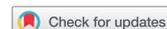


The impact of venous thromboembolism on the outcomes of patients with cervical carcinoma, a retrospective analysis at a single institution

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Background: Venous thromboembolism (VTE) is a frequent cause of morbidity in patients with cervical cancer. The aim of this study was to investigate the survival outcomes of patients with cervical cancer and VTE in a South African population.

Material and methods: The records of 47 cervical cancer patients with a concomitant diagnosis of a deep vein thrombosis (DVT)/VTE who were admitted to the radiation oncology ward at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in 2015 and 2016 were identified and analysed retrospectively. Data collected included the age, stage, human immunodeficiency virus (HIV) status and details of diagnosis of VTE and the treatment received. The survival of patients from diagnosis of VTE and the two-year overall survival (OS) rate was calculated using the Kaplan–Meier method. Univariate and multivariate analyses of factors influencing survival were performed on selected clinical variables.

Results: The majority of patients (60%) had stage IIIB cervical cancer; 60% of patients were HIV-positive. The median survival of patients from the time of diagnosis of VTE was 2.7 months (interquartile range [IQR]: 0.97–6.93 months) and the 12-month survival from diagnosis of VTE for this cohort was 17%. Once a VTE was diagnosed the survival becomes poor irrespective of age, stage or HIV status. The two-year OS of this cohort from date of diagnosis of cancer was 29.8%. Patients who were diagnosed with a VTE before or during radiotherapy had a significantly lower OS than that of patients who were diagnosed with a VTE after radiotherapy (12.5% versus 38.7%), $p = 0.004$.

Conclusion: The diagnosis of VTE is a poor prognostic factor in patients with locally advanced cervical cancer.

Keywords: cervical cancer, deep venous thrombosis, venous thromboembolism, survival

Introduction

Cervical cancer is the second commonest cancer in South African women.¹ The country's age-standardised incidence of cervical cancer is 32 per 100 000.² The burden of disease and the greatest mortality from cervical cancer occurs in less developed countries and is frequently associated with advanced disease at presentation.^{3,4}

Independent prognostic risk factors for survival in patients with cervical cancer include: race, stage, histology, and whether radiotherapy and/or chemotherapy was received.^{5,6} HIV infection is also associated with poorer survival in countries with a high incidence of HIV.^{7–9} Venous thromboembolism has been reported as a poor prognostic factor in several gynaecological malignancies including cervical cancer.¹⁰

The reported incidence of venous thromboembolism in patients with cervical cancer is between 3.3% and 15.7%.^{11–13} Jacobson *et al.* observed in their cohort that if patient with cervical cancer developed a VTE, it was diagnosed within one year following the diagnosis of cervical cancer or recurrence in the majority of patients.¹⁴ They also observed significant associations between thromboembolism and cervical cancer stage, with patients with more advanced stages having a higher incidence.¹⁴

Amongst patients with gynaecological malignancies who develop VTE, cervical cancer patients have the worst prognosis.¹⁵ Morgan *et al.* reported a median survival of 7.8 months in cervical cancer patients from the time of VTE diagnosis. Less than 20% of patients were alive at five years in their cohort.

Furthermore, they reported that the survival was significantly lessened in patients with cervical cancer who had radiation therapy within three months of a DVT diagnosis.¹⁵ Jacobson *et al.* have shown that thromboembolism independently confers a poorer prognosis in patients with cervical carcinoma. They reported a five-year survival of less than 40% in patients with cervical cancer with VTE vs. 80% in patients without VTE.¹⁴

The primary outcome of this study was survival from diagnosis of VTE/DVT and OS in patients with cervical cancer and a concomitant diagnosis of VTE, who were treated with radiotherapy at our centre.

Materials and methods

The data in this study were obtained by a retrospective chart review of patients with cervical cancer who were diagnosed with a DVT/VTE and admitted to the radiation oncology ward at CMJAH during the period January 1, 2015 to December 31, 2016. The study period extended from the January 1, 2015 to September 30, 2018 to have at least two years of follow-up. The data obtained from the records included, age, HIV status and CD4 count, the date of diagnosis of VTE, International Federation of Gynaecology and Obstetrics (FIGO) stage, histology, and the details of the chemotherapy and radiotherapy that was administered. The alive status or date of death was to be obtained by contacting the patients or their relatives telephonically.

The date of biopsy was taken as the date of diagnosis of cervical cancer. The diagnosis of a deep vein thrombosis (DVT) was determined by duplex doppler ultrasound, which confirmed the

laterality and extent of the DVT. The date of the doppler ultrasonography study was taken as the date of diagnosis of the DVT/VTE.

At the time of the study, patients with stage IIB cervical cancer were treated with chemoradiation (cisplatin 80 mg/m² three-weekly, EBRT 50Gy in 25 fractions and high dose rate (HDR) brachytherapy to point A: 24Gy in 3 fractions), whilst stage IIIB patients received radiotherapy alone (EBRT: 42.5Gy in 17 fractions and HDR: 18Gy in 2 fractions to point A). Patients with Stage IVA and IVB received palliative radiotherapy to the pelvis. Stage IVB cancer patients were referred for systemic chemotherapy. Anaemia during radiotherapy was managed with transfusions of packed red blood cells to maintain haemoglobin of at least 10 g/dl.

Statistics

Data were imported from Microsoft Excel (Microsoft Corp, Redmond, WA, USA) and were subsequently analysed using SPSS for Microsoft Windows, 25.0 (IBM Corp, Armonk, NY, USA). Univariate and multivariate analyses were performed using the Cox proportional hazards regression model and survival from diagnosis of VTE and overall survival were estimated by the Kaplan–Meier method.¹⁶ The OS period was calculated from diagnosis of cancer to date of death. Multivariate analysis of factors influencing OS and survival from diagnosis of VTE/DVT were performed on selected clinical variables by means of Cox's proportional hazards regression. Only variables that had a *p*-value of < 0.1 on univariate analysis were entered into the multivariable analysis. All tests were assumed to have a 95% confidence interval. In the multivariate analysis, a *p*-value of less than 0.05 was considered statistically significant.

Ethics

Approval to conduct the study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (Clearance certificate number: M181019).

Results

A total of 52 patients with cervical cancer who were admitted to the radiation oncology ward during the study period were identified as having a concomitant, confirmed diagnosis of DVT on a doppler ultrasonography. Of these, 47 patients had adequate stored data.

The clinicopathological characteristics of the patients with venous thromboembolism are given in Table 1.

Forty-six patients had lower limb deep venous thromboses and one patient was diagnosed with a concomitant pulmonary embolism in addition to a DVT. One patient had an upper limb DVT. Two patients had bilateral lower limb deep venous thromboses. Sixteen patients were diagnosed with a DVT before or during treatment with radiotherapy. The remaining 31 patients were diagnosed with a DVT after treatment with radiotherapy. The median time from diagnosis of cancer to the diagnosis of VTE was 7.73 months (IQR 2.87–14.08 months). Of the patients who were diagnosed with a DVT after radiotherapy, the median time after the last fraction of radiation to the diagnosis of DVT was 7.63 months. Ten patients did not complete the prescribed course of radiation; 6 died during the course of radiotherapy and the remaining 4 were lost to follow up.

For the 47 patients, the 12-month survival from diagnosis of VTE was 17% (Figure 1). The median survival from diagnosis of VTE was 2.77 months (IQR 0.97–6.93 months; Appendix Table A1).

Table 1: Clinicopathological characteristics of patients with cervical cancer and VTE

Characteristic	Category	n = 47	%
Histology	Squamous	43	91%
	Adenosquamous	1	2%
	Adenocarcinoma	2	4%
	Neuroendocrine	1	2%
FIGO stage	2B Proximal	4	9%
	2BDistal	8	17%
	3B	29	62%
	4A	3	6%
	4B	3	6%
Age (years)	≥ 50	21	45%
	< 50	26	55%
HIV status	Positive	28	60%
	Negative	19	40%
CD4 count (n = 27)	< 200	7	26%
	200–350	4	15%
	> 350	16	59%
ART (n = 27)	Yes	25	93%
	No	2	7%
Completed radiation	Yes	37	79%
	No	10	21%
Concurrent cisplatin	Yes	15	32%
	No	32	68%
Site of DVT	Upper limb	1	2%
	Lower limb	46	98%
	Associated PE	1	–
Recurrence	Local recurrence	9	–
	Metastases	16	–
	Unknown	28	–
Diagnosis of DVT relative to RT	Before/during RT	16	34%
	After RT	31	66%

RT = radiotherapy.

Parameters of age, stage, HIV status and the timing of the diagnosis of VTE in relation to radiotherapy did not confer prognostic significance.

The OS of the cohort was 55.3% at 12 months (median not reached) and 29.8% at 2 years (median 14.3 months, 95% CI 8.39–20.11 months). On multivariate analysis patients who were diagnosed with a DVT before or during the course of radiation were found to have a much shorter OS compared with patients who developed a DVT after radiation. The OS at 2 years was 12% for patients who were diagnosed with a DVT before or during radiotherapy versus 38.7% at 2 years for patients who developed a DVT after radiation. The median OS for patients diagnosed with a DVT before or during radiotherapy was 5.4 months (95% CI 1.47–9.47 months) vs. 16.73 months (95% CI 10.40–23.05 months) *p* = 0.001 (Figure 2). HIV status did not confer any prognostic significance in the cohort on multivariable analysis, *p* = 0.39 (Table 2).

Discussion

This study showed that the short-term survival for patients with cervical cancer and VTE is extremely poor. At 12 months from the time a DVT/VTE was diagnosed the survival was only 17%. The two-year OS from diagnosis of cancer was only 29.8%.

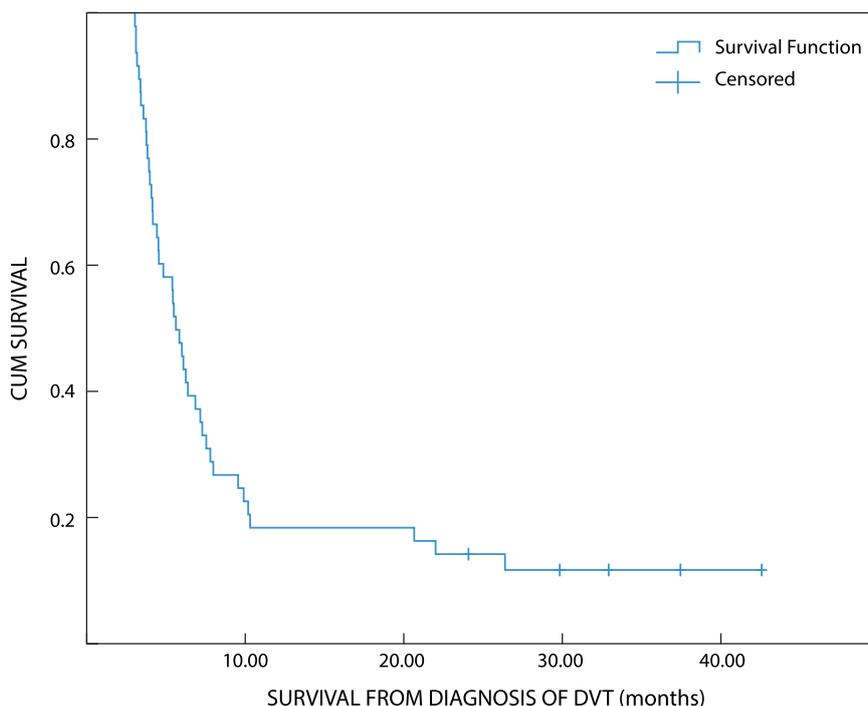


Figure 1: Kaplan–Meier graph indicating survival from diagnosis of DVT/VTE.

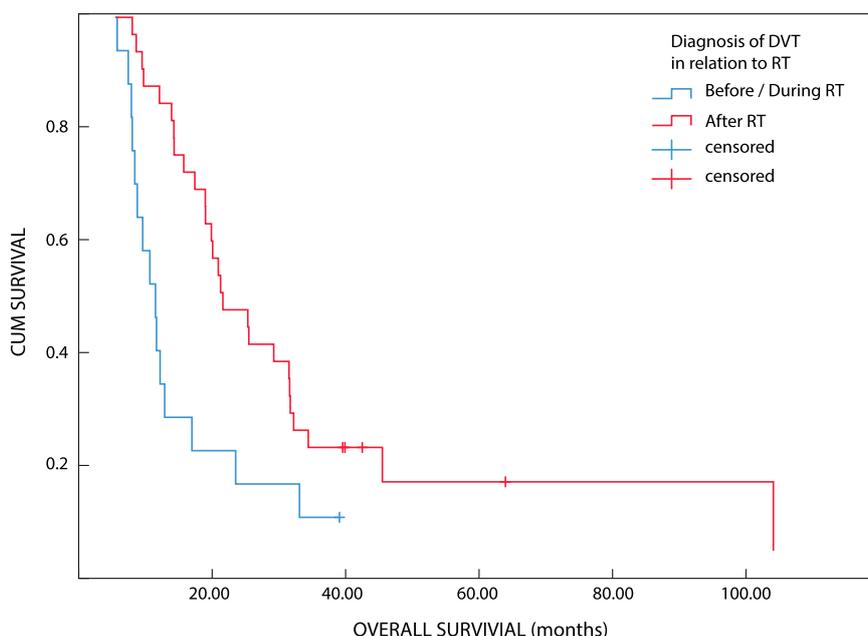


Figure 2: Kaplan–Meier graph indicating overall survival as affected by the timing of the diagnosis of DVT/VTE in relation to radiotherapy.

Poor survival in cervical cancer patients with VTE has also been reported in other studies (Table 3).^{14,15,17}

Venous thromboses are known to occur with greater frequency in patients with metastatic disease compared with patients with non-metastatic disease.¹⁸ Matsuo *et al.* reported a cumulative incidence of VTE in cervical cancer of 11.3% but a 44.8% incidence in the setting of metastatic disease.¹⁷ The majority of patients in the present study cohort, however, had stage IIIB disease. Whether patients with stage IIIB disease are more likely to develop venous thromboses compared with earlier stage disease is uncertain. A possible mechanism may be due

to pelvic sidewall extension and bulky nodal disease, which increases the risk of venous stasis and thereby predisposes to the development of a thrombosis. Stage IIIB disease, however, also has a greater propensity for loco-regional recurrence and distant nodal and metastatic disease.

The pathophysiology of VTE in malignancies is known to be complex. Immobility and the release of procoagulant factors by the malignancy can all contribute to the development of VTE in cancer patients.¹⁹ These factors can also be responsible for the poor prognosis in patients with VTE. VTE may therefore represent a manifestation or predictor of more advanced

Table 2: Prognostic factors of overall survival: univariate and multivariate analysis

Variable		Median (months) 95% CI	p-value (log rank test)	HR 95% CI	p-value (Cox model)
Age (years)			0.971	-	-
	≥ 50	14.3 (7.75–20.90)			
	< 50	12.63 (1.05–24.21)			
Stage			0.002		
	IIB	16.37 (10.16–22.58)		-	
	IIIB	14.30 (8.22–20.38)		1.02 (0.44–2.36)	0.970
	IVA & IVB	4.33 (2.93–5.73)		3.91 (1.17–13.08)	0.027
Diagnosis of DVT in relation to RT			0.001		
	Pre-RT	5.47 (1.47–9.47)		-	
	Post-RT	16.73 (10.40–23.05)		0.36 (0.17–0.72)	0.004
HIV status			0.141		
	Negative	17.10 (2.23–15.63)		-	
	Positive	8.93 (11.61–22.59)		1.39 (0.653–2.96)	0.393

RT = radiotherapy.

Table 3: Studies investigating VTE in cervical cancer

Series	No. of patients with cervical cancer and VTE	Five-year survival rates: cervical cancer with VTE vs. cervical cancer without VTE
Morgan <i>et al.</i> ¹⁴	21	20% vs. NR*
Jacobson <i>et al.</i> ¹⁵	98	40% vs. 80%
Matsuo <i>et al.</i> ¹⁷	51	55.1% vs. 90%

*Not reported.

disease or occult metastases, which could account for the poor prognosis of the group.

The survival of patients with metastatic disease is known to be unfavourable.²⁰ Only 6/47 patients in the present cohort were staged as stage IV at the outset. FIGO staging based only on clinical examination has limitations and patients could have therefore been under-staged. Given the poor survival in this group it is possible, therefore, that metastatic disease may have been higher in this cohort than estimated by the FIGO staging system, as patients are not routinely sent for staging CT scans before treatment is initiated. Information regarding local recurrence or metastatic disease at the time of admission was not always documented, as imaging studies were not routinely ordered to prove metastatic disease for patients with negative clinical findings on physical examination. The true prevalence of local recurrence and metastatic disease in this cohort could, therefore, not be determined accurately. Nevertheless 9 patients had documented evidence of local recurrence based on clinical and imaging studies and 16 patients had metastatic disease at the time of admission or follow-up. Frequent sites of metastases were lung, nodal and bone.

The study investigated overall survival and not disease-specific survival. With recurrent disease being documented in some of the patients, progressive disease is more likely to explain the poor survival as opposed to VTE being the cause. Interestingly, Matsuo *et al.* reported no deaths directly from VTE in their cohort.¹⁷

A variable that affected OS in this group was the timing of the diagnosis of the DVT in relation to radiotherapy. Patients who

were diagnosed with a DVT before or during the course of radiation had a much poorer survival at two years compared with patients who developed a DVT after completing their course of radiotherapy (12.5% vs. 38.70%, $p < 0.004$ (Table 2). This indicates that the development of VTE is strong predictor of poor survival. Once VTE is diagnosed in patients with a cervical cancer, survival becomes poor even if chemoradiotherapy or radiotherapy for the cancer is initiated. HIV infection is associated with a prothrombotic state.²¹ In a large prospective study, Simonds *et al.* recently reported differences in survival between HIV-positive and HIV-negative patients with HIV-positive patients having a poorer survival.⁸ HIV status did not, however, confer any prognostic significance in this cohort on multivariate analysis, $p = 0.393$.

Based on the fact that the incidence of VTE in patients with cervical cancer is higher than in the general population the question that arises is whether primary thromboprophylaxis is likely to reduce mortality or alter their prognosis. In a Cochrane review of nine trials investigating the use of thromboprophylaxis in ambulatory cancer patients, thromboprophylaxis with low-molecular-weight heparin (LMWH) reduced the incidence of symptomatic VTE.²² Thromboprophylaxis was, however, associated with a significant increase in bleeding complications. The number needed to treat to prevent one symptomatic VTE was 60. LMWH was associated with a 45% reduction in overall VTE and a 60% increase in major bleeding when compared with inactive control. The one-year mortality difference between the LMWH and control groups was, however, not statistically significant. Data from the studies included in the Cochrane review cannot necessarily be extrapolated to patients with cervical cancer, as the number of patients with cervical cancer was relatively low.²² Cancer patients, in general, with a concomitant VTE tend to have higher risks of bleeding complications than patients without cancer.^{18,23,24} The bleeding risk associated with cervical cancer probably outweighs the benefit of primary thromboprophylaxis.

Five major open-label, multicentre, randomised controlled trials have established that LMWH is the agent of choice in the treatment of VTE in cancer.^{24–28} LMWH is considered the standard of care for the treatment of cancer-associated venous thromboembolism.²⁹ Despite recommendations being published in major guidelines supporting the use of LMWH over warfarin, many cancer centres internationally continue to use warfarin in up

to 50% of patients.³⁰ At CMJAH, it is routine to anticoagulate the majority of patients with warfarin. The choice between warfarin and LMWH is made based on individual patient characteristics, e.g. co-morbidities, suitable route of administration, need for monitoring, concomitant medication and convenience. The reasons for using warfarin preferentially at our institution are usually the ease of administration of an oral agent for prolonged anticoagulation, adherence to therapy and cost. Based on the poor survival from diagnosis of DVT in this cohort, it is probably reasonable to anticoagulate patients with LMWH instead of warfarin where feasible.

There is a need to better understand the pathophysiology of cancer-related venous thrombosis and its risk factors for both prognosis and treatment. Studies specifically investigating VTE in cervical cancer are relatively sparse, despite VTE being a common occurrence. Research is required to evaluate whether asymptomatic patients should actively be screened for venous thromboses using doppler ultrasonography. Clinical trials evaluating the safety and effect of secondary thromboprophylaxis need to be conducted to effectively guide the management of patients with cervical cancer and VTE.

Limitations of the study

A limitation of this study is its retrospective nature and small sample size. As there was no control group, a comparison between age- and stage-matched groups was not possible.

As patients were staged clinically using only the FIGO staging system, there may have been patients who were under-staged and may have had metastatic disease already, despite being offered curative radiotherapy. This subgroup of patients may have had a poorer prognosis and may account for the poor survival in this cohort overall.

Conclusion

The presence of a DVT/VTE is associated with poor survival in patients with locally advanced cervical cancer. Once a DVT is diagnosed, the patient's prognosis becomes poor irrespective of initial stage, age or HIV status.

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Appendix

Table A1: Survival from diagnosis of VTE

Twelve-month survival from diagnosis of VTE					
Variable		Median survival (months) (95% CI)	p-value (log rank test)	Hazard ratio 95% CI	p-value (Cox model)
Age (years)			0.846	–	–
	≥ 50	1.93 (0.0–3.989)			
	< 50	3.00 (2.00–4.00)			
Stage			0.150	–	–
	IIB	2.63 (2.23–3.04)			
	IIIB	3.27 (1.78–4.78)			
	IVA & IVB	0.60 (0.00–1.52)			
Diagnosis of DVT in relation to RT			0.755	–	–
	Pre RT	2.77 (0.0–5.79)			
	Post RT	2.63 (1.17–4.09)			
HIV status			0.466	–	–
	Negative	2.57 (1.41–6.73)			
	Positive	4.07 (1.09–4.05)			

RT = radiotherapy.