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ARTICLE

A cohort study of treatment outcomes after radiotherapy in vulva carcinoma patients

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Background: Carcinoma of the vulva is an uncommon tumour. For locally advanced vulval cancer with proximity to the urethra or anal margin, surgery often involves exenteration with colostomy or urinary diversion, which results in significant physical and psychological morbidity. The use of neoadjuvant or primary chemoradiation is an acceptable treatment option for those patients deemed unsuitable for primary surgery in advance. In addition, if the patient has poor locoregional control this has a significant impact on quality of life following treatment. This study aimed to evaluate radiotherapy curative and palliative treatment outcomes for patients in a single institution.
Methods: A quantitative retrospective cohort analysis of all women diagnosed with vulval cancer managed in a single institution was undertaken. Eligible patients included patients with vulval carcinoma referred for radiotherapy (RT)—primary, adjuvant and palliative. Demographic and clinical data, treatment time and radiotherapy fractionation were noted. The primary end-points were local control (LC) and overall survival (OS).
Results: Forty-two patients were referred during the study period. Among the 33 evaluable patients, all patients completed treatment. At 12 months' follow-up, 20 women were alive (4 with evidence of recurrent/persistent disease) and 13 had died (4 with documented recurrent disease). At the time of data analysis, 22 patients received curative treatment: definitive chemoradiation or radiation alone (n = 17) or adjuvant RT (n = 5). Of the 22 patients, 11 were in remission, 8 had been lost to follow-up, and 3 had documented local recurrence. In total, 11 patients received palliative treatment. The overall survival at 12 months for the patients who received primary surgery followed by adjuvant radiotherapy was 100%. There was, however, no significant difference between the survival for the definitive CRT/RT (57.5%) and the high-dose palliative RT (49.1%) groups. However, the dose of radiotherapy was significant; women who received a total dose of radiotherapy greater than 60 Gy had improved local control compared with those who received a total dose of less than 45 Gy.
Conclusion: Surgery followed by adjuvant treatment had a superior overall survival outcome compared with definitive chemoradiation or radiotherapy alone in this small cohort, reflecting poorer outcomes for advanced disease.

Keywords: chemotherapy, radiotherapy, treatment outcome, vulval cancer

Introduction

Carcinoma of the vulva is an uncommon tumour, representing about 4% of gynaecological malignancies.[1] In 2014, the National Cancer Registry of South Africa reported 343 new cases of vulval cancer in all population groups, comprising 0.91% of all reported malignancies.[2] There are approximately 1.24 cases of vulval cancer per 100 000 per year. In South Africa, vulval carcinoma is a disease with an increased incidence in young females, which is contrary to the situation in the developed countries.[3] This high incidence in young women is associated with the high incidence of oncogenic human papilloma virus (HPV), which has been proved to be linked with the rising incidence of vulval cancer in young women among the South African population.

For years, stage T3–4 locally advanced vulval cancer was thought of as a surgically managed disease.[4] In the 1980s, there was a paradigm shift in treatment, with studies from the Gynaecologic Oncology Group (GOG) reporting good outcomes with radiotherapy followed by surgery.[5] The decision to move away from standard management (e.g. primary surgery where possible) in advanced vulval disease is driven by the need to reduce the mortality and morbidity associated with extensive surgery, especially in elderly patients.[6] Extensive surgery also affects the quality of life for younger patients in terms of body image and psychosexual morbidity.

End-points of loco-regional control, survival and quality of life need to be evaluated with this management approach.

Objective

The aim was to evaluate treatment outcomes for vulval carcinoma patients following definitive chemoradiation, radiation alone, adjuvant radiation and high-dose palliation at a single institution.

Methods

This was a quantitative retrospective cohort study enrolling a cohort of patients with vulval carcinoma referred for radiotherapy between January 1, 2015 and December 31, 2017.

The data source used to find the study participants was the radiotherapy treatment planning system MOSAIQ®—search by ICD10 code and treatment records. Demographics, including HIV status, clinical data and the treatment parameters, were noted.

Patient plan outline

All patients were discussed and examined at the multidisciplinary team (MDT) staging meeting with the referring gynaecological oncology surgeons. On the first visit after the MDT discussion, a full medical and gynaecological history was

Table 1: Patient characteristics of the cohort

Characteristic	Number of patients = 33 (%)
Age (years):	
≤45	11 (33.3%)
46–59	16 (48.4%)
≥60	6 (18.1%)
Performance status:	
0	2 (6.1%)
1	24 (72.7%)
2	5 (15.1%)
3	2 (6.1%)
FIGO stage:	
IB	2 (6.1%)
II	6 (18.1%)
IIIA	4 (12.1%)
IIIB	6 (18.1%)
IIIC	8 (24.2%)
IVA	6 (18.1%)
IVB	1 (3.0%)
HIV status	
Positive	13 (39.4%)
Negative	20 (60.6%)

taken. Physical examination, review of all staging and pre-treatment investigations, counselling and consent was undertaken according to the treatment intent decided upon at the MDT staging meeting. A radiotherapy planning scan was performed on the same visit.

Surgery

Primary surgery was offered to patients who were found to be resectable. The surgery comprised a wide local excision of the primary vulval cancer or vulvectomy with bilateral groin dissection. Post-surgery, these patients received adjuvant radiotherapy if needed, based on the pathological report.

Radiotherapy

Patients treated with primary radical intent received radiation therapy to the vulva, pelvic lymph nodes and inguinofemoral lymph nodes. The treatment consisted of 1.8 Gy/daily fractions 5 days per week to a total dose of 54 Gy–66.6 Gy in 30–37 fractions to gross disease. Nodal regions were covered to 45 Gy for at-risk nodal areas and up to 54 Gy for involved nodes. Adjuvant radiotherapy was prescribed in a dose range of 45–54 Gy depending on pathological findings. Treatment interruptions were avoided by ensuring adequate analgesia and immediate treatment of any treatment-related toxicity.

Patients treated with high-dose palliative intent received radiation therapy to the vulva, pelvic lymph nodes and inguinofemoral lymph nodes. A dose of 40.5 Gy in 15 fractions, 2.7 Gy per fraction, was delivered 5 days per week.

Chemotherapy

Concurrent chemotherapy consisted of cisplatin (40 mg/m^2 to a maximum dose of 70 mg), administered weekly throughout the radiotherapy with pre-hydration and post-hydration. Chemotherapy was deferred if the granulocyte count was below 1.0×10^9/l, platelets less than 75×10^9/l, or if electrolyte or creatinine levels were deranged. If these abnormalities persisted despite attempts made to correct them, concurrent chemotherapy was discontinued. HIV-positive patients were maintained on anti-retroviral therapy with co-trimoxazole prophylaxis—they received standard-dose chemoradiation if the CD4 count was > 150 cells/ul.

Treatment and patient evaluation

Each patient during treatment was assessed once weekly for acute treatment-related toxicities, which were documented and graded according to the Common Terminology Criteria for Adverse Events version 3 (CTCAE V3) by the National Cancer Institute (NCI) in grades 0 to 4. At completion of treatment, patients were reviewed at six weeks post-treatment, and thereafter three-monthly for the first year, then six-monthly during the second year.

Statistical considerations

All data processing and analysis was performed using the Statistical Package for the Social Scientists (SPSS) version 22 data management tool (IBM Corp, Armonk, BY, USA). Continuous variables were summarised using mean and standard deviation (SD). Categorical data were presented using frequency tables. Association between two categorical variables was assessed using the standard Pearson's chi-square test. A *p*-value of less than 0.05 was regarded as significant. Continuous numerical variables were presented using t-tests. Rates of local recurrence (LR) and overall survival (OS) at one year were estimated using the Kaplan–Meier methods. The primary end-point was local recurrence (LR) and overall survival (OS), defined as date of start of RT to date of relapse (LR), or death (OS). The impact of individual factors on outcome was evaluated with univariate analyses. The multivariate logistic regression model was used to determine the overall impact of significant co-factors on outcome.

Ethics approval

Ethics approval was obtained from the Stellenbosch University Health Research Ethic Committee (HREC) and the Research Ethics Committee of Tygerberg Hospital (Ethics Reference #: S18/01/020).

Results

From January 1, 2015 to December 31, 2017, a total of 42 women with vulval cancer were referred for radiotherapy at Tygerberg Hospital. Of these patients, 33 were eligible for the inclusion criteria. Eleven patients were excluded from the study for the following reasons: two patients were upstaged to metastatic disease following PET/CT staging. Two patients declined treatment, four patients did not arrive for their treatment, and one patient received a single fraction of radiotherapy. The clinical and pathological criteria are described in Table 1. Approximately half the cohort was between the ages of 46–59 years, and more than 50% had stage III vulval cancer; 60.6% of the cohort was HIV negative, while 39.4% were HIV-positive. Twenty-two patients received definitive treatment: 15 received chemoradiation, 5 received adjuvant radiotherapy (of whom 3 received concurrent chemotherapy), and 2 received radiotherapy alone. The remaining 11 patients received high-dose palliative radiotherapy.

Treatment response

Among the 33 evaluable patients, all patients completed treatment. At 12 months of follow-up, 20 women were alive (4 with evidence of recurrent/persistent disease), and 13 had died (4 with documented recurrent disease). At the time of data

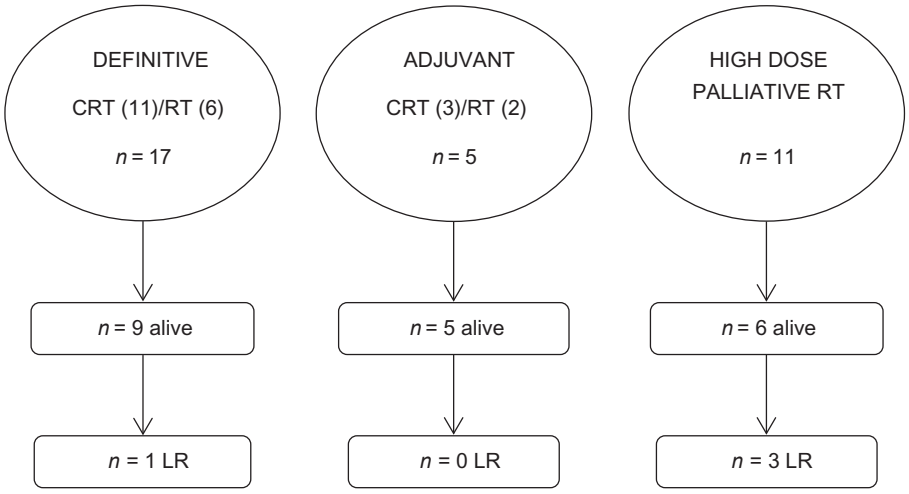

Figure 1: Recurrence at 12 months. CRT- chemoradiotherapy, RT- radiotherapy, N- number of patients.

analysis, 22 patients had received curative treatment: definitive CRT/RT (n = 17), adjuvant RT (n = 5). Of the 22 patients, 11 were in remission, 3 with documented local recurrence, and 8 died due to unknown causes. The 3 patients with documented local recurrence had received definitive CRT/RT. Eleven patients received palliative treatment, three patients were in remission, five had documented local recurrence, and three died due to unknown causes (Figure 1).

Overall survival

Those who received adjuvant radiation had a 100% survival outcome at one year. There was, however, no significant difference between the survival for the definitive CRT/RT (57.5%) and the high-dose palliative RT (49.1%). The mean was not reached (Figure 2).

In total, 13 evaluable patients were HIV-positive and 20 were HIV-negative. There was no significant survival difference between the positive and negative patients (70% vs. 49.5%; p = 0.51) though there was a trend towards improved survival in the HIV-negative patients.

More than 50% of our cohort was made up of stage III vulval cancer patients (n = 18); at 12 months, their overall survival was 54.5%. The stage I and II (n = 8) combined survival outcome was 75.0%, and stage IV (n = 7) was 71.4% (Figure 3).

Nine patients who received less than 45 Gy total dose had an overall survival of 38.9% at one year follow up. When compared with the 1 who received 45–59 Gy total dose, a survival of 60.6% was found, while 13 patients who were treated with doses of 60 Gy and above had a 76.9% overall survival at one year (Figure 4). It is noted this is a heterogeneous group of adjuvant and primary radiation patients.

Discussion

This small cohort study at a single institution interrogated outcomes at one year in all those who received radiotherapy. The

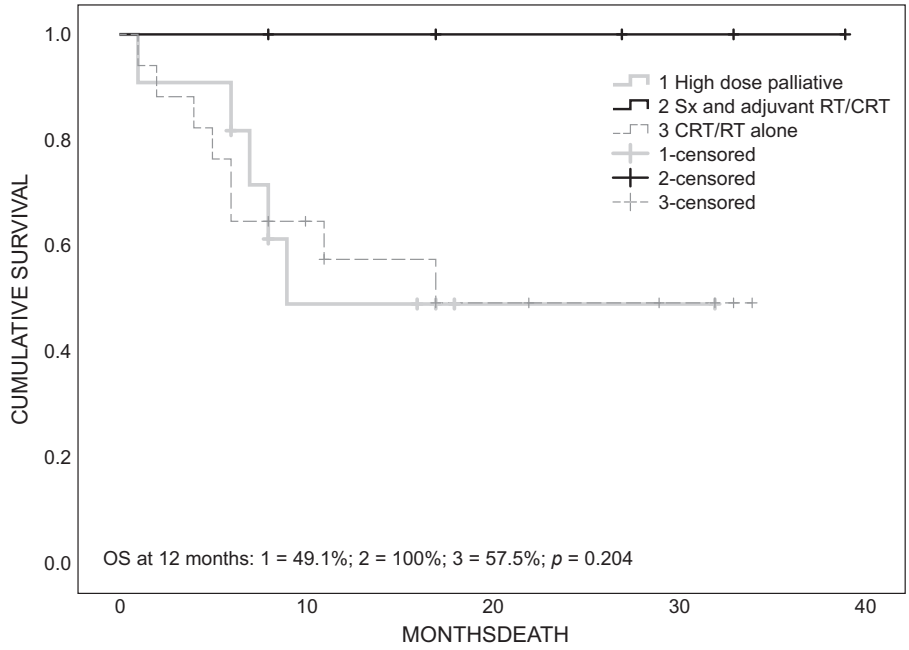

Figure 2: Overall survival at 12 months by treatment modality.

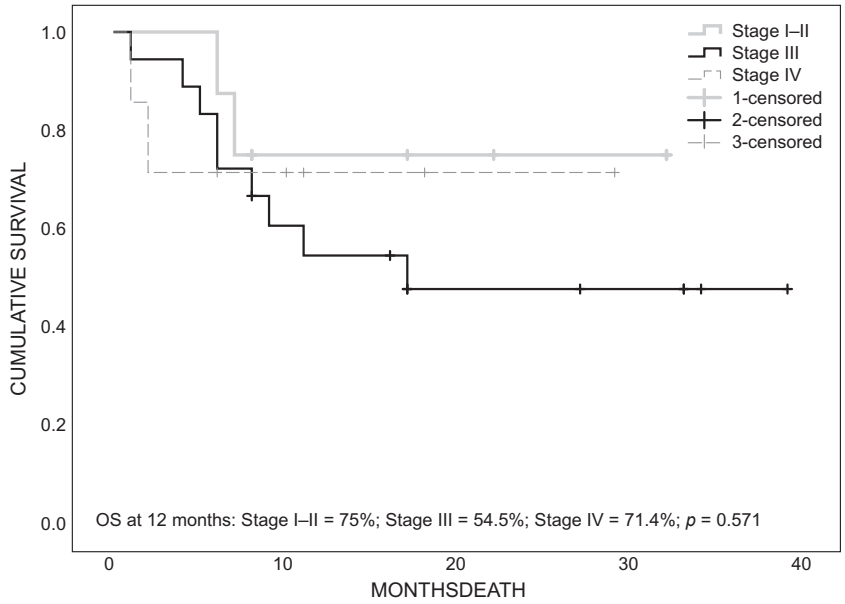

Figure 3: Overall survival at 12 months by stage of disease.

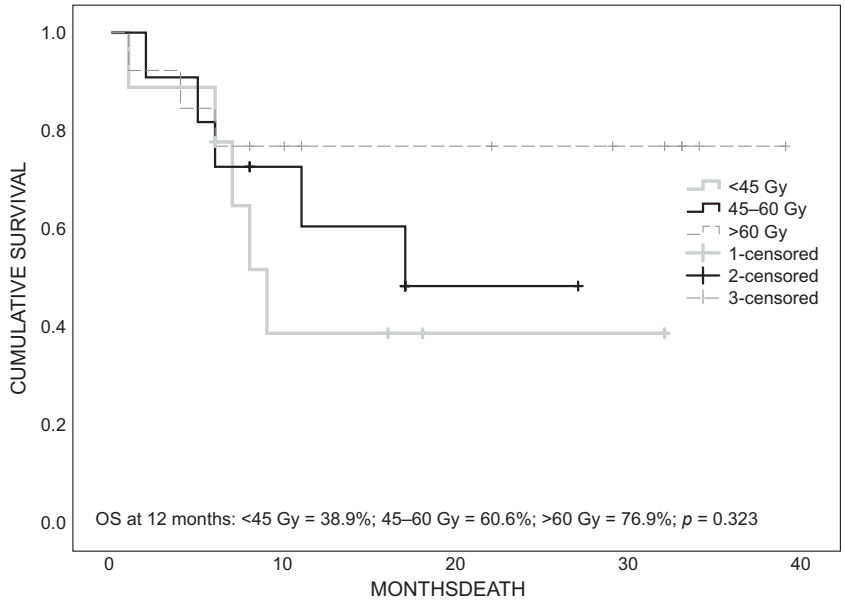

Figure 4: Overall survival at 12 months by total dose received.

intention of primary chemoradiation is to evaluate patients for post RT surgical excision if there is evidence of disease. This rationale is based on the outcomes of two GOG studies.

The GOG 101 trial studied the use of concurrent cisplatin and 5-flouraracil (5-FU) chemotherapy plus radiation before surgery.[5] In that study, 48% of patients had clinically complete responses, and only 3% of patients needed urinary diversion or colostomy.

Study design changes that led to the phase II GOG 205 trial where the chemotherapy was changed from cisplatin-5FU to weekly infusions of cisplatin alone as is used in cervical cancer treatment.[4] The radiation dose of 47.6 Gy in GOG 101 was intentionally low because all patients were expected to undergo surgical resection; radiation was given twice daily with a treatment break between the first and second cycles of therapy to limit the potential for severe acute toxicity.[5] However, in the GOG 205 study, the total dose was increased by 20% to 57.6 Gy with the hope to maximise the chemotherapy–radiation interaction; here the radiation was once daily, and the treatment break was eliminated.[4] The most common toxicities were hematologic adverse events, dermatitis, pain and metabolic disturbances.

In the GOG 101, 48% had a complete clinical response and 31% pathological response compared with GOG 205 at 64% and 50%, respectively.[5] The escalation of the radiation dose was thought to be the most significant factor in the improved results in the GOG 205 trial. Elimination of the treatment break may also have played a role. Among the 58 evaluable patients, 40 (69%) completed the study treatment in the GOG 205 trial.[4] In all, 37 (64%) patients had a complete clinical response, and 29 (78%) underwent a surgical excision with a complete pathological response and acceptable toxicity.[1,3]

In our setting, there are multiple challenges to this approach: theatre waiting times, the extent of disease precluding salvage surgery, and patient reticence regarding colostomies and extensive surgery. In our cohort no patients were suitable for surgery following primary chemoradiation.

In our analysis we observed that patients with locally advanced vulval carcinoma had an improved one-year overall survival with both surgery and adjuvant radiation, which was superior to definitive chemoradiation or radiotherapy alone. The dose of radiotherapy was significant; for women who received a total dose of radiotherapy > 60 Gy, better local control was observed when compared with those who received a total dose of less than 45 Gy. High-dose radiotherapy (60–70 Gy) achieves a high rate of local control with a low risk of major long-term side effects in locally advanced vulval carcinoma.[7]

The relationship between HPV infection and female lower genital tract neoplasia has been established in the past 20 years.[8] During the same period of time, studies have also shown that patients infected with HIV have a propensity to develop certain neoplastic diseases. Invasive vulval carcinoma is not uncommon in the younger age group as it has been linked with immunosuppression caused by HIV infection.[3]

The outcomes of HIV-infected patients were not reported in any of the literature reviewed. In our study, we found no significant influence on outcome for local control; however, survival (70.0%) was better for the HIV-negative group. HIV status and outcomes may be of importance in our setting due to the increasing incidence of HPV and the HIV epidemic.

There were limitations to our research study and interpretation of results. A retrospective study is at an inferior level of evidence compared with a prospective study with limited statistical power. Given that vulval cancer is such a rare disease, our study sample was small and our duration of follow-up was short to allow for an in-depth analysis of survival and local recurrence. We relied on the accuracy of written records.

Despite these limitations, the strengths of the study included: all patients in the cohort completed the treatment, findings reflect the reality in vulval cancer treatment outcomes in a resource-constrained environment, our cohort was accurately staged at a multidisciplinary staging meeting and PET/FDG scanning was offered prior to radiotherapy for many patients.

Conclusions

Vulval carcinoma is a rare malignancy. In the developed world, vulval carcinoma is generally encountered in older patients at an earlier stage than in the patients reported in this study. With the increase in the disease burden in young South African women as a result of the increasing incidence of HPV, it is essential to explore the outcomes of the preferred treatment of chemoradiation for locally advanced carcinoma of the vulva.

The findings of this study have demonstrated that surgery and adjuvant radiotherapy in women with locally advanced disease results in a good overall survival at one year. The dose of radiotherapy is also vital, as patients who received a dose greater than 60 Gy had a superior overall survival and local control compared with patients who received doses less than 45 Gy. Concurrent chemoradiation remains a challenge because our patient population is in poor clinical condition due to the advanced stage of disease at presentation and medical co-morbidities, resulting in the omission of chemotherapy. It is evident that high-dose palliative radiotherapy provides excellent palliation for local control and short-term survival outcomes.

Radiotherapy remains part of the primary treatment for patients with locally advanced vulval carcinoma. Given its importance, further prospective clinical trials are needed to identify the optimal radiotherapy techniques and dosing.

Disclosure statement – No potential conflict of interest was reported by the authors.

References

1. Hacker NF, Eifel PJ, van der Velden J. FIGO CANCER REPORT 2012 Cancer of the vulva. Int J Gynaecol Obstet. 2012;119S2:S90–6. https://doi.org/10.1016/S0020-7292(12)60021-6.
2. National institute for communicable disease. National Cancer Registry 2014 Full Report; 2014 [cited 2019 Oct 1]. Available from: nicd.ac.za/wp-content/uploads/2017/03/2014-ncr-tables-1.pdf
3. Butt JL, Botha MH. Vulvar cancer is not a disease of the elderly: treatment and outcome at a tertiary referral centre in South Africa. South African Med J. 2017;107(11):1000–4. https://doi.org/10.7196/SAMJ.2017.v107i11.12497
4. Moore DH, Ali S, Koh WJ, et al. A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: A gynecologic oncology group study. Gynecol Oncol. 2012;124(3):529–33. https://doi.org/10.1016/j.ygyno.2011.11.003
5. Moore DH, Thomas GM, Montana GS, et al. Preoperative chemoradiation for advanced vulvar cancer: a phase II study of the Gynecologic Oncology Group. Int J Radiat Oncol Biol Phys. 1998;42(1):79–85. https://doi.org/10.1016/S0360-3016(98)00193-X
6. Shylasree TS, Bryant A, Howells REJ. Chemoradiation for advanced primary vulval cancer. Cochrane Database Syst Rev. 2011;2011(4). https://doi.org/10.1002/14651858.CD003752.pub3
7. Stecklein SR, Frumovitz M, Klopp AH, et al. Effectiveness of definitive radiotherapy for squamous cell carcinoma of the vulva with gross inguinal lymphadenopathy. Gynecol Oncol. 2018;148(3):474–9. https://doi.org/10.1016/j.ygyno.2018.01.007
8. Rao T, Bellam S, Gurupuprasad P. Vulvar invasive squamous cell carcinoma in a young patient with Human Immunodeficiency Virus-seropositivity. Indian J Sex Transm Dis. 2015;36(2):204–6. https://doi.org/10.4103/0253-7184.167180

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