Retrospective review of 37.4 Gy in 11 fractions for the palliation of advanced cervical cancer

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Background: Bleeding, pain and discharge are common symptoms of cervical cancer that can be effectively palliated with radiotherapy.

Aim: To evaluate the effectiveness of an external beam radiotherapy dose of 37.4 Gy in 11 fractions for the local palliation of advanced cervical cancer.

Methods: This study is a retrospective review of all patients receiving palliative radiotherapy (37.4 Gy in 11 fractions) at the Department of Oncology, Universitas Hospital, Bloemfontein South Africa, from 2009 to 2013. The data from 324 cases were analysed. Data obtained included patient age, ECOG performance status, FIGO staging, histological type and grade, HIV status and CD4 count. The presence of renal impairment and patient-reported symptoms before and after treatment, as well as the duration of therapy, was also documented. The five-year overall survival was determined from available follow-up data.

Results: The majority of patients (50.9%) were between 40 and 59 years of age, 138 (42.6%) were HIV-positive and most patients presented with FIGO stage 4 disease 228 (70.4%). Squamous cell carcinoma (SCC) was the most frequent histological type (n = 292; 90.4%). Tumour grade was well differentiated in 16 (4.9%) patients, moderately differentiated in 171 (52.8%) cases and poorly differentiated in 113 (34.9%). Most patients reported improvement of pain, while bleeding and discharge had resolved in 99.5% and 79.3% of patients, respectively. Similar observations were noted at 3-, 6- and 12-month follow-up. Morphine analgesia was required in less than 10% of patients over the 12 month follow-up period. Of the initial cohort, 11 (3.4%) patients were still alive five years after completing palliative radiotherapy.

Keywords: cervical cancer, palliative care, pelvic pain, radiation, symptom control, vaginal bleeding, vaginal discharge

Introduction

Cervical cancer is the most common cancer of the female genital tract worldwide and the third most common cancer in females. It is the leading cause of cancer-related female deaths in developing countries. In 2018 the World Health Organization (WHO) reported that the incidence of cervical cancer in South Africa was 12.1% with a 9.8% mortality rate.2 Hence many patients are now being identified at an earlier stage.

Patients with cervical cancer are most often from poor socioeconomic backgrounds and frequently have comorbid HIV infection. Screening programmes are available at local clinics and district hospitals and are often directed towards those who are HIV-positive.3 Hence many patients are now being identified at an earlier stage.

Despite the availability of screening programmes, late presentation remains a problem due to lack of patient awareness or challenges with accessing healthcare facilities due to lack of finance.

The WHO defines palliative care as “an approach that improves the quality of life of patients and their families facing the problems associated with a life-threatening illness, through the prevention and relief of suffering through early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.”4 When a patient is not a candidate for curable therapy, symptom control and quality of life become the main focus of treatment.4

The decision to palliate a patient is determined by the local disease stage and patient-related factors. At the Department of Oncology, Universitas Annex Hospital, indications for palliative radiotherapy include FIGO stage IV disease, a poor patient ECOG performance status and impaired renal function secondary to prolonged hydronephrosis and advanced disease.

Radiation is often used in this setting to manage symptoms, most often bleeding and pain. The decision to offer palliative radiotherapy is based on effectiveness of the treatment, treatment-related side effects and the impact on quality of life. There is still a need to compare the different fractionation regimens.5 Patient status, the extent of local disease and tolerance of the surrounding normal tissue to radiotherapy are factors to consider when choosing a radiotherapy schedule.6 Palliative radiotherapy is offered with the aim of providing quick, effective symptom control and improving quality of life.7

Assessing the effectiveness of palliative radiotherapy is subject to the patient’s ability to describe the physical symptoms and the psychosocial factors that may impact on the expression of this.6

The Department of Oncology, Bloemfontein, utilises a unique external beam radiotherapy dose schedule of 37.4 Gy in 11 fractions delivered to the true pelvis with a 15MV photon beam. This fractionation schedule has historically been used at this department alone and originated there. It continued to yield excellent results, which has resulted in its sustained use.
There are no published data to support this schedule and this retrospective analysis was conducted to determine its efficacy in order to support its continued use. Given the lack of data available regarding fractionation schedules for this subgroup of patients, the researchers also aim to provide another treatment option.

**Methods and materials**

This was a retrospective review of patients receiving palliative radiotherapy at the Department of Oncology, Universitas Annex Hospital, Bloemfontein, South Africa between 2009 and 2013. All patients were treated as per protocol with an external beam radiotherapy, 11 fractions of 340cGy per fraction. Only patients who presented for follow-up review were included in the analysis. A total of 2,083 cases were identified using the cervical cancer ICD 10 coding. The files were assessed by the principal researcher to select those cases that met the inclusion criteria. Each file was assigned a unique study number to maintain patient confidentiality.

Inclusion criteria included histologically proven cervical cancer, patients from the Free State province, patients treated with 37.4 Gy in 11 fractions, and patients with at least one recorded follow-up visit. Patients were excluded from the study if they received 300cGy x 10 fractions, 400 cGy x 5 fractions, or 1 fraction of 800 cGy; if they were from Lesotho or the Northern Cape province, as these patients were referred back to these areas for further follow-up after having received their radiotherapy; if patients initially started radical therapy, but due to circumstances were changed to palliative radiation; and if they received palliative brachytherapy.

The data collection sheet listed pre-treatment information including patient age, ECOG status, FIGO stage, histological type and grade, HIV status and CD4 count if known, the presence of renal impairment (including a raised creatinine, renal failure or hydronephrosis), and the presence of vaginal bleeding, pain, vaginal discharge and urinary symptoms. The presence of bleeding, pain and discharge was recorded at the 1-, 3-, 6- and 12-month follow-up visits as well as if any morphine was required for additional pain control.

Patients in the cohort, as well as today, are locally staged clinically. Chest X-rays are used to evaluate lung fields. Any suspicious findings on chest X-rays prompt CT scans. Abdomino-pelvic ultrasound is used to evaluate the kidneys, liver and lymph nodes, as well as for bladder and rectal infiltration. It was noted during data collection that ultrasound findings were not confirmed with cystoscopy or proctoscopy as they are today.

The radiotherapy was given using a 3D Conformal radiotherapy technique. An anterior-posterior field arrangement encompasses the true pelvis limited inferiorly by the obturator foramen and projecting laterally to 2 cm across the pelvic brim. Fields are extended to encompass gross disease outside the standard field borders. The latter may include tumours extending to the distal vagina or disease involving the inguinal glands clinically.

A dose of 37.4 Gy is delivered four times a week, often with Fridays omitted, but is dependent on the day on which treatment is initiated. The dose is prescribed to the midline.

Upon completion of a course of palliative radiotherapy, patients are followed up one month after completion of treatment, three-monthly for the first two years, six-monthly for the next three years, and annually thereafter. Patients who remain in good clinical condition may be offered systemic therapy if they have developed new symptoms on follow-up.

**Missing data**

In the absence of a documented ECOG score, an assumption was made from description in the records. Patients who were in good or even excellent condition were assigned to the ECOG PS 0 or 1 group. Patients who were in fair condition but chronically ill were assigned to either the ECOG PS 2 or 3 group.

Renal impairment was defined as raised creatinine levels, as creatinine clearance could not be calculated on available information.

Urinary symptoms were determined from described symptoms including urinary frequency, leakage or pain upon urination.

Follow-up visits did not always coincide with scheduled times. Hence the interval was widened to compensate for this. One, 3, 6 and 12 months was defined as 3–5 weeks, 3.5–4.5 months, 6–8 months and 11–13 months after treatment, respectively.

The researcher was required to extrapolate symptom data based on available clinical notes. If no symptoms were reported during history-taking and the vaginal examination was normal, the assumption was that bleeding or discharge was absent. In the absence of required information, the data were input as missing or unknown. Symptom grading was unavailable in this retrospective analysis.

The date of diagnosis, treatment start and completion dates as well as dates of last follow-up were documented. The number of patients who followed up at five years post-treatment, the date of last follow-up and the date of death, if known, were also recorded. After an initial pilot review of 20 files, the data sheet was deemed acceptable to proceed with data collection. The data were transcribed to Excel format (Microsoft Corp, Redmond, WA, USA). Data were submitted to the department of Statistics, Free State University for assistance with analysis.

**Data analysis**

Results were summarised by frequencies and percentages (categorical variables) and means and standard deviations or percentiles (numerical variables).

**Ethical considerations**

The study received ethical approval from the Health Sciences Research Ethics Committee (HSREC) (information blinded for peer review). Appropriate permission was also received from the Head of the Department of Oncology and the Free State Province Department of Health. In view of the retrospective nature of the study, informed consent was waived by the Ethics Committee. All patient information remained confidential through the use of study numbers.

**Results**

Of the 2,083 files obtained, 324 met the inclusion criteria. Table 1 summarises the demographic data of the patient cohort. The majority of patients were ≥40 years of age, with 17.3% (n = 56) between 20 and 39 years. The majority of patients (94.4%) patients had an ECOG performance status of either 1 or 2. In total, 138 patients (42.6%) were HIV-positive. The CD4 counts
of HIV-infected patients ranged from 4 to 1 350 cells/µL, with a median count of 306 cells/µL; 31.2% of the HIV-positive patients had CD4 counts less than 200 cells/µL.

An increased creatinine level was noted in 67 (22.3%) patients with creatinine levels above the maximum limit of the normal range (90 µmol/L).

Table 2 describes the cohort in terms of FIGO stage, histological classification and tumour differentiation. Most patients (n = 318; 91.1%) presented with FIGO stage 3 or 4 disease. Squamous cell carcinoma (n = 292; 90.4%) was the most common histological variant and approximately 60% (n = 171; 57.7%) of tumours were well or moderately differentiated.

Presenting symptoms included urinary complaints, 66.9% (n = 182/272) of cases; pain, 95.0% of cases (n = 301/317); vaginal bleeding, 92.5% (n = 296/320) and vaginal discharge, 80.2% of recorded cases (n = 154/192).

Table 1: Age, ECOG* performance status (PS) and HIV status of patients with cervical cancer receiving palliative radiation (n = 324)

| Variable            | n (%)       |
|---------------------|-------------|
| Age group:          |             |
| 20–39 years         | 56 (17.3)   |
| 40–59 years         | 165 (50.9)  |
| ≥ 60 years          | 103 (31.8)  |
| ECOG PS:            |             |
| 1                   | 170 (52.5)  |
| 2                   | 136 (42.0)  |
| 3                   | 15 (4.6)    |
| 4                   | 3 (0.9)     |
| HIV status:         |             |
| Positive            | 138 (42.6)  |
| Negative            | 163 (50.3)  |
| Unknown             | 23 (7.1)    |

*ECOG: Eastern Cooperative Oncology Group.

HIV testing is routinely done on all patients who visit the department as it is imperative to have patients with well-controlled HIV disease before initiating chemotherapy. The protocols for testing and treatment of HIV have altered significantly over the last decade. Twenty-three (7.1%) patients in the cohort had no information on their HIV status, with 42.6% being positive. Women who are HIV-positive have a five times higher risk of developing cervical cancer when compared with women who are HIV-negative. It was noted that a low CD4 count alone had been used in some cases to decide whether a patient was eligible for palliative treatment.

Discussion

In this retrospective review, 37.4 Gy in 11 fractions provides excellent control of symptoms in locally advanced cervical cancer, with relief of pain, bleeding and discharge.

Half of the patients in this cohort were in the 40–59 years age group, which was in keeping with other international studies. The decision for palliative treatment is determined by both patient and tumour factors. The ECOG performance status is important guide for decision-making. At presentation, 94.5% of the patients had an ECOG PS score of 1 or 2. Poor patient follow-up may be related to decline in performance status as well as patient death.

The local staging of the tumour, or FIGO classification, is used to indicate the extent of disease, with 70.4% of the patients in the cohort having stage 4 disease. We did not distinguish between stage 4A and 4B, as this does not alter treatment decision-making.

Slightly more than a quarter (n = 90; 27.8%) of patients in the cohort had stage 3 disease. Patients with stage 3 disease are amenable to curable treatment. However, poor ECOG status, the presences of multiple comorbidities, bilateral hydronephrosis and impaired renal function or advanced patient age may influence the decision to offer palliative treatment.

The histological type and grading did not guide treatment decisions and these features were recorded to classify the tumours. The majority of tumours were squamous cell carcinomas, with tumour grade most often moderately differentiated.
radiation, with 31.2% of the HIV-positive patients having CD4 counts lower than 200 cells/µL. No notes were made to indicate what the cut-off value for the CD4 count was, or if it was used in conjunction with other factors in decision-making.

HIV guidelines have changed over the years, and all patients who test positive for HIV now qualify for antiretroviral therapy, regardless of CD4 count.12

Renal impairment, which was observed as an elevated creatinine level in 67 (22.3%) patients in this study, is another factor considered when deciding on radical or palliative treatment. However, available resources preclude aggressive measures to correct renal function to allow for curative treatment in these patients. In addition to the disease burden coupled with poor ECOG PS and poor long-term prognosis in these patients, palliative treatment is justified in this group of patients.

The main objective of this study was to evaluate how the main symptoms suffered by patients with cervical cancer responded to palliative radiation. Symptoms at presentation are dependent on the stage of the disease. In a Nigerian study, it was found that up to 89.3% of patients presented with advanced disease, with bleeding resulting in death in approximately 6% of patients.13 The main symptoms evaluated in our study were vaginal bleeding, pelvic pain and vaginal discharge, as these symptoms are common and have also been investigated in previous studies.7, 14

The majority of the patients had vaginal bleeding as the main complaint before starting treatment. Some patients had severe bleeding requiring immediate radiation, while others had vaginal spotting and contact bleeding. As expected, pelvic pain was also found to be a common symptom experienced by most patients. Vaginal discharge was the least commonly recorded symptom.

Patients often present with urinary frequency, painful urination, haematuria or vesicovaginal fistula.15 These symptoms were not evaluated at follow-up visits after radiation. Pelvic radiation is also known to cause dysuria and haematuria as a side effect of radiation.15 As there was no quality-of-life scoring system, the pre- and post-treatment urinary symptoms were not assessed. It would also be difficult to determine who developed a vesicovaginal fistula because of the radiation alone, due to the shrinkage of the tumour after radiation therapy or because of tumour progression after radiation. As urinary symptoms are not symptoms looked at in the literature, they were not included in the main objective of the study. It is, however, recommended that future studies could focus on the side-effect profile of this radiation schedule.

Many radiation regimes that are unique to gynaecological malignancies are used in the palliative setting, with 10 Gy given monthly for up to three fractions being one of the most commonly used schedules.5 Onsrud et al.14 described the results of such a radiation schedule. Forty-six patients were included in the study. Ten patients received one dose of 10 Gy to the pelvis, 34 received a second dose of 10 Gy, and only 2 required the third dose. Each 10 Gy dose was separated by 3–4 weeks. In their study, 88% of patients had control of their bleeding and 36% achieved an improvement in vaginal discharge. However, they reported no notable decrease in pain experienced by these patients.14 The patients who were included in this study all had a life expectancy of less than a year before starting treatment. This schedule has been shown to cause late toxicities with a rate of 6–12% and is therefore not recommended for patients with a life expectancy of more than a year.4 The authors concluded that 10 Gy single fraction could be used with effective management of bleeding in patients with a life expectancy of less than a year, due to the tumour recurrence rate and toxicities experienced after that time.

In another study, Kim et al.7 described giving a mean dose of 25 Gy in five fractions with good results. Seventeen patients who received palliative radiation for cervical cancer were evaluated retrospectively, of whom 93.8% had resolution of vaginal bleeding and 66.7% reported a reduction in pelvic pain. The radiation was claimed to be well tolerated with few late complications.7

A Japanese study showed that the most commonly used palliative radiation schedule was 30 Gy in 10 fractions. Although it is the most commonly used schedule in patients needing haemostasis, re-bleeding did occur in 36% of patients.16 It is not
expected that patients with advanced disease of the cervix have prolonged survival, with most patients often dying within a year of receiving palliative treatment. It was reported according to international guidelines and are seen one month after receiving treatment. It was also interesting to note that all these patients were completely symptom-free at that stage.

It was reported in the early 1990s that radiation was effective for managing vaginal bleeding in patients with cervical cancer, with all patients reaching control of bleeding in 2–6 fractions of radiation. Corn et al. found that radiation alleviated pain and bleeding in 83% and 90% of patients, respectively, when a median dose of 35 Gy (7.5–45 Gy) with a median fraction size of 2.5 Gy (1–5 Gy) was administered. It has not been specified in the literature reviewed at precisely what time frame during radiation symptoms were controlled. When a time frame was mentioned, however, it was generally a broad range, for example, in a study investigating symptom control using palliative radiation, a follow-up period of 4 to 24 months was reported. In our department, patients are followed up according to international guidelines and are seen one month after completing radiation, then three-monthly for the first two years, thereafter six-monthly. As shown by our findings, patients did not always adhere to follow-up schedules due to multiple factors, including transport problems, incorrect dates being given to them and being admitted to other hospitals for non-cancer-related problems.

Pain control was achieved in 76.7% of patients by one month after completing treatment and remained stable throughout follow-up, with 76.6% of the cohort still having pain control at 12-month follow-up. These results reflected better pain control when compared with other regimens described in the literature, with only 66.7% of patients reporting pain improvement after receiving 25 Gy.

Vaginal bleeding is often the most bothersome symptom experienced by patients. More than 90% of the patients who were seen at all the follow-up intervals had resolution of their bleeding, which was similar to other previously described regimens, confirming that radiation is an excellent means to control bleeding. Unfortunately, bleeding often occurred with tumour recurrence and occurred at different stages throughout follow-up in those patients affected, possibly due to the varying nature of the individual tumours. These findings confirm how effective palliative radiation is at alleviating bleeding.

With regard to vaginal discharge as a post-radiation symptom, 79.3% of patients had resolution of their vaginal discharge at one-month follow-up, which remained stable throughout follow-up, with 76.3% of the cohort having no discharge at 12-month follow-up. This outcome was superior to findings reported for patients who had been treated with 10 G a month, of whom only 36% experienced an improvement in vaginal discharge. None of the files had any record of when patients died. The researchers did not expect patients to have prolonged survival, and no conclusions regarding the patients who did not attend follow-up could be made.

The main limitation of this study was the need to rely on old clinical notes due to the retrospective nature of the study.

Files often had incomplete note-keeping that limited the information which could be used. Another limitation was the high rate of patients being lost to follow-up. This could lead to selection bias. It is not, therefore, known whether the patients who did not attend follow-up had died or if they could not come to the clinic due to logistical complications, and thus their symptom control could not be evaluated.

**Conclusion**

The primary focus of this study was to evaluate symptom control in patients with cervical cancer who were treated with palliative intent with the radiation dose that is unique to the department, namely 37.40 Gy administered in 11 fractions. This study showed that in the patients who were followed up, adequate symptom control was reached. We recommend this unique fractionation for palliative symptom control of patients with cervical cancer who do not meet the criteria to be treated radically.

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