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# A retrospective analysis of concurrent chemoradiation for squamous cell carcinoma of the anus in Johannesburg

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**Background:** Anal cancer is a major cause of mortality and morbidity in low- and middle-income countries (LMICs).

**Aim:** A retrospective analysis to understand presentation and outcomes of patients with anal cancer, who were treated with a curative intent.

**Setting:** A radiation oncology unit in quaternary level hospital in South Africa.

**Methods:** Medical records of patients with invasive squamous cell carcinoma (SCC) of the anal canal who were treated between 2014 and 2019 were reviewed with follow-up until June 2021. The 2D-radiotherapy planning and delivery techniques were used to a dose of 50 Gy, with a boost dose of 6 Gy – 10 Gy for patients with residual disease and concurrent chemotherapy.

**Results:** Eighty-four patients were included in the analysis. Median age was 45 years (range: 25–73 years), 75% were female patients, 80% of the cohort was human immunodeficiency virus (HIV)-positive, and 17% with a CD4 count below 200 cells/mm$^3$. Eighty-seven percent had locally advanced stage three disease. Concurrent 5-fluorouracil (5-FU) and mitomycin C-based chemotherapy was given in four patients, while 50% had 5-FU plus cisplatin and 16% had radiotherapy alone. Complete clinical response was observed in 54 out of 66 evaluable patients (81.8%) at 6 months post-chemoradiation. Overall survival at 2 years could not be determined because of a significant loss to follow-up rate.

**Conclusion:** A high HIV-postive rate and an advanced disease stage were observed among cohorts with anal canal SCC treated with a definitive curative intent. Tumour response rates at 6 months were favourable although the 2-year overall survival could not be established.

**Contribution:** This study contributes to the growing body of research on anal cancer outcomes in LMICs.

**Keywords:** anal cancer; squamous cell carcinoma; chemotherapy; chemoradiation; HIV; antiretroviral therapy; mitomycin; HPV.

## Introduction

Squamous cell carcinoma of the anus (SCCA) represents the most common histological form of anal carcinoma and its incidence is increasing worldwide, especially among persons living with HIV.[1] According to Global Cancer Statistics (Globocan) 2020, there were 50 865 new cases of anal carcinoma and 19 293 new deaths registered worldwide.[2] The South African National Cancer Registry reported a total of 472 individuals (181 male and 291 female patients) who were histologically diagnosed with anal cancer in South Africa during 2019.[3]

It is well established that SCCA is strongly associated with the human papilloma virus (HPV), most frequently subtypes 16–18.[1,4] Before the 1980s, the standard of care for anal cancers was surgical management with an abdominal-perineal resection (APR), which was associated with permanent colostomy and significant morbidity.[5] A major shift towards organ preservation came in 1974, when Nigro et al. first reported on the use of combined chemoradiation using 5-fluorouracil (5-FU) and mitomycin-C (MMC) for patients with SCCA.[6] Follow-up showed that pathologic complete response (pCR) translated into improved 5-year overall survival (OS) and avoided APR surgery in 60% of patients at 5 years.[6] The primary aim of curative combined chemoradiation for patients with stage II – III anal cancer is to achieve locoregional control, while preserving the anal sphincter with intact function and avoiding a colostomy, with a good quality of life.[7] Two randomised trials established the superiority of chemoradiotherapy over radiation

alone.[8,9] Chemoradiation with 5-FU and MMC has been the standard of care for more than two decades, but it is associated with clinically substantial adverse effects, notably myelosuppression and renal dysfunction.[7,10,11] James et al. showed no differences in complete response (CR), colostomy-free survival (CFS) or progression-free survival (PFS) between MMC and cisplatin; however, MMC has remained the standard of care because of its ease of use.[12] Currently, surgical resection is considered only for patients with superficially invasive SCC, and for T1N0 and select T2N0 lesions at the anal margin or as salvage for recurrent disease or persistent tumours after combined chemoradiation. The recall of MMC in 2019 by the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom and other regulatory authorities because of concerns regarding quality control and manufacturing processes led to a worldwide shortage of this chemotherapeutic agent (*alert reference SDA/2019/006*).[13]

Omission of MMC reduces haematological adverse reactions, but is associated with a decreased primary tumour control rate.[14] The Radiation Therapy Oncology Group (RTOG) 8704/Eastern Cooperative Oncology Group (ECOG) 1289 trial confirmed the superiority of 5-FU/MMC over 5-FU alone when combined with radiation.[15] Most of the evidence looking at outcomes in persons living with HIV and anal cancer comes from retrospective studies, a few of which found worse outcomes in this population.[16,17,18] Other studies, however, have found outcomes to be similar in persons living with HIV and human immunodeficiency virus (HIV)-negative patients.[19,20,21,22] Fraunholz et al. concluded that HIV-positive patients with anal cancer can be treated with standard combined chemoradiation with the same tolerability and adverse reactions as HIV-negative patients, and that long-term local control and survival rates are not significantly different between these groups. To gain insight into our institutional results for clinical response rates, and to evaluate trends in outcomes and adverse reactions for patients treated with a curative intent between 2014 and 2019, a retrospective analysis was performed.

# Methods

## Patient selection and work-up

Data were captured from the medical records of 84 patients with histologically proven invasive anal carcinoma treated with a curative intent between 01 January 2014 and 31 December 2019 at the Radiation Oncology Department at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), South Africa with follow-up recorded until 30 June 2021.

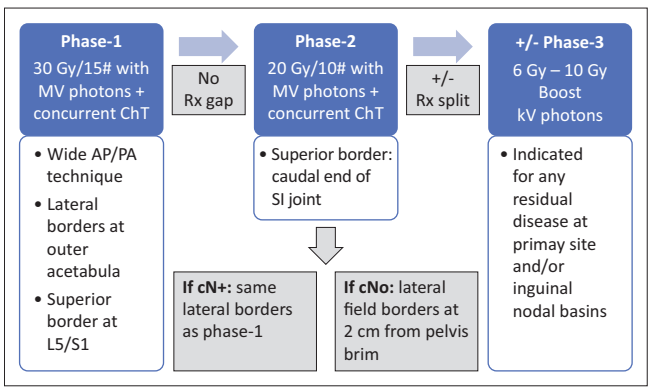
Male and female patients of all ages with locoregional (*non-metastatic*) SCCA, regardless of the HIV-status were included in the study. Biopsies were assessed and graded by the National Health Laboratory Service (NHLS) Histopathology Departments of the referring hospitals. The HIV-status and baseline cluster of differentiation 4 (CD4) count were determined at the base hospital as part of the diagnostic work-up. It was a standard practice in the unit to omit concurrent chemotherapy for patients with a CD4 count below 200 cells/mm$^3$. Disease staging was carried out following the tumour, nodes, and metastasis (TNM) and American Joint Committee on Cancer (AJCC) 7th edition, which was subsequently updated to the 8th edition in 2018.[23] For patients with incontinence, a colostomy was inserted prior to starting with treatment to increase the likelihood of successfully completing the combined chemoradiation.

## Data collection process

A data collection form was used to capture the following data from the patients' medical records: age at first consultation, gender, TNM staging, tumour histology, degree of tumour differentiation and HPV status, ECOG performance status, HIV status and CD4 count. All information relating to the radiation dose received and whether a boost dose was administered was retrieved from the treatment chart of each patient. Where prescribed, chemotherapy charts were also retrieved and any recorded justifications for chemotherapy dose reduction or alteration were captured on the data collection form. Treatment interruptions during the 50 Gy course and any split of treatment prior to the boost dose were recorded and the reasons were noted. Documented adverse reactions were evaluated using the RTOG adverse event criteria.[24] The data collection form was also used to record the tumour responses from the patients' files at several visits, from completion of combined chemoradiation up to 24 months following treatment. All data were electronically captured onto the Wits RedCap online database.

## Radiotherapy

Patients were treated with conventional external beam radiation therapy (EBRT) using the 2D-radiation therapy (RT) planning and delivery technique. The standard tumour, inguinal and pelvic nodal dose of 50 Gy was prescribed and chemoradiation consisted of three phases, which are summarised in Figure 1. Patients were simulated on a conventional simulator, either lying supine in a frog-leg position or lying prone. A 5 mm bolus was used to increase




#, fraction; MV, megavoltage; kV, kilovoltage; AP/PA, anterior-posterior/posterior-anterior field; ChT, chemotherapy; Rx, treatment; cN+, clinically node positive; cNo, clinically node negative.

**FIGURE 1:** Chemoradiotherapy delivery for anal carcinoma at Charlotte Maxeke Johannesburg Academic Hospital.

the dose superficially, especially where there was infiltration of the perineal skin. A radio-opaque marker was placed at simulation to mark the anal verge or the most inferior extent of the tumour.

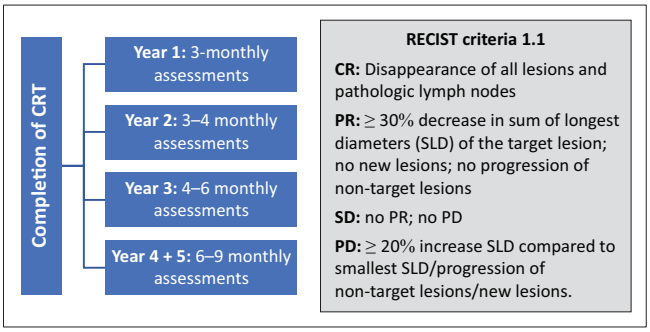
Phase-1 was treated to a dose of 30 Gy in 15 fractions and the radiation field was as follows: superior border (a line drawn through L5/S1 junction [the intervertebral space between L5 and S1 vertebrae]), lateral border (includes both inguinal nodal regions and lies lateral to the femoral head), inferior border (3 cm below the anal verge for tumours confined to the anal canal or 3 cm below most inferior extent of the tumour). The field extends from the posterior edge of the sacrum posteriorly to encompass all disease anteriorly. Phase-2 was treated to 20 Gy in 10 fractions and superior border was dropped from L5/S1 junction to the caudal end of the sacroiliac junction. The lateral borders remained unchanged for clinically node positive patients, but it was moved to 2 cm from the pelvic brim for clinically node negative patients. For all the fields, the treatment was delivered at 2 Gy per fraction, Mondays to Fridays. Both phase-1 and phase-2 were treated with anterior–posterior and posterior–anterior (AP/PA) beam arrangements on the linear accelerator machine using MV photons. The sequential boost dose of 6 Gy – 10 Gy was delivered on the orthovoltage machine using superficial (kV) photons with an energy range of 95 kV – 180 kV and an appropriately sized applicator for patients with residual disease. For phase-3 (boost treatment), a clinical mark-up was performed by the treating Radiation Oncologist and a direct field was used to treat residual disease with a 2 cm margin. No treatment gaps were planned between phase-1 and phase-2 of RT. However, a 2-week treatment split was allowed after phase-2 to allow for recovery of adjacent normal tissues prior to delivering the boost dose where it was indicated for residual disease.

## Chemotherapy

During this period, three concurrent chemotherapy regimens were used at CMJAH. Options included two cycles of bolus 5-FU 400 mg/m$^2$ intravenous (IV) on days 1–4 and 22–25 of RT over 30 min, plus cisplatin 70 mg/m$^2$ IV over 3 h on day 1 of RT. Another regimen used the same bolus dosing for 5-FU plus MMC 12 mg/m$^2$ on day 1 of RT, although access to MMC was limited during this period because of worldwide shortages.[13] In patients with age > 70 years and/or severe comorbidities 5-FU was prescribed alone. Persons living with HIV having a low neutrophil count (< 2.5 × 10$^9$/L) or a low CD4 count (< 200 cells/mm$^3$) were prescribed radiotherapy only because of concern for severe haematological adverse effects, although there is no data supporting this practice.

## Follow-up

During combined chemoradiation, patients were reviewed weekly at the RT clinic to assess their clinical condition, document, and manage any acute reactions.




CRT, combined chemoradiation; RECIST, Response Evaluation Criteria in Solid Tumours; CR, complete response; SD, stable disease; PR, partial response; PD, progressive disease.

**FIGURE 2:** Follow-up assessment schedule after completion of treatment.

Figure 2 outlines the follow-up schedule after combined chemoradiation. It was a standard practice to evaluate patients' response to treatment with a clinical examination and with no use of imaging because of resource constraints. Treatment response and adverse reactions were determined and evaluated during these visits. Tumour response was assessed using the Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria[25] as outlined in Figure 2. Depending on the needs of the patients, more or less visits could be scheduled. Patients with persistent disease, suspicion of local recurrence or of metastatic disease were referred for further work-up with a repeat biopsy for histological confirmation and imaging with either magnetic resonance imaging (MRI) or a computerised tomography (CT) scan to identify local and/or distant disease. No further reviews were scheduled after 5 years.

## Statistical analyses

The targeted sample size was 118 using the Fleiss continuity correction; however, only 84 patients could be included in the analysis.[26] The power is 80% at 0.05 alpha and 95% confidence interval.

Mean and standard deviation or median and interquartile range was summarised. Proportions and percentages were tabulated in STATA-16; this software was also used to generate graphs and charts.[27] The estimated incidence of relapse in the study participants was 25% locoregional relapse.[8] A treatment interruption refers to any unplanned missed treatment days during the 50 Gy course, whereas a treatment split refers to a treatment gap in the event of severe acute reactions to allow tissue recovery prior to delivering the boost dose.

## Ethical considerations

The protocol for this study was approved by the University of the Witwatersrand (Wits) Human Research Ethics Committee (HREC) on 20 August 2021 (No. M210320). Confidentiality of the data collected from medical records to the data collection forms was maintained by ensuring that there are no personal identifiers on the study documents.

Permission was obtained from the CMJAH chief executive officer and from the Radiation Oncology Head of Department

to access the patients' medical records. The study was registered on the National Health Research Database (GP202210 044).

## Results

A total of 84 patients with SCCA were treated with a radical intent between 01 January 2014 and 31 December 2019 and were included in the analysis.

Primary characteristics of this study population are described in Table 1, showing a mean age at first presentation of 45 years and a female predominance (75% of the patients). A high proportion of patients were HIV-positive (80%), with a CD4 count below 200 cells/mm$^3$ in 16.7% of the cohort. Performance status was measured using the ECOG scale at presentation.[28] Seventy-seven percent of the patients were ECOG-1 at presentation, 21% were ECOG-2 and 1.2% did not have a recorded performance status. Seventy-three patients had locally advanced stage-three disease. The majority of the tumours in this cohort (78.6%) were moderately differentiated squamous cell carcinomas. Information regarding risk factors for anal cancer, including sexual history, smoking history and a history of sexually transmitted infections was lacking in the patient files.

Among those who are HIV-positive ($n$ = 67), 36 patients (98.5%) were on antiretroviral therapy (ART) prior to starting combined chemoradiation. The one patient who was not on ART was referred to initiate treatment prior to starting combined chemoradiation. Sixty-nine percent of the cohort had a colostomy inserted prior to combined chemoradiation. As a result of poor documentation on follow-up and a high loss to follow-up rate, it was not established whether the colostomies had been reversed following the completion of combined chemoradiation.

Treatment characteristics are outlined in Table 2, and although the inclusion criteria specified that patients were required to have received at least one cycle of 5-FU-based chemotherapy with the radiation treatment, 13 patients (15.47%) received radiotherapy alone and were included in the analysis.

Among the patients who received concurrent chemotherapy, only four patients (4.8%) received standard of care chemotherapy, which consisted of MMC and 5-FU before MMC became unavailable in 2019. Forty-two patients (50%) received the combination of 5-FU and cisplatin, while 25 patients (30%) received concurrent 5-FU alone.

Interruptions of treatment during the 50 Gy course occurred in 58 patients, with reasons outlined in Table 1. Fifty-seven patients received a radiotherapy boost dose of 6 Gy – 10 Gy and of these, 53 patients required a split of treatment prior to the RT boost dose because of acute adverse reactions. Adverse reactions were graded using the RTOG or European Organisation for Research and Treatment of Cancer (EORTC) Radiation Toxicity Grading.[24]

As shown in Figure 3, the commonest adverse effect observed was radiation dermatitis. Grade ≥ 3 acute effects documented

**TABLE 1:** Patient and tumour characteristics.

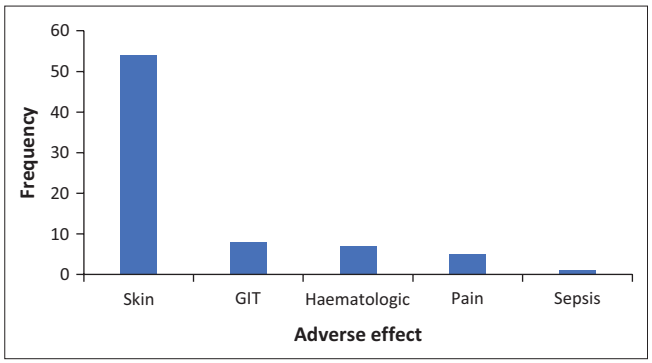
| Variable | *n* | % |
|---|---|---|
| **Age** | | |
| Mean age (years) | 45 | - |
| Age range (years) | 25–73 | - |
| **Gender** | | |
| Male | 21 | 25 |
| Female | 63 | 75 |
| **HIV status** | | |
| Negative | 17 | 20.2 |
| Positive | 67 | 79.8 |
| **CD4 at presentation (per mm$^3$)** | | |
| 0–200 | 11 | 16.7 |
| 201–500 | 30 | 45.4 |
| > 500 | 25 | 37.9 |
| Unknown | 1 | 1.49 |
| **Degree of tumour differentiation** | | |
| Well | 3 | 3.6 |
| Moderate | 66 | 78.6 |
| Poor | 12 | 14.2 |
| Unknown | 3 | 3.6 |
| **TNM staging** | | |
| 2A | 8 | 9.5 |
| 2B | 3 | 3.6 |
| 3A | 23 | 27.4 |
| 3B | 48 | 57.1 |
| 3C | 2 | 2.4 |

HIV, human immunodeficiency virus; TNM, tumour, nodes, and metastasis; CD4, cluster of differentiation 4.

**TABLE 2:** Chemo-radiation delivery patterns.

| Treatment characteristics | *n* | % |
|---|---|---|
| **Prescribed chemotherapy** | | |
| 5-FU + MMC | 4 | 4.8 |
| 5-FU + Cisplatin | 42 | 50.0 |
| 5-FU only | 25 | 30.0 |
| RT only | 13 | 15.5 |
| **Reason to alter/omit chemotherapy** | | |
| ECOG PS > 2 | 1 | 2.1 |
| CD4 count < 200 cells/mm$^3$ | 11 | 23.4 |
| Age > 70 years | 1 | 2.1 |
| Treating Physician decision | 34 | 72.4 |
| **RT boost administered (6 Gy – 10 Gy)** | | |
| No | 27 | 32.1 |
| Yes | 57 | 67.9 |
| **RT interrupted** | | |
| No | 26 | 31.0 |
| Yes | 58 | 69.0 |
| **Reasons for RT interruption** | | |
| Adverse effects | 39 | 67.2 |
| Machine breakdown | 7 | 12.1 |
| Logistics | 9 | 15.5 |
| Unknown | 3 | 5.2 |
| **Length of split by (in days)** | | |
| < 10 | 27 | 50.9 |
| 10–20 | 17 | 32.1 |
| > 20 | 9 | 17.0 |

5-FU, 5-fluorouracil; RT, raidation therapy; MMC, mitomycin-C; ECOG, Eastern Cooperative Oncology Group; CD4, cluster of differentiation 4.




GIT, gastrointestinal tract.

**FIGURE 3:** Documented grade ≥ 3 acute adverse effect.

**TABLE 3:** Tumour response assessments after completion of chemo-radiation.

| Tumour response | Complete | | Partial | | Stable | | Progressive | |
|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *n* | % |
| 6 weeks (*n* = 82) | 23 | 28.0 | 57 | 69.5 | 1 | 1.2 | 1 | 1.2 |
| 3 months (*n* = 78) | 36 | 46.2 | 38 | 48.7 | - | - | 4 | 5.1 |
| 6 months (*n* = 66) | 54 | 81.8 | 4 | 6.06 | - | - | 8 | 14.8 |
| 12 months (*n* = 48) | 35 | 72.9 | 3 | 8.57 | - | - | 10 | 20.3 |
| 18 months (*n* = 28) | 26 | 93.0 | - | - | - | - | 2 | 7.1 |
| 24 months (*n* = 21) | 19 | 90.5 | - | - | - | - | 2 | 9.5 |

in the patients' files included cutaneous (*n* = 54), gastrointestinal (*n* = 8), haematologic (*n* = 7), pain (*n* = 5), as well as neutropenic sepsis (*n* = 1). The numbers reported in Figure 3 are not exclusive as many of the patients had several acute adverse reactions documented. The duration of the treatment split was less than 10 days for 27 patients (50.9%) of those requiring a treatment split, and more than 20 days for nine patients (17%). The grading of adverse reactions was poorly documented in the patients' medical files.

Tumour responses were assessed using the RECIST Criteria Version 1.1[25] at different time intervals following the completion of treatment and is charted in Table 3. Thirty-six out of 78 evaluable patients had a complete treatment response at 3-months, 54 out of 66 evaluable patients had achieved a CR at 6-months, while 14.8% had disease progression. Out of 84 patients included in the analysis, only 21 patients (25%) were followed-up to 24 months after treatment and of these, 19 (90.5%) patients had achieved a CR 2 years after completing treatment while 9.5% had disease progression.

Among the 21 patients who were followed-up to 24 months, 6 were HIV-negative and 15 HIV-positive. A total of 12 of those who were HIV-positive had achieved and maintained a CR at 24-months, while 6 (100%) of those who were HIV-negative had achieved and maintained CR at the 24-months' assessment. None of the patients who had received standard of care concurrent chemotherapy regimen (5-FU and MMC) had achieved CR at 6-months post-treatment.

Among the 35 patients who had achieved CR at 12-months post-combined chemoradiation, 37% (*n* = 13) had received 5-FU and cisplatin, 54% (*n* = 19) had received 5-FU alone, and 8.6% (*n* = 3) had received radiation alone, while none had received the standard of care regimen of 5-FU and MMC.

**TABLE 4:** Recorded outcome at last visit and interventions for residual disease.

| Variable | *n* | % |
|---|---|---|
| **Response assessment at last follow up (*n* = 84)** | | |
| Complete | 39 | 46.4 |
| Partial | 22 | 26.2 |
| Stable disease | 0 | 0.0 |
| Progressive disease | 23 | 27.4 |
| **Reviewed for intervention (*n* = 42)** | | |
| Referral for surgery | 13 | 31.0 |
| Palliative radiation therapy | 4 | 9.5 |
| Palliative care | 14 | 33.3 |
| No intervention | 11 | 26.2 |

Among the patients who achieved CR at 6-months, 3% had received RT alone. Tumour responses at the last recorded follow-up visit are tabulated in Table 4, with only 46.4% of the treated cohort having achieved a CR at the last recorded follow-up visit and 53.6% having either partial response or progressive disease. Out of the 45 patients who did not have a CR at the last documented review, further interventions were recorded for 42 of those patients and included referral for surgery, palliative RT, referral to a palliative care unit or no intervention.

## Discussion

This is a single institution retrospective analysis of 84 patients with localised SCCA who were treated with a curative intent during a 6-year period. This study reports an HIV-positive rate of 79.8%, which is consistent with the literature findings that people with advanced HIV disease have an elevated risk for both in situ and invasive HPV-associated cancers, including anal squamous cell carcinoma.[29,30,31] Earlier trials that established chemoradiotherapy as the standard of care for anal cancer demonstrated an improved local control and CFS, but they relied on older radiation techniques using 2–4 fields that provide substantial radiation doses to organs at risk nearby the target volume.[8,9,32] In this study that was conducted in a resource constrained setting that still uses the same older techniques, a CR rate of 81.8% at 6 months post-combined chemoradiation was observed, which is comparable to the complete clinical response rate of 78% at 26 weeks observed by Glynne-Jones et al., using data from the ACT II trial.[33] That analysis found that many patients who do not have a complete clinical response when assessed at 11-weeks after combined chemoradiation do in fact respond by 26 weeks, and that an earlier assessment could lead to some patients having unnecessary surgery.[33] In our study, treatment was split only when patients developed acute grade 3 cutaneous, gastrointestinal and/or haematologic toxicities, and the treatment split was indicated in 53 out of the 57 patients requiring a boost dose of RT. The duration of the treatment split depended on the patients' time to recovery. Planned or unplanned interruptions in the delivery of RT used in many trials may have diluted the biological effects of treatment because they permit repopulation, leading to loss of local control.[34] Modern RT techniques, such as intensity modulated RT (IMRT) have led to a more conformal approach to targeting tumour volumes while sparing critical normal surrounding tissues and reducing toxicity.[35,36]

More conformal treatment strategies may allow for escalated doses to be achieved within a shorter overall treatment time with limited unplanned treatment interruptions.[37,38] The consensus of the RTOG panel is that IMRT is preferable to both 2D- and 3D-conformal RT in the treatment of anal carcinoma.[38,39] Chemotherapy with MMC and 5-FU remains the standard of care in the management of SCCA, and elimination of MMC results in almost doubling of 5-year local recurrence and a 17% decrease in 5-year disease-free survival (DFS).[5] The use of cisplatin as an alternative radiation sensitiser was inspired by its effectiveness in terms of response rate in other SCC in preliminary studies.[15] Observations of severe skin reactions when cisplatin was added to 5-FU led to a decision to omit cisplatin for some patients, treating with concurrent 5-FU alone. A CR rate of 81.8% at 6-months post-completion of treatment was observed and among those who had a CR at 6-months, 57% had received concurrent 5-FU and cisplatin regimen.

As 33% of those who had disease progression at 6-months received RT only, this finding is consistent with existing literature that concurrent chemotherapy is essential for improved treatment outcomes.[9] A systematic review and meta-analysis by Camandaroba et al. found that patients with localised SCCA and HIV-positive treated with combined chemoradiation tend to experience higher risk of toxicities and worse DFS and OS rates.[18] In this study, 49% of those with a CR at 6 months were females who are HIV-positive with stage-three disease. Prior to the widespread use of ART, HIV-positive patients, particularly those with a CD4 count below 200 cells/mm$^3$ were believed to experience greater adverse reactions from combined chemoradiation than uninfected patients and such reactions were thought to impair their ability to complete treatment.[17] More recent evidence suggests that patients who are HIV-positive and are treated with ART have similar response and survival rates to those who are HIV-negative.[1] Eighty-seven percent of the study population had stage-3 disease, and it is well established that in anal cancer TNM stage is an important prognostic factor, with advanced stage associated with inferior outcomes.[40] The author found a 69% rate of unplanned treatment interruptions during the 50 Gy course.

In a study by Meyer et al. of SCCA treated with combined chemoradiation, the authors found no adverse effect of treatment delays on local control, OS, and CFS. The treatment was halted when patients developed relevant acute grade $\geq$ 3 cutaneous, gastrointestinal or haematologic reactions, and was restarted after recovery from adverse effects, while the duration of the treatment break depended only on the patient's time to recovery.[41] To address specific effects of treatment time and RT time on outcomes in SCCA, pooled data from RTOG 8704 and 9811 were analysed by Ben-Josef et al.[34] The authors concluded that treatment time was significantly associated with CFS and local control. However, duration of RT itself was not associated with any outcome.[34]

This study was able to determine multiple data variables and outcomes were collected and analysed. However, it has several limitations. These include the retrospective study design, which is subject to biases, errors in retrospective assessment of outcomes and adverse effects, and failure to identify confounding variables that may influence results. The limited number of patients, in addition to the poor and inconsistent grading of adverse reactions in the patients' files were other limitations. One of the objectives of this study was to determine the OS rate at 2-years. However, with a loss to follow-up rate of 75% at 24 months, the researcher was unable to determine OS outcomes.

# Conclusion

This 6-year cohort study established that patients treated with a curative intent for anal cancer in our regional referral centre achieved a locoregional control rate of 81.8% at 6 months post-combined chemoradiation. A significant proportion of patients presented with locally advanced stage-3 disease and the majority neither received the standard of care concurrent chemotherapy (5-FU and MMC) nor the alternative regimen of 5-FU and cisplatin. Although the study could not determine the OS at 2 years because of a high loss to follow-up rate, it contributes to the existing body of literature looking at clinical outcomes of anal canal squamous cell carcinoma treated with a curative intent in limited resource settings where 2D-radiotherapy planning techniques are still being applied.

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## Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

## Authors' contributions

P.T. conceived and designed the study, collected data from the medical files, captured the data on an electronic platform, analysed the data and took the lead in writing the manuscript. The supervisors, V.S. and P.R. provided critical feedback and helped to shape the research, analysis and manuscript. The corresponding author and co-authors granted approval of the final version to be published.

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## Data availability

Raw data required to reproduce the given findings are available to download from Wits RedCap (https://redcap.core.wits.ac.za/redcap/), and the hard copies of the data collection forms are available from the corresponding author, P.T.

## Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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