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ORIGINAL RESEARCH

Retrospective study of the treatment outcomes of cervical cancer in young women treated at a single institution

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Background: Cervical cancer affects mostly young women from poor countries and disadvantaged populations. Limited information is available that specifically outline the presenting features and treatment outcomes of young patients treated for cervical cancer.

Objectives: The aim of this study was to evaluate treatment decisions and outcomes in young women (under the age of 39 years) with cervical cancer who were treated at a single institution in South Africa.

Design and methods: Retrospective analysis was used to review medical records of patients younger than 39 years of age with cervical cancer who were referred for radiation from January 2015 to December 2017. Data were collected on patient demographics, HIV status, stage, treatment and survival outcome.

Results: During the study period, 92 patients under the age of 39 years of age were referred for radiotherapy. The median age was 33 years of age (24–38 years). Overall, 35.9% (n = 33) were HIV-positive. Disease characteristics indicated that 65.2% (n = 60) were Stage IIIB and above. Seventy patients (76.1%) received primary chemoradiation, radiation or adjuvant chemoradiation. HIV-negative patients were significantly more likely to be prescribed curative therapy (86.2% compared to 60.6%; p = 0.05).

Two-year overall survival was 71.8% (65.1–78.5%) for the primary chemoradiation cohort and 80% (78.2–81.8%) for patients who received adjuvant chemoradiation. The outcome was significantly impacted by the delivery of concurrent chemotherapy in the primary chemoradiation group but not by HIV status of the patients.

Conclusion: Young women presenting with cervical carcinoma at our institution had a high prevalence of HIV and were mostly at an advanced stage. Though the HIV status of a patient impacted treatment intent, more than 80% of the cohort received a > 40 Gy external beam radiotherapy (RT) and the two-year overall survival was greater 70% in the curative group.

Keywords: cervical cancer, treatment outcomes, young women

Introduction

Cervical carcinoma is the fourth most common malignancy affecting women worldwide.[1] It is the leading cause of cancer-related deaths in many parts of Africa and affects mostly young women from poor countries and disadvantaged populations.[2] The highest incidence rates are recorded in sub-Saharan Africa.[3] In South Africa (SA), cervical carcinoma is the second most common cancer affecting women. The South African National Cancer Registry (NCR) recorded an age-adjusted incidence rate (AAIR) of 29.1/100 000 women and listed cervical carcinoma as the major cause of cancer-related deaths among South African women.[4]

Some prognostic factors influencing treatment outcomes for cervical carcinoma have been well documented.[5-7] However, the impact of age on treatment outcomes is less well researched. Results from previous studies have not shown a consistent effect of age on a patient's survival rate.[8] Some studies reported that progression free survival (PFS) and overall survival (OS) outcomes for cervical carcinoma were independent of age,[9] while other studies reported that in patients younger than 45 years, age was a poor prognostic factor.[10] Furthermore, an inverse relationship between patients' age and their OS was also reported in some studies. Although results indicated an improved five-year OS rate for cervical carcinoma patients who were younger than 40 years,[11] this finding was not consistent with results obtained by other studies. In Roque et al.,[12] age of patients influenced the treatment they received but had no significant effect on cancer-specific mortality either in patients over 65 years of age or those who were younger. Similar results were obtained in a larger cohort, multi-institutional study by De Rijke et al.[13] where age was not an independent prognostic factor for cervical carcinoma.

In sub-Saharan Africa, two cohort studies assessed prognostic factors in cervical carcinoma in HIV-positive and -negative cohorts. Simonds et al.[14] looked at 6-week response rates in 383 patients with no difference in age group; however, the average age for HIV-positive patients was 10 years younger than the HIV-negative cohort. Dryden-Peterson et al.[15] showed a decreasing trend in OS in young women who were co-infected with HIV.

The findings from these studies illustrate the ambiguity around the prognostic impact of young age in the treatment outcome of cervical carcinoma; therefore, there is a need to further evaluate as well as streamline a clear relationship between age and cervical carcinoma prognosis. There are not only inconsistencies in age-related outcomes, but also variations in the age gap used to separate younger and older patients treated for cervical carcinoma. In this study, we evaluated the treatment outcomes

of young patients treated radically for cervical carcinoma at Tygerberg Academic Hospital (TAH).

Objectives

To describe two-year OS for young cervical carcinoma patients (< 39 years) referred to radiation oncology. Secondary objectives include description of the demographic features of the cohort and to determine prognostic features for outcome.

Study design and methodology

Study site and population

The study was a retrospective cohort review of treatment outcomes for young women diagnosed with invasive cervical carcinoma from January 2015 to December 2017 treated at the division of radiation oncology at TAH in the Western Cape Province, SA. We included patients who had histologically confirmed diagnoses of cervical carcinoma, who were younger than 39 years of age and who had complete medical records. We excluded all patients who were treated before 2015, who had incomplete medical records and who were older than 39 years of age.

A predetermined data extraction tool was used to isolate study variables from eligible patient records and electronic databases in the division of radiation oncology. Demographic details comprised age, race and socio-economic status. Clinical data collected were the performance status at the start of treatment, tumour histology, HIV status, disease stage at the start of treatment, treatment modality and toxicity profile. The collected data were censored at 31 December 2018, date of last follow-up and date of death or recurrence. The primary endpoint was OS calculated from the date of start of radiotherapy (RT) to the censor date.

Treatment details

Patient selection and staging

All patients were treated using the departmental gynaecological oncology protocol. Patients were recruited through the gynaecological multidisciplinary team (Gyn MDT) comprising gynaecological oncologists, radiation oncologist, medical oncologist, pathologist and radiologist. Investigations performed were plain chest radiography, abdominal ultrasound, cystoscopy and baseline bloods – haematology, biochemistry, HIV status and CD4 count, if relevant. The cases were individually discussed at the MDT, followed by a comprehensive gynaecological examination by a pair of clinicians from gynaecological oncology and clinical oncology to finalise the staging according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging. Locally advanced and inoperable tumours were referred for primary chemoradiation (CRT). Patients with Stage III disease underwent an 18F-fluoro-deoxyglucose positron emission tomography/computerised tomography (FDG-PET/CT) planning scan when slots were available. Early disease that was borderline between Stage IB and Stage IIB underwent magnetic resonance and imaging (MRI) scanning of the pelvis with final staging after radiological review.

External beam radiotherapy

A four-field technique (anterior-posterior, left and lateral beams) with energy ranging from 6 megavoltage (MV) to 18 MV prescribed to the isocenter was used. Patients with Stage IB to Stage IIB received treatment ranging from 45 Gray (Gy) in twenty-five fractions at 1.8 Gy per fraction to 46 Gy in 23 fractions at 2 Gy per fraction. Those patients with Stage III disease were treated with doses of 50–50.4 Gy in 25–28 fractions. For para-aortic nodes at risk, an additional 45 Gy in 25 fractions was delivered to the para-aortic nodal (PAN) volume. Treatment fractions were given daily from Monday to Friday using an Elekta® linear accelerator machine.

Concurrent chemotherapy

All patients who were suitable (based on renal function) received concurrent chemotherapy with primary radiotherapy and, if indicated, with adjuvant RT. A nuclear glomerular filtration rate (GFR) was done prior to the start of treatment. Platinum-based chemotherapy with cisplatin was prescribed at 40 milligrams per body surface area, capped at 70 mg every week to a total of five cycles. Dose modifications were made based on the creatinine clearance, such that a drop in the creatinine clearance of 10% from baseline and/or creatinine clearance less than 60 resulted in cisplatin dose reduction of 25%. Carboplatin area under the curve 2 (AUC2) was used for low creatinine clearance (< 50 ml/min) or if the chemotherapy was delayed for 2 weeks as a result of renal toxicity.

Brachytherapy

High dose rate (HDR) treatment with iridium 192 was prescribed at 22–25 Gy in 4–5 fractions on alternate days to Manchester point A.

Postoperative patients treated with adjuvant RT/CRT were treated using a vaginal cylinder brachytherapy applicator prescribed to 0.5 cm depth and 5 cm upper vaginal length, and received 11 Gy in two fractions.

Posttreatment follow-up assessment

Patients who completed treatment received post-treatment counselling and were booked for a routine follow-up. Hormone replacement therapy was prescribed after completion of treatment. The first follow-up was scheduled at six weeks after completion of treatment, where the treatment response was assessed. Thereafter, patients were followed-up on every three months during the first year, four-monthly during the second year and every six months from the third to fifth years.

Statistical analysis

Statistical significance of differences in demographic factors, clinical parameters, and toxicity between study subjects and controls were evaluated by means of t-tests for continuous variables and chi-squared tests for categorical variables. The Kaplan–Meier method was used to determine OS. Cox proportional hazards regression models were developed to analyse the associations of age with mortality, controlling for

confounding variables. A *p*-value of 0.05 was set to be statistically significant for inferences.

Results

Demographic and clinical data

From January 2015 to December 2017, 93 patients were identified who were younger than 39 years and treated for cervical carcinoma at our institution. This accounted for 11.39% of the 816 cervical carcinoma patients referred to our division for radiation during the study period. In total, 92 patients met the inclusion criteria. One patient was excluded due to missing records. Seventy patients were treated radically, out of which 64 received primary chemoradiotherapy or RT and six had adjuvant chemoradiotherapy or RT. Twenty-two patients were treated with palliative intent.

The median age was 33 years (24–38) and the majority of the patients were 30–34 years old, making up 46.7% of the total cohort. Only 14.1% of the patients were younger than 30 years old (Table I).

The majority of this cohort (65.2%) had advanced disease (Stage III to Stage IVb) compared to 34.8% of the patients who had relatively early disease. The predominant histology was squamous cell carcinoma. In addition, 35.9% of the patients were HIV-positive at the time of diagnosis.

Table I: Patient demographics

Variable	*n* = 92	%
Median age (yrs)	33 (24–38)	
Age (yrs)		
• < 30	13	14.7
• 30–34	43	46.3
• ≥ 35	36	38.9
FIGO stage		
• IB–IIB	32	34.8
• **III–IVB**	60	**65.2**
Histology		
• **SCC**	84	**91.3**
• Adeno	6	6.5
• Other	2	2.2
HIV status		
• Negative	58	63.0
• **Positive**	33	**35.9**
• Unknown	1	1.1

Treatment data

HIV-negative patients were significantly more likely to be prescribed curative therapy than HIV-positive patients (86.2% vs 60.6%; $p = 0.05$). The majority of patients (71.9%) completed more than four cycles of platinum-based chemotherapy given concurrent with RT with a combination of external beam radiotherapy (EBRT) and brachytherapy. The median equivalent radiotherapy dose at 2 Gy (EQD2) was 76.7 Gy interquartile range (IQR) (74.4–81.2 Gy) (Table II). Seventy-six patients (82.6%) received > 40 Gy (Table II).

Table II: Treatment details

Variable	*n* = 92	%
Treatment intent		
• **Primary CRT/RT**	64	**69.6%**
• Adjuvant RT	6	6.5%
• Palliative RT	22	23.9%
Chemo. cycles for CRT/RT	*n* = 64	
• 0–3	18	28.1%
• **≥ 4**	**46**	**71.9%**
Median RT dose EQD2 CRT/RT	76.7 Gy IQR (74.4–81.2)	

CRT – chemoradiation, RT – radiotherapy, EQD2 – equivalent dose at 2 Gray per fraction

Survival data

Six patients were censored at last date seen and were subsequently lost to follow-up. Including these cases, the two-year OS was 71.8% (95% CI 65.1–78.5%) for the primary chemoradiation cohort and 80% (95% CI 78.2–81.8%) for patients who received adjuvant chemoradiation. No palliative patient survived beyond two years (Figure 1).

There was a trend toward a significant difference in survival between the HIV-positive women at 46.5% (95% CI 37.5–55.5%) and the HIV-negative at 68.7% (95% CI 62.4–75%); $p = 0.06$. However, this difference was negligible if the palliative cases were excluded (Table III). Comparing survival by stage for patients treated with curative intent only, 59.5% (95% CI 50–69%) of the cohort with Stage IIIB disease survived at two years, while the survival rate for Stage IB to IIB disease was markedly better at 88.3% (95% CI 78.8–94.8%); $p = 0.04$. There was no difference in OS between patients above or below the age of 30 years.

Patients who received less than three cycles of platinum-based chemotherapy had an OS of 48.4% (36.3–60.5%) compared to 86.7% (81.6–91.8%) for the cohort who had four or more cycles of chemotherapy ($p = 0.02$). Of the patients treated with primary RT or CRT an EQD2 of greater than 70 Gy was delivered to 95.3% of the 64 patients.

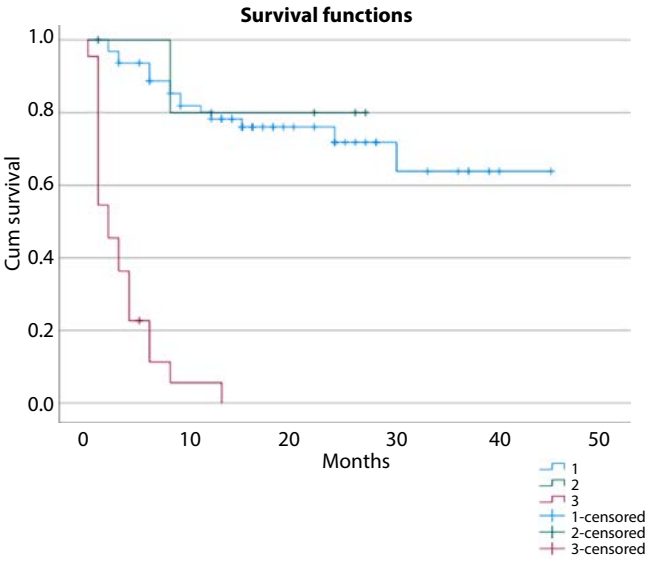

Figure 1: Kaplan–Meier estimate of overall survival by treatment intent
*Intent 1 – Primary; 2 – Adjuvant; 3 – Palliative

Table III: Overall survival for curative intent patients

Variable	% survival at 2 years	*p*-value
HIV status		
• Negative	77.2	0.834
• Positive	74.4	
Stage		
• IB–IIB	**88.3**	**0.04**
• IIIB	59.5	
Age		
• < 30	71.1%	0.9
• 30–34	78.8%	
• ≥ 35	65.8%	

For the 70 patients who were treated with curative intent, a multivariate analysis was performed on specific co-founder variables including HIV status, tumour stage and number of chemotherapy cycles completed. There was a significantly improved survival rate among the patients who completed more than four cycles of platinum-based chemotherapy (Table IV). There were no significant differences in survival by tumour stage or HIV status.

Table IV: Multivariate analysis of overall survival for curative treatment intent

Variable	OR	CI	*p*-value
Stage			
• IB–IIB	Referent		
• III–IVA	2.9	(0.82–10.52)	0.1
Chemo. cycles			
• ≥ 4	Referent		
• 0–3	3.0	(1.1–8.31)	**0.03**
HIV status			
• Negative	Referent		
• Positive	1.4	(0.49–4.2)	0.51

OR – odds ratio, CI – confidence interval

Discussion

This study conducted among women younger than 39 years of age who were treated at our institution found cervical carcinoma to be rare – less than 12% of all referrals to RT with a median age of 33 years. Previous studies that reported younger age as a poor prognostic factor in the treatment outcome of cervical carcinoma have variable conclusions. Lau et al.[16] linked the poor prognosis of cervical carcinoma in young women to tumour characteristics, which included non-squamous histology. Kong et al.,[17] despite acknowledging that non-squamous histology was the common histological subtype, found that the OS for this young age group was not less than that of the older group.

The majority of patients in our cohort had squamous cell carcinoma (SCC), contrary to the often-reported higher incidence of adenocarcinomas in young patients. A review of the SEER registry focusing on the prognostic value of histopathology in cervical carcinoma found that adenocarcinoma was associated with poor prognosis and increased incidence in young women.[18] Liu et al.[19] and Wang et al.[20] reported similar findings. The predominance of SCC (92.1%) in our study may have masked the prognostic effect of non-SCC histology reported in other studies.

Several studies have associated cervical carcinoma with HIV infection, mainly due to associated persistent HPV infections. Sub-Saharan Africa has one of the highest incidences of cervical carcinoma globally.[3] We found that a high percentage of our patients were HIV positive, which is consistent with the patterns of incidence of cervical carcinoma in HIV-positive women; occurring on average 10 years earlier than in HIV-negative women.[21] Available data show contrasting inferences on the effect of HIV status on treatment outcome of cervical carcinoma. Ferreira et al.[22] reviewed 222 patients treated with RT at the Brazilian Institute of Cancer. Their findings revealed that the HIV-infected cohort had similar outcomes to the HIV-negative cohort (hazard ratio [HR] 0.98; 95% CI 0.58–1.66).[22] Grover et al.,[23] report on 143 women evaluated in Botswana who were diagnosed with cervical carcinoma and treated with CRT. The two-year OS rate was 65% for the HIV-positive cohort (95% CI 54–74%) and 66% for the HIV-negative cohort (95% CI 49–79%), indicating no significant effect of HIV infection in cervical carcinoma on OS.[23] A recent prospective cohort of cervical carcinoma patients in Uganda examined the association between HIV and cervical carcinoma survival and presentation. In this study, Wu et al.[24] reported that HIV status was associated with stage at diagnosis but weakly linked to shorter OS. Our findings were consistent with those reported in other studies showing no significant HIV status related difference in OS. The two-year OS was similar between HIV-negative and HIV-positive women. Of note, Simonds et al.,[14] also from this institution, observed that in a large cohort of all ages, HIV-positive women did worse than HIV-negative women who were treated with CRT due to a more advanced stage and a lower likelihood of completing chemotherapy.

The standard of care for locally-advanced cervical carcinoma is concurrent CRT. At our institution, all cervical carcinoma patients are staged by a multidisciplinary panel with inputs from the gynaecological oncologist, pathologist, radiologist and clinical oncologist. Inoperable patients are referred to the Department of Radiation Oncology for non-surgical management. Many patients in our cohort were diagnosed with locally-advanced disease consistent with delays in diagnosis and access to health care in the local population.

During the study period, the majority of the cohort received primary RT or CRT or adjuvant therapy. Patients treated with primary surgery alone were not included. Overall, patients tolerated CRT well with a high adherence to completion of both modalities, over 70% completing more than three cycles of chemotherapy with the median EQD2 RT dose of 76.7 Gy. Previous studies have reported improved OS with treatment using concurrent CRT compared to RT alone. Eifel et al.[25] in the RTOG 90-01 trial, randomised cervical carcinoma patients to the CRT and RT arms. They found that the former was associated with improved OS.[25] A meta-analysis of 18 randomised control trials revealed that CRT improved the 5-year OS of cervical carcinoma by 6% compared to RT alone (HR 0.81; $p < 0.0001$).[26] Our analysis revealed findings similar to the findings from these previous studies. We found that patients who completed more than three cycles of chemotherapy recorded a higher two-year OS.

In our study, we found that the OS of these young women was relatively higher than what has been previously reported. A single-institution observational study reported a 59.1% two-year OS of patients treated for cervical carcinoma at the same institution during an earlier time period.[21] Similar findings were noted in other previous studies conducted in India and the United Kingdom.[27,28] The study by Grover et al.[23] from Botswana is more consistent with our cohort with a two-year OS of 65%. In our cohort, the improved OS of 71.8% may be due to improved treatment modalities over the more recent years (i.e. PET/CT scan planning for advanced disease, use of conformal radiotherapy) and potential improved HIV-immunocompetence due to combination antiretroviral therapy (cART) adherence. It is noted that four patients were lost to follow-up after radical RT.

Limitations of our study are attributed to the retrospective study design conducted at a single institution. As such, there was potential for limited information due to record-keeping. The assessment of post-treatment follow-up may not have been consistent as it was based on the clinical acumen of different medical doctors who worked through the gynaecology and oncology departments over the study period.

However, a strength of our study is that, to our knowledge, it is one of the few studies with a relatively large sample size, compared to other studies, to report on the prognostic effect of young age in cervical carcinoma. This study was conducted at an academic, tertiary level of healthcare with consistent multi-disciplinary standard of care management for all patients.

Conclusion

Younger patients with cervical carcinoma at our institution had a high adherence to therapy and good short-term outcomes, with over 70% of the cohort who received curative intent therapy alive at two years. The number of chemotherapy cycles completed during treatment was a significant prognostic factor. We recommend that the cohort be followed-up for long-term survival as well as further studies with a larger sample size to evaluate the prognostic effect of age in cervical carcinoma.

Conflict of interest

The authors declare no conflict of interest.

Funding source

No funding was required.

Ethical approval

The study was reviewed and approved by the Stellenbosch University Human Research Ethics Committee HREC (HREC approval number – S18/01/009) and consent to access medical records was obtained from the Department of Health through the TAH management. A waiver of consent was requested as the project was a retrospective analysis.

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