with T3 or T4 vulvar tumours demonstrated that, of the 70% of patients who initially required exenterative surgery, only one patient required exenterative surgery and two patients required colostomy to resect residual disease following the use of neoadjuvant chemoradiation.[10]

For patients who are not candidates for any form of surgical excision, primary chemoradiation or radiotherapy is recommended. This recommendation is however based on low quality evidence and the efficiency of this treatment modality in the clinical setting as primary treatment is not fully known. Slevin et al reviewed the outcomes of 58 patients with unstaged vulvar cancer and found local control rates of 52% and five-year disease-free survival of 56%.[11] Further small studies by Pohar and Sharma also revealed good clinical response.[12,13]

In settings similar to ours, the success of primary radiation or chemo-radiation (RT/CRT) in advanced stage vulva cancer is unknown. The completion and outcomes of this treatment options are unstudied. Patients with advanced stage cancer who are not operated seem to have poor outcomes. The percentage of these patients who are not operated with advanced stage of vulva cancer and the reasons why they are considered not operable is unknown in our setting. It is also not known whether the factors that render patients inoperable are amendable to intervention.

Aim & objectives
The aim of our study was to help elucidate current treatment decisions for late stage vulva cancer. Our objectives were to determine the percentage of women operated with late stage vulva cancer, the reasons why patients are considered not operable and whether the factors that render these patients inoperable are amenable to intervention or not.

Method
We conducted a retrospective descriptive audit. Records of women treated during the period from 2001 to 2013 for FIGO stage II+ vulva cancer at Steve Biko Academic and Kalafong Provincial Tertiary Hospitals were reviewed. Data including demographics, co-morbidities, tumour characteristics, treatment modalities and treatment decisions, completion and outcomes were collected using clinical and laboratory notes. The study protocol was reviewed and approved by the Research Ethics Committee of the University of Pretoria (134/2013).

Results
The files of 134 women with complete data were included in this study. The median age of the patients was 43 years (range: 16 - 80 years). The majority of patients, 56.3%, were HIV negative, while 66.4% had a performance status of 1-2 and 28.1% had a performance status of 3. The haemoglobin (Hb) levels in 32.8% of patients were below 10 g/dl and 42.7% had an albumin value below 30 g/dl. The FIGO stage distribution was 26.9%, 35.8%, 29.9% and 6% for FIGO stages II, III, IVa and IVb respectively. The majority of patients, 75.3%, had moderately to well

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differentiated tumors. Age distribution as well as clinical characteristics of the HIV positive versus HIV negative groups are shown in Table 1. Forty-nine (36.6%) patients received primary surgical treatment. Surgery in 20/49 (40.8%) patients were considered curative. Decision not to offer surgical treatment included factors such as young age, poor performance status, low Hb value, late FIGO stage and larger tumour diameter. Forty-one percent (55/134) of patients were HIV positive and amongst the HIV positive patients, 80% (44/55) were not operated. Thirty-four patients with performance status of three and two patients with performance status of one were inoperable. Forty-one percent (35/85) of patients in the inoperable group had anaemia and 43.5% had albumin values of below 30 g/l. Table 2 shows the clinical characteristics of patients treated surgically and inoperable patients.

Table 1. Age distribution and clinical characteristics of HIV positive and HIV negative groups

	HIV pos group n (%)	HIV neg group n (%)	P value
Age category (in years)	n = 55	n = 71	
≤ 40	37 (29.6)	3 (0.2)	< 0.0001
41 – 50	12 (9.6)	12 (9.6)	1.00
51 – 60	3 (0.2)	19 (15.2)	0.0031
61 – 70	2 (0.2)	18 (14.4)	0.0041
> 71	1 (0.1)	18 (14.4)	0.0079
Unknown	0 (0)	1 (0.1)	0.8153
Pre-operative blood results			
Albumin ≤ 30 g/l	28/48 (58.3)	18/57 (31.6)	0.0028
Hb < 10 g/dl	27/54 (50.0)	13/67 (19.4)	0.0003
Performance status			
Performance status > 1	46/54 (85.2)	52/67 (77.6)	0.2835
FIGO staging			
Figo stage II	10/55 (18.2)	25/71 (35.2)	0.0353
Figo stage III	19/55 (34.5)	27/71 (38.0)	0.6868
Figo stage IV	26/55 (47.3)	18/71 (25.4)	0.0109

Table 2. Clinical characteristics of patients treated surgically versus no surgical treatment

	Treated surgically n (%)	No surgical treatment n (%)	All patients n (%)
	n = 49	n = 85	N = 134
HIV status			
HIV pos	11 (22.4)	44 (51.8)	55 (43.7)
HIV neg	35 (71.4)	36 (42.4)	71 (56.3)
Unknown status	3 (6.1)	5 (5.9)	
Performance status			
PS 1	24 (49.0)	2 (2.4)	26 (19.4)
PS 2	22 (45.0)	37 (43.5)	59 (44.0)
PS 3	2 (4.1)	34 (40.0)	36 (26.9)
PS 4	0	7 (8.2)	7 (5.2)
Unknown	1 (2.0)	5 (5.9)	6 (4.5)
Hb value (g/dl)			
< 10	7 (14.3)	35 (41.1)	42 (31.3)
≥ 10	40 (81.6)	46 (54.1)	86 (64.2)
Unknown	2 (4.1)	4 (4.7)	6 (4.4)
Albumin value (g/l)			
≤ 30	10 (20.4)	37 (43.5)	47 (35.1)
> 30	30 (61.2)	33 (38.8)	63 (47.0)
Unknown	9 (18.4)	15 (17.6)	24 (17.9)
FIGO stage			
FIGO stage II	26 (53.1)	10 (11.8)	36 (26.9)
FIGO stage III	18 (36.7)	30 (35.3)	48 (35.8)
FIGO stage IV	3 (6.1)	45 (52.9)	48 (35.8)
Tumour size (cm)			
< 2	0	1 (1.1)	1 (0.7)
2 – 4	12 (24.5)	3 (3.5)	15 (11.2)
> 4	37 (75.5)	81 (95.3)	118 (88.1)

Among women with advanced vulva cancer (FIGO II+) only 11.2% had a tumour diameter < 4 cm. The frequency of positive nodes was 36.7% (18/49) and of close margins was 34.7% (17/49). Of the 49 patients who were planned for primary surgery, 29 patients were considered for adjuvant RT/ CRT) (29/49, 59.2%).

Sixty-five patients were referred for primary CRT/RT. Figure 1 shows the treatment outcomes of patients who were referred for primary CRT/RT.

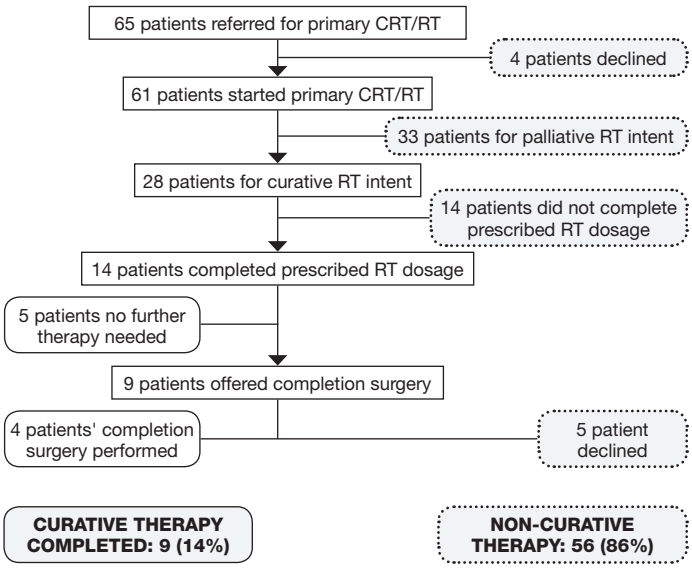
Discussion

The majority of patients (52.2%) who presented with advanced stage vulva cancer were below the age of fifty years. The young age and poor clinical characteristics of this group of patients with large or advanced vulva carcinoma is disturbing and not in keeping with historical reports, mostly from developed countries. [2,3,11,14] The high prevalence of high-risk HPV in this population, as demonstrated in local studies, offers a possible explanation of this finding. A study from our region reported an overall HPV prevalence of 58%[15], while high prevalence of HPV was also demonstrated in a larger population study.[16]

Another contributing factor to this problem is the high background HIV prevalence and associated immune compromise in our population. Earlier data estimated that in 2008 about 14% of South African women aged 15-49 years were HIV positive.[17] This is further supported by the Antenatal Survey trend data from 2007 to 2010, showing that HIV prevalence was increasing among women aged 30 and older.[18]

Although positive HIV status does not preclude primary surgery,

Figure 1. Primary CRT/RT treatment outcomes



patients in this study population who were HIV positive often had poor general health, poor nutritional and performance status and presented with later stage disease. These patients were younger than those who were HIV negative. HIV infection has adverse effect on the nutritional status of the individual, which is further worsened by opportunistic infections. HIV positive patients tend to be more malnourished, anaemic and hypoalbuminemic than socio-economically matched individuals, despite similar caloric intake.[19] In our population, the general uptake of HIV testing is very low, with late initiation of antiretroviral therapy. It is crucial that HIV testing be promoted among women who present in a health facility for either treatment or screening.

Patients who were selected for primary surgery had a different profile from those received other primary treatments. HIV status, performance status, haemoglobin and albumin all tended to predict treatment decisions. Only 49/134 (36.6%) patients presenting with late stage vulva carcinoma had primary surgery. Patients who were considered non-operable had poorer clinical and tumour characteristics and later stage disease. It is possible that amenable factors such as haemoglobin, albumin and general nutritional status are factors that render patients inoperable.

Sixty-five patients were referred for radiotherapy; 50% of the patients referred for treatment received palliative radiotherapy and only 50% of the remaining patients, who were referred for curative radiotherapy, completed their treatment. This finding raises a concern about whether this modality of treatment is better suited for our population given the poor follow up rates.

Primary radiotherapy has been offered as an alternative to upfront surgery in patients with local advanced tumours. Observational studies support the use of this sequence of treatment as it decreases local tumour burden and allows for a less radical resection.[20] Despite this promising data, this study demonstrated a surprisingly low number of 9 patients referred for radiotherapy with an intention to perform secondary surgery, and only 4 patients that underwent secondary surgery.

Conclusion

During the last 10 years, 36.6% of women presenting with late stage vulva carcinoma had primary surgery. Patients who were not considered operable had poorer clinical and tumour characteristics as well as later stage disease. It is possible that amenable factors such as haemoglobin, albumin and general nutritional status are factors that render patients inoperable.

In light of the poor treatment completion rates of non-surgical therapy, it may be important to consider surgery for patients with organ involvement even if incontinence will result. To this end, it will be further investigated whether surgery was offered less often to patients of comparable characteristics with posterior position tumours. It is also important to collect data on completion rates of adjuvant radiation and of the outcome of the different treatment groups.

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