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THE IMPACT OF VENOUS THROMBOEMBOLISM ON THE OUTCOMES OF PATIENTS WITH CERVICAL CARCINOMA, A RETROSPECTIVE AUDIT FROM JANUARY 2015 TO DECEMBER 2016

Preyesh Thakorbhai Goven Shiba

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfillment of the requirements for the degree of Master of Medicine in the branch of Radiation Oncology.

Johannesburg 2020

DECLARATION

I, Preyesh Thakorbhai Goven Shiba declare that this thesis is my own work. It is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.



.....

14 th day of August 2020

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS PROJECT

Poster Presentations

Preyesh Goven Shiba and Vinay Sharma (2019). **The impact of venous thromboembolism on the outcomes of patients with cervical carcinoma, a retrospective audit from January 2015 to December 2016.** Poster number 78 South African Congress of Oncology (SACO), Cape Town, South Africa, August 2019.

Preyesh Goven Shiba and Vinay Sharma (2019). **The impact of venous thromboembolism on the outcomes of patients with cervical carcinoma, a retrospective audit from January 2015 to December 2016.** Poster number 84, Wits School of Clinical Medicine Research Day (SOCM), Johannesburg, October 2019.

Publications

Goven Shiba P and Sharma V. **The impact of venous thromboembolism on the outcomes of patients with cervical carcinoma, a retrospective analysis at a single institution.** South African Journal of Gynaecological Oncology. 2019; 11(2):11-16.

ACKNOWLEDGEMENTS

I would like to thank my supervisor and mentor, Prof Vinay Sharma for his inspiration, guidance and support during the course of the project. I would also like to thank the staff of the Department of Radiation Oncology at Charlotte Maxeke Johannesburg Academic Hospital for their assistance during the data collection phase of the project. To my wife, Yashika for her constant encouragement and support, this enabled the completion of this thesis. And finally to all patients whom I had come into contact with during the registrar programme; they have taught me to appreciate the value of life and allowed me to grow both as a doctor and a human being.

ABSTRACT

Background

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

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 2 year overall survival (OS) rate was calculated using the Kaplan and Meier method. Univariate and multivariate analyses of factors influencing survival were performed on selected clinical variables.

Results

Forty seven patients had a concomitant diagnosis of cervical cancer and VTE. The majority of patients (60%) had stage IIIB cervical cancer. Sixty percent of patients were HIV positive and 40% of patients were HIV negative. 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 deep venous thrombosis was diagnosed the survival becomes poor irrespective of age, stage, HIV status. The 2 year overall survival of this cohort was 29.8%. The 2 year overall survival of patients who were diagnosed with a DVT before or during radiotherapy was significantly lower than that of patients who were diagnosed with DVT after radiotherapy, (12.5% versus 38.7%), p = 0.004.

Conclusion

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

TABLE OF CONTENTS

DECLARATION.....ii

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS PROJECT.....iii

ACKNOWLEDGEMENTS.....iv

ABSTRACT.....v

TABLE OF CONTENTS.....vii

LIST OF FIGURES.....ix

LIST OF TABLES.....x

NOMENCLATURE.....xi

Chapter 1 INTRODUCTION AND LITERATURE REVIEW.....1

1.1 General introduction.....1

1.2 Cervical cancer.....1

1.2.1 Epidemiology of Cervical cancer.....1

1.2.2 Natural history of cervical cancer.....1

1.2.3 Staging.....3

1.3 Prognostic factors in cervical cancer.....5

1.3.1 Age.....5

1.3.2 Race.....5

1.3.4. Stage and chemoradiotherapy.....6

1.3.5 Histology.....8

1.3.6 HIV Status.....8

1.4. Treatment.....9

1.5 Venous thromboembolism and Cancer.....11

1.5.1 Introduction.....11

1.5.2 VTE in cervical cancer.....14

1.5.3 Management of venous thromboembolism.....16

1.6 Justification of the study.....16

1.7 Study objectives.....17

Chapter 2 METHODS.....18

2.2 Statistics.....18

2.3 Ethics.....19

Chapter 3 RESULTS.....20

Chapter 4 DISCUSSION.....33

4.1 VTE as a poor prognostic marker in cervical cancer.....33

4.2 Primary thromboprophylaxis in patients with cervical cancer.....35

4.3 Treatment of VTE in patients with cervical cancer.....36

Chapter 5 LIMITATIONS, RECOMMENDATIONS AND CONCLUSION.....39

5.1 Limitations of the study.....39

5.2 Recommendations from this research.....40

5.3 Conclusion.....40

REFERENCES.....44

SUPPLEMENTARY INFORMATION.....47

APPENDICES:

APPENDIX 1: Human Research Ethics Committee (Medical) Clearance certificate.49

APPENDIX 2: Plagiarism report.....50

LIST OF FIGURES

Chapter 1

Figure 1.1 Lymph node spread in cervical cancer.....2

Figure 1.2 Annual relative survival rates of cervical cancer by population group in South African women.....6

Figure 1.3 Overall survival by tumour stage.....7

Figure 1.4 Five year overall survival status in cervical cancer patients by HIV status.9

Figure 1.5 Pathophysiology of cancer associated thrombosis.....12

Figure 1.6 Thromboembolism and inpatient mortality.....13

Chapter 3

Figure 3.1 Flow chart indicating the patient record selection process 20

Figure 3.2 Bar chart indicating the and clinical characteristics of patients by HIV status.....23

Figure 3.3 Survival from diagnosis of DVT.....28

Figure 3.4 Overall survival.....28

Figure 3.5 Survival from diagnosis of DVT by age category.....29

Figure 3.6 Overall survival by age category.....29

Figure 3.7 Survival from diagnosis of DVT by stage.....30

Figure 3.8 Overall survival by stage.....30

Figure 3.9 Survival from diagnosis of DVT by HIV status.....31

Figure 3.10 Overall survival by HIV status.....31

Figure 3.11 Survival from diagnosis of DVT as affected by the timing of the diagnosis of DVT in relation to radiotherapy.....32

Figure 13.12 Overall survival as affected by the timing of diagnosis of DVT in relation to radiotherapy.....32

LIST OF TABLES

Chapter 1

Table 1.1 FIGO staging for cervical cancer.....4

Table 1.2 Key results of systematic review and meta-analysis of concurrent chemoradiotherapy vs. radiotherapy in locally advanced cervix cancer.....7

Table 1.3 Treatment protocols according to stage at CMJAH……10

Chapter 3

Table 3.1 Clinicopathologic characteristics of patients with cervical cancer and venous thromboembolism.....22

Table 3.2 Survival rates from diagnosis of DVT.....26

Table 3.3 Overall survival rates.....27

Chapter 4

Table 4.1 Studies investigating VTE in cervical cancer 33

Table 4.2 Rates of major bleeding between VKA and LMWH…….....37

NOMENCLATURE

ART	Antiretroviral therapy
ASIR	Age standardised incidence rate
ASMR	Age adjusted mortality rate
CD	Cluster of differentiation
CI	Confidence Interval
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CT	Computed Tomography
DFS	Disease free survival
DVT	Deep Venous Thrombosis
EBRT	External Beam Radiotherapy
ECOG	Eastern Cooperative Oncology Group
EQD2	Equivalent dose in 2 gray fraction
FIGO	International Federation of Gynecology and Obstetrics
Gy	Gray
HDR	High dose rate (Brachytherapy)
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
INR	International Normalised ratio
OR	Odds ratio
OS	Overall survival
PE	Pulmonary embolism
PFS	Progression free survival
RT	Radiotherapy
VTE	Venous thromboembolism

Chapter 1

Introduction and Literature review

1.1 General introduction

Cervical cancer is a relatively common cancer in developing countries and is associated with significant morbidity and mortality. Whilst patients with early stage disease can achieve high cure rates, a proportion of patients still develop recurrent disease and suffer a poor prognosis with poor survival (1). Risk factors that may compromise survival need to be identified in order to optimise the management of patients with cervical cancer. Venous thromboembolism (VTE) has emerged as a risk factor for poor survival in cervical cancer but has been relatively understudied. The aim of the introduction is to briefly describe the epidemiology, natural history and established prognostic factors associated with cervical cancer. In the second part of the introduction the evidence of VTE as a poor prognostic factor in cancer is described and a summary of the available published studies on cervical cancer and venous thromboembolism is presented.

1.2 Cervical cancer

1.2.1 Epidemiology of Cervical cancer

Globally, cervical cancer is the fourth most common cancer in women. In 2012, 528 000 new cases were reported (2). The burden of disease and the greatest mortality occurs in less developed countries due to advanced disease presentation and lack of infrastructure (3,4). Cervical cancer is the second commonest cancer in South African women (5). The country's age-standardised incidence of cervical cancer is 32 per 100 000 (2).

1.2.2 Natural history of cervical cancer

Cervical cancer originates at the squamous columnar junction of the endocervix of uterus. Premalignant dysplastic lesions referred to as cervical intraepithelial neoplasia (CIN) may progress to invasive malignancy. According to the Bethesda system precursors are named squamous intra-epithelial lesions (SIL), which are

divided into low grade SIL (similar to CINI) and high-grade SIL (for CIN II and CIN III) (6). The time interval for the progression from a precursor lesion to invasive cancer ranges from approximately 10 – 20 years (7).

Invasive cervical cancer can be one of several histological subtypes namely, squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma or neuroendocrine carcinoma. Morphologically cervical cancer appears as a fungating, ulcerative or infiltrative lesion on the cervix (8). The tumour frequently extends to involve the upper vagina, uterine corporus, vaginal fornices, paracervical and parametrial tissues. Spread may occur to adjacent organs particularly the bladder and rectum. Regional spread is to lymph nodes in the pelvis namely obturator, external iliac, internal iliac and presacral lymph nodes. From the pelvic nodes, spread may occur to the para-aortic group of nodes. Spread via haematogenous spread occurs via the venous plexus and paracervical veins. The lung is the most frequent site of distant metastases. Others sites include the abdominal cavity, bones and supraclavicular nodes. (9)

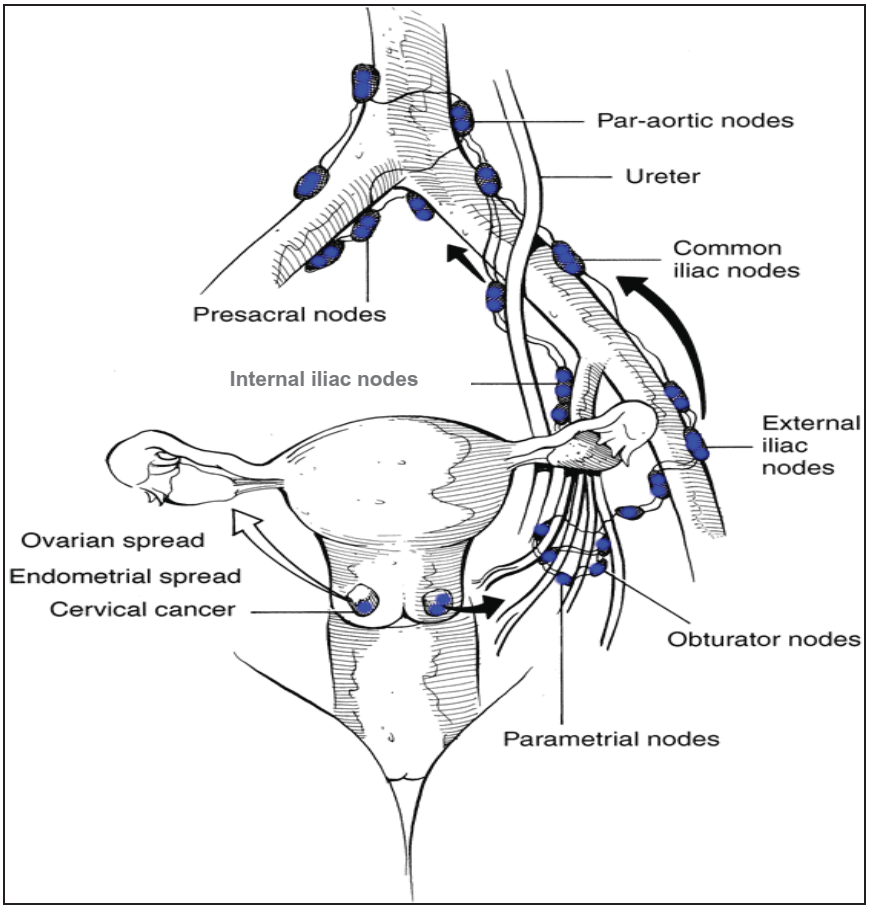


Figure 1.1 Lymph node spread in cervical cancer (10)

Premalignant and early invasive lesions are usually asymptomatic and are detected by periodic Papanicolaou smears. Patients with more advanced disease may present with abnormal vaginal bleeding, a clear or foul smelling vaginal discharge, and pelvic pain. Extension to the pelvic side wall is often associated with leg oedema and hydronephrosis. Bladder and rectal symptoms are associated with infiltration of the bladder or rectal walls in advanced disease.(11)

1.2.3 Staging

The International Federation of Gynaecology and Obstetrics (**FIGO**) staging system (FIGO) is the most widely used staging system used for the staging of cervical cancer (12). See table 1.

Table 1.1 FIGO staging for cervical cancer (2009) (12)

Primary Tumour	
I	Cervical carcinoma confined to the uterus
IA	Preclinical invasive carcinoma diagnosed by microscopy only
IA1	Minimal microscopic stromal invasion
IA2	Tumour with an invasive component ≤ 5 mm in depth taken from the base of the epithelium and ≤ 7mm in horizontal spread
IB	Clinical lesions confined to the cervix or preclinical lesions greater than IA
IB1	Clinical lesions ≤ 4cm in size
IB2	Clinical lesions ≥ 4cm in size
II	Cervical carcinoma invades beyond the uterus but not to the pelvic wall or to the lower third of the vagina
IIA	Tumour in the upper two thirds of the vagina without parametrial invasion
IIA1	Tumour in the upper two thirds of the vagina without parametrial invasion ≤ 4cm in greatest dimension
IIA2	Tumour in the upper two thirds of the vagina without parametrial invasion > 4cm in greatest dimension
IIB	Tumour with parametrial invasion
III	Cervical carcinoma extends to the pelvic wall and / or involves the lower third of the vagina and /or causes hydronephrosis or non functioning kidney
IIIA	Tumour involves the lower third of the vagina with no extension to the pelvic wall
IIIB	Tumour extends to the pelvic wall and or causes hydronephrosis or non functioning kidney
IVA	Tumour invades mucosa of the bladder or rectum and/or extends beyond the true pelvis
IVB	Distant metastases

1.3 Prognostic factors in cervical cancer

Independent prognostic risk factors for survival in patients with cervical cancer, include, age, stage, histology and whether radiotherapy and/or chemotherapy are received. (13, 14)

1.3.1 Age

Age has been identified as a prognostic factor by some authors; however data in published reports have been conflicting. Women younger than age 40 have been reported to have a poorer survival(15). Rutledge et al showed that age is associated with poorer survival in patients with more advanced stages while women with earlier stage disease tend to have similar rates of overall survival (16). Olorunfemi et al reported that over 65% of deaths occurred in the 40 – 60 year age group in South African women from 2004 to 2012. Only 2.2% of deaths were in women less than 30 years of age. The mean age at death was 56.1 years (17).

1.3.2 Race

Olorunfemi et al reported marked differences in mortality rates based on ethnicity in South Africa. The age adjusted mortality rate (ASMR) in Black, Coloured, Indian and White women were, 15, 9.2, 2.9, 2.6 per 100 000 respectively in 2012. Black and coloured women had lower 5 year survival rates compared to Asian/Indian and White women (17). These disparities have been attributed to socio economic status, smoking habits, sexual behaviours, access to health care facilities, parity, HIV prevalence and differential ethnic high risk HPV prevalence (17).

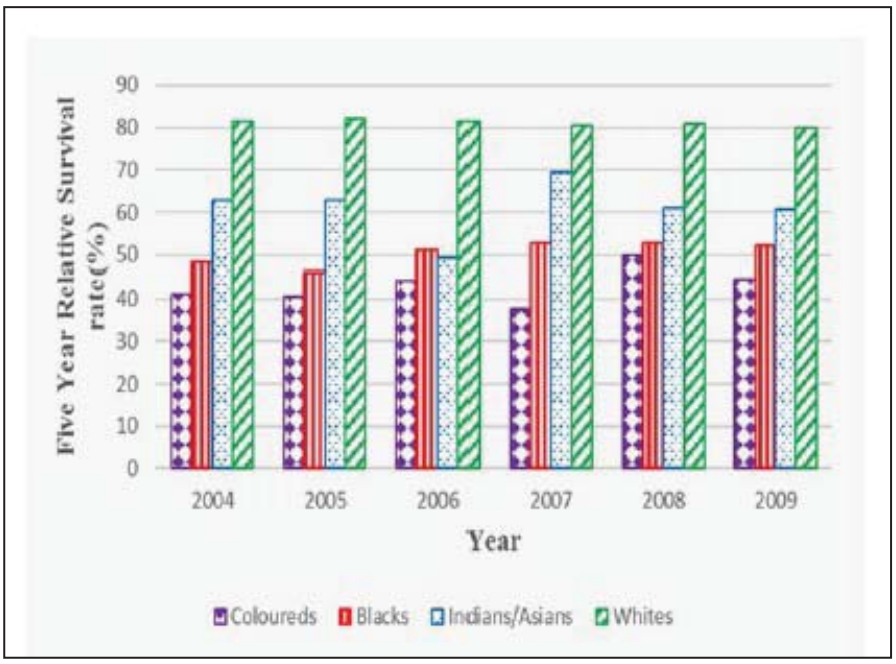


Figure 1.2 Annual relative survival rates of cervical cancer by population group in South African women (17)

1.3.4. Stage and chemoradiotherapy

Clinical stage is the strongest prognostic predictor in patients with cervical cancer, with survival rapidly declining with advancing clinical stage (9).

Worldwide chemoradiotherapy has become the standard of care for patients with locally advanced cervical cancer (18). A Cochrane meta- analysis reported an absolute 5 year overall survival benefit of 6% and an 8% benefit in disease free survival benefit (DFS) with chemoradiotherapy over radiotherapy alone (19). A recent meta- analysis of studies limited to patients with locally advanced cervical cancer showed that chemoradiotherapy improved outcomes for complete response (10.2%), loco-regional control (8.4%) and overall survival (7.5%) compared to radiotherapy alone. Acute toxicities were significantly higher in patients receiving chemoradiotherapy. The majority of studies included in this meta-analysis used cisplatin based chemotherapy.(20)

Table 1.2 Key results of the systematic review and meta-analysis of concurrent chemoradiotherapy vs. radiotherapy in locally advanced cervix cancer (Datta et al (20))

Outcome	Chemoradiotherapy	Radiotherapy	OR	p value
Complete Response	79.4%	69.8%	1.73	0.01
Loco-regional control	69.5%	61.8%	1.48	0.005
Survival at last follow up	67.9%	61.1%	1.38	<0.001
Acute toxicities Grade III/IV	16.4%	4.9%	3.74	<0.001

In a retrospective audit in the UK, the 3 year overall survival rates were 73%, 53% and 44 % for stages IB, IIB and IIIB respectively in the radiotherapy group versus 74%, 71% and 51% in stages IB, IIB and IIIB respectively in the chemoradiotherapy group (21). Figure 1.3 shows the disease specific survival rates for patients treated with radiotherapy and chemoradiotherapy by stage (21).

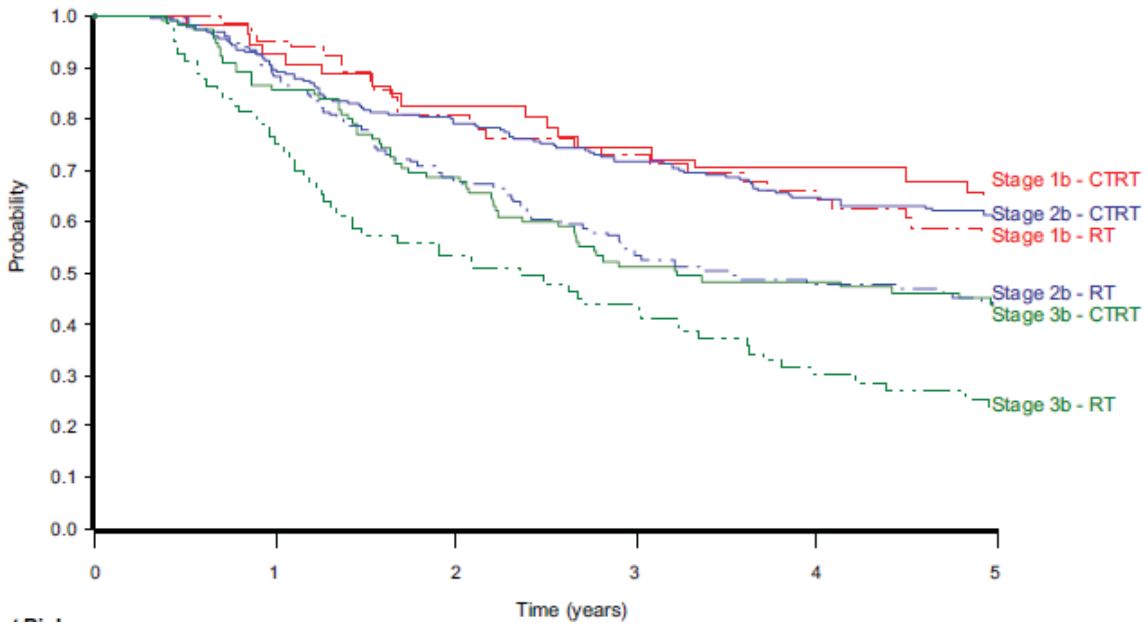


Figure 1.3 Overall survival by tumour stage (Radiotherapy and Chemoradiotherapy groups) (21)

1.3.5 Histology

Rose et al analysed 1671 patients treated on the GOG studies. Of the patients who were analyzed, 1489 (89.1%) were squamous, and 182 (10.9%) had adenocarcinoma or adenosquamous cancers. Adenocarcinomas and adenosquamous carcinomas of the cervix are associated with worse overall survival when treated with radiation alone but with similar progression-free and overall survival compared to squamous cell carcinomas of the cervix when treated with cisplatin based chemoradiation. When treated with radiation therapy alone, the 70 patients with adeno- and adenosquamous carcinoma of the cervix showed a statistically poorer overall survival ($p = 0.0499$) compared to the 647 patients with squamous cell carcinoma of the cervix. However, when treated with radiation therapy and concurrent cisplatin-based chemotherapy, 112 patients with adeno- and adenosquamous carcinomas had a similar overall survival ($p = 0.459$) compared with 842 patients with squamous cell carcinoma (22).

1.3.6. HIV Status

Studies done evaluating the survival of patients with and without HIV have shown conflicting results. HIV infected women had a poorer survival compared to HIV negative patients (23–27). However there were possible biases in these studies. Other studies showed no difference in survival in patients who were on antiretroviral therapy compared to the HIV negative population.

In a prospective study of women with cervical cancer in Botswana, HIV infection nearly doubled the risk of death. In unadjusted analysis, participants with HIV had shorter overall survival (median, 21.7 months; 95% CI, 16 to 24 months) than those without HIV (23). Gichangi et al reported higher acute radiation toxicity and pelvic failure in HIV positive patients receiving radiotherapy compared to HIV negative patients (28). Mangena et al reported, in a cohort of 50 patients in South Africa, that HIV infection adversely affected the ability to complete treatment and led to poor overall survival (29).

In a recent prospective study of 492 patients, Simonds et al reported a 2 and 5 year survival of 59.1% and 47.6% respectively in a South African population. In this study, HIV positive patients had a statistically significant poorer survival compared to HIV

negative patients. HIV negative patients had an OS of 62% (95% CI: 57.2% - 66.7%) at 2 years and 49.2% (95% CI; 44.6% - 54.4%) at 5 years. HIV positive patients had a poorer OS, 41.6% (95% CI 29.5% - 53.7%) at 2 years and 35.9% (95% CI; 23.9% - 48.0%) at 5 years (p=0.002) (30). In this cohort, the majority of HIV positive patients who died, died within 2 years after diagnosis (30).

In a recent phase 2 study conducted in sub-Saharan Africa, the AIDS malignancy consortium reported a 12 month overall survival of 81.6% (95% CI; 65.2 – 90.8%) and a progression free survival of 76.3% (95% CI; 59.4 -86.9%) (31).

Simonds et al reported a 2 year survival rate for stage 1B1 – IIIA patients of 74.3% and 52.2% for stage 3B disease. The 5 year survival rates were 61.5% vs. 41.3% respectively (30).

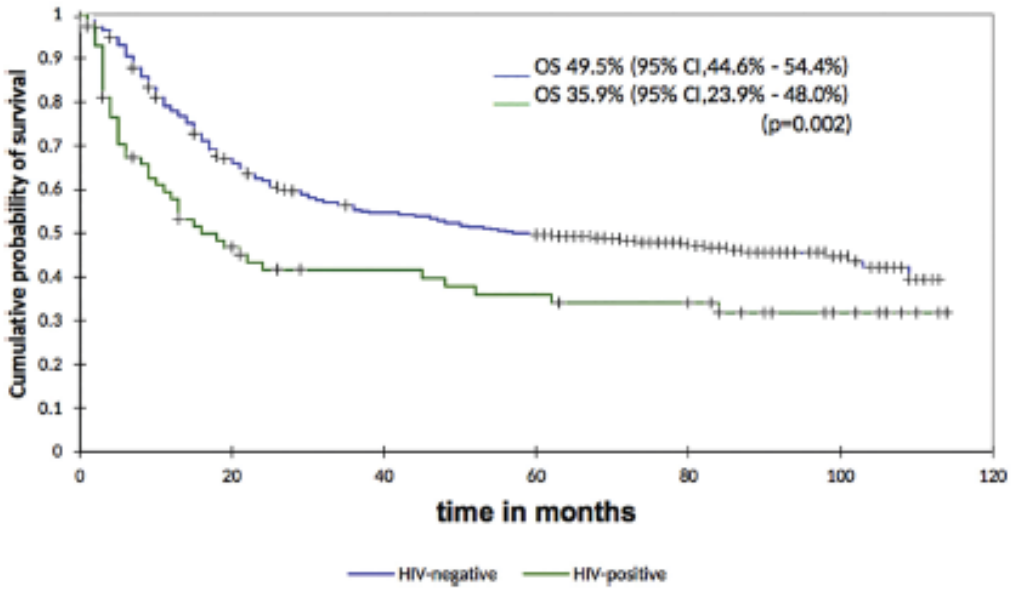


Figure 1.4 Five year overall survival in cervical cancer patients by HIV status (30)

1.4. Treatment

Depending on availability, persistent premalignant lesions are managed with surgical methods such as cryotherapy, laser ablation, cold knife conisation, or loop electrosurgical excision (9).

Invasive malignancy is managed according to stage. Very early stage disease is managed surgically whereas for patients with locally advanced disease chemoradiation remains the standard of care (18). Treatment of locally advanced cervical cancer includes radiotherapy, which consists of external beam radiotherapy (EBRT), and brachytherapy, and concurrent cisplatin based-chemotherapy(26). At Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), patients with cervical cancer are treated with protocols according to the International Federation of Gynaecology and Obstetrics (FIGO) stage. At the time of this study, patients with stage IIB cervical cancer at CMJAH were further divided into stage IIB proximal and stage IIB distal based on whether parametrial involvement exceeded 50%. Table 2 below shows the treatment protocols at CMJAH at the time of study for patients according to stage:

Table 1.3 Treatment protocols according to stage at CMJAH

Stage	EBRT	Brachytherapy	EQD2	Cisplatin
1B2	46 Gy/23 Fractions	26gy / 4 Fractions	81.8 Gy	80mg/m2, 3 weekly
2B Proximal	46 Gy /23 Fractions	26 Gy / 4 Fractions	81.8 Gy	80mg/m2, 3 weekly
2B Distal	50 Gy / 25 Fractions	24 Gy / 3 Fractions	86Gy	80mg/m2, 3 weekly
3B	42.5 Gy / 17 Fractions	18 Gy/ 2 Fractions	72.8 Gy	Nil
4A	10 Gy /2 Fractions monthly or 18 Gy / 3 Fractions alt days	Nil	33Gy or 24 Gy	Nil
4B*	10 Gy /2 Fractions monthly or 18 Gy / 3 Fractions alt days	Nil	33Gy or 24 Gy	Nil

*Patients with metastatic disease are offered palliative radiation to the pelvis for bleeding and pain

Patients with HIV and a CD4 count of less than 200 are offered radiation without concurrent chemotherapy. Patients with stage IIIB cervical cancer received radiotherapy with a hypofractionated protocol without concurrent chemotherapy.

1.5 Venous thromboembolism and Cancer

1.5.1 Introduction

Venous thromboembolism manifests as a deep venous thrombosis and or pulmonary embolism. A deep venous thrombosis is a clot in the deep veins, usually of the leg or arm. A pulmonary embolus occurs when a clot breaks away from the walls of a vessel and travels to the pulmonary circulation blocking off part of the blood supply. It is a relatively common problem in the community as well as hospitalized patients, and is associated with significant morbidity and mortality (32). Major risk factors for VTE include increasing age, prolonged immobility, major surgery, major trauma, prior VTE, chronic heart failure and malignancy (33).

Invasive cancer is a well known risk factor for developing venous thromboembolism (34). Whilst arterial events can occur, the prevalence of arterial thrombosis in cancer patients is rare (35).

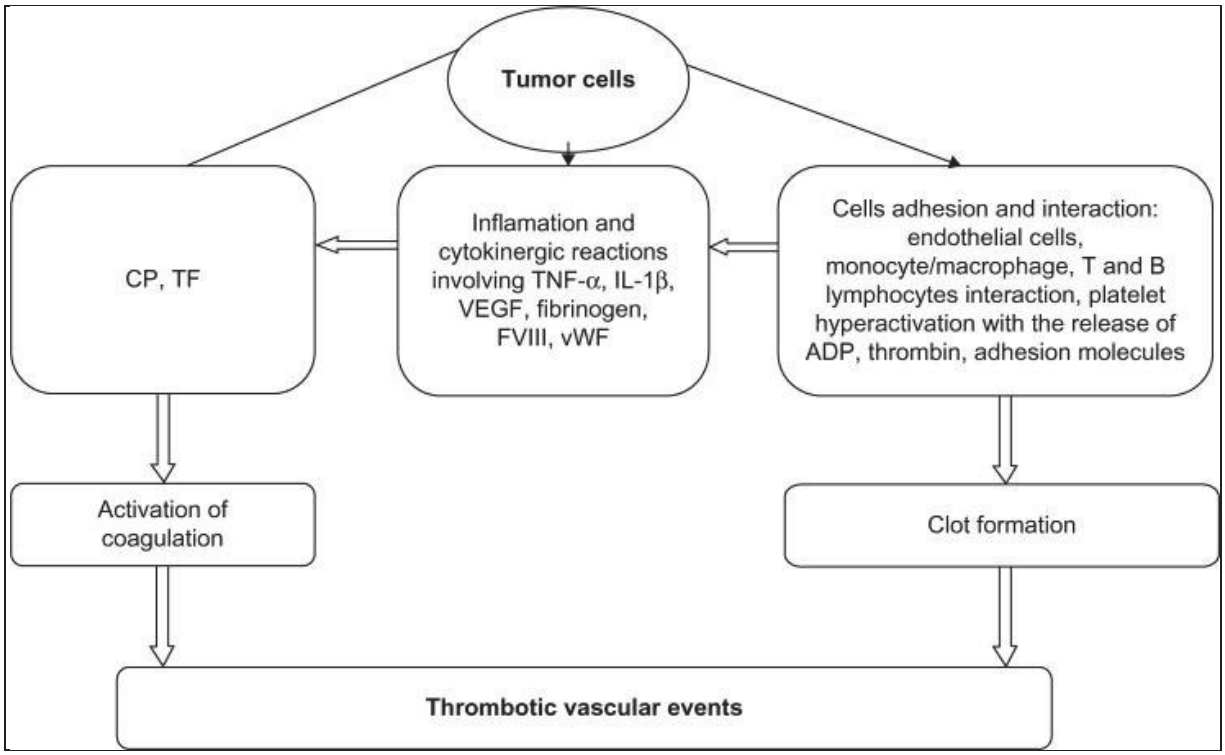
Historically venous thromboembolism has been thought to develop as a result of a combination of endothelial damage, venous stasis and hypercoagulability (36). The risk of developing venous thromboembolism in the presence of cancer increases 7 fold. With the presence of distant metastases, this risk further increases by 20 fold (37).

As cancer is a heterogeneous disease, risks for the development of a venous thrombosis depend on the cancer type and stage. Cancers that are thought to be aggressive and have early metastatic potential are associated with the highest risk of venous thrombosis (34). Pancreatic, brain, lung, and ovarian cancers are associated with particularly high risk, whilst prostate and breast cancer are associated with a lower relative risk (38). Cervical cancer has been reported to have an intermediate risk for the development of VTE (39).

The incidence of venous thrombosis is highest in the first 6 months after cancer diagnosis. It generally decreases after 12 months. At 10 years after cancer diagnosis, there is no elevated risk (34).

Cancer treatment modalities can also increase the risk of venous thrombosis. Surgery, chemotherapy, hormonal therapy are known to increase the risk of venous thrombosis (40,41). The effect of radiotherapy is less clear (42).

Several underlying molecular mechanisms have been described in patients with cancer, with up to 95% demonstrating abnormalities in coagulation tests. It is believed that the tumour itself produces thrombotic compounds that may predispose patients to the development of venous thromboembolism (43).



Abbreviations: CP, Cancer procoagulant; TF, Tissue factor; TNF- α, Tumour necrosis alpha; IL-1β, Interleukin 1 beta; FVIII, Factor VIII; vWF, von Willebrand's Factor; ADP, Adenosine diphosphate

Figure 1.5 Pathophysiology of cancer associated thrombosis (44)

The most important consequence of the development of venous thromboembolism in patients with malignancies is its effect on mortality (35).

Death in cancer patients with a deep venous thrombosis can be as a result of a thromboembolic event itself. However the majority of deaths in patient with cancer and venous thromboembolism cannot necessarily be attributed to thrombosis itself (45). Progressive disease in cancer is the commonest cause of death in cancer and venous thromboembolism is the second leading cause of death in cancer patients (45). However direct mortality from VTE is usually related to pulmonary embolism rather than DVT alone (40).

In the RIETE registry the 3 month mortality rate in patients with cancer and VTE was 26 % versus 4 % in patients with VTE without cancer (41).

Amongst cancer patients, those who develop VTE have a much lower survival compared to patients who do not develop VTE (41).

Mortality in hospitalised patients is significantly worse in patients with VTE vs. patients who have no VTE. In a study by Khorana et al, of an analysis of 1824 316 hospitalizations in 1 015 598 cancer patients, in 133 United States medical centres over an 8 year period, the mortality in patients with VTE was reported as 16.3% in patients with VTE vs. 6.3% in patients who did not have a VTE. ($p<0.0001$) (45).

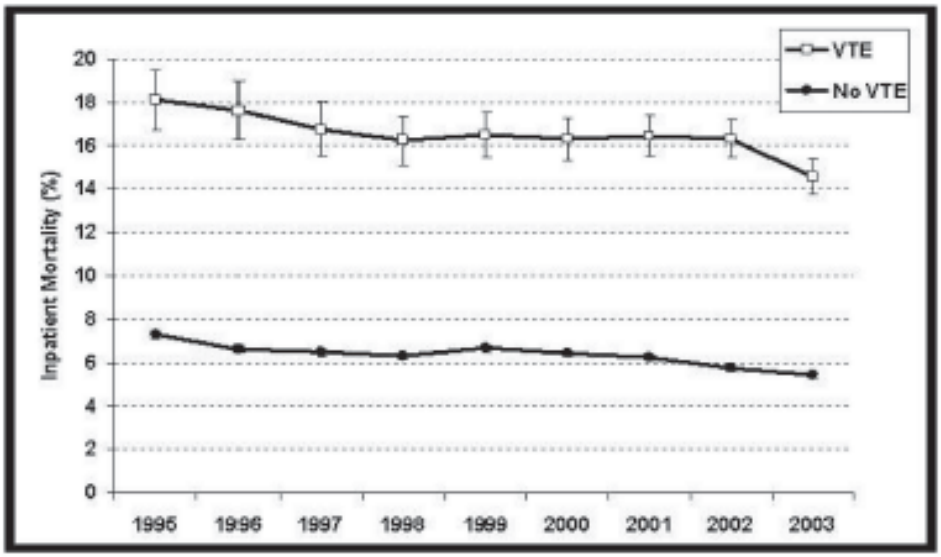


Figure 1.6 Thromboembolism and inpatient mortality (45)

VTE has also been shown to have a significant impact on long term survival in patients with cancer. In a study by Sorensen et al where 668 cancer patients with DVT were compared to 5371 matched control cancer patients, the mortality in the cancer group with DVT was found to be 36% at 1 year compared to 12% in the control group (P <0.001) (46). Chew et al also reported an increased risk of death in cancer patients with VTE. Furthermore the risk of death was independent of stage and cancer type (47). In a study of hospitalized neutropenic patients the presence of VTE resulted in similar mortality in patients with and without metastases (48).

1.5.2 VTE in cervical cancer

Several gynaecological malignancies, including endometrial, ovarian, vulval and cervical cancers have been associated with increased risk of developing venous thromboembolism (49–51).

The incidence of deep venous thrombosis in patients with cervical carcinoma is higher than the general population. The reported incidence of venous thromboembolism in gynaecological malignancies ranges between 0 -34 % (52). The reported incidence of venous thromboembolism in patients with cervical cancer is between 3.3 to 15.7 % (39,52–54).

In a cohort by Jacobson et al, venous thromboembolism was diagnosed within one year following the diagnosis of cervical cancer. They also noted significant associations between thromboembolism and cervical cancer stage, with patients with more advanced stages having a higher incidence (55).

In addition to the classic triad of risk factors for venous thromboembolism in patients with malignancies namely, hypercoagulable states, endothelial injury and venous stasis, independent risk factors for venous thromboembolism in patients with cervical cancer have been identified (53). In a retrospective review, Matsuo et al identified 3 risk factors for the development of thromboembolism in patients with cervical cancer, namely advanced disease stage, a low serum albumin level, and systemic chemotherapy (53). The risk of developing a VTE was increased 4 – 6 fold with the presence of these parameters. It has been postulated that lower albumin levels may be associated with higher fibrinogen and factor VII levels which predispose to a hypercoagulable state. Decreased albumin also causes increased synthesis of

protein in the liver which may result in higher concentrations of coagulant factors (53).

Patients with gynaecological malignancies and VTE have a reduced survival. Amongst patients with gynaecological malignancies who develop VTE, cervical cancer patients, have the worst prognosis (46,53–56). Morgan et al reported a median survival of patients from the time of VTE diagnosis of 7.8 months (56). Less than 20% of patients were alive at 5 years in their cohort. They reported that in patients with cervical cancer who had radiation therapy within 3 months of DVT diagnosis had significantly lessened survival. Jacobson and others have shown that thromboembolism independently confers a poorer prognosis in patients with cervical carcinoma (55). They reported a 5 year survival of less than 40% in patients with cervical cancer and VTE (55).

Matsuo and others however, reported no deaths directly from thromboembolism in their study (53).

In South Africa a significant number of patients with cervical cancer are HIV positive (14). The burden of cervical disease in patients with HIV is significantly higher and the receiving of combination antiretroviral therapy does not appear to decrease cervical abnormalities in this population (57).

Furthermore HIV is associated with a prothrombotic state and is associated with a higher incidence of venous thromboembolism (58). Various abnormalities predisposing to a hypercoagulable state have also been described in patients with HIV infection. These abnormalities include deficiencies of antithrombotic proteins, such as, protein S, protein C, and antithrombin; the presence of procoagulants, such as, lupus anticoagulant, antiphospholipid antibodies, and increased levels of factor VIII/von Willebrand factor. These abnormalities have been described to correlate with the degree of HIV-associated immunosuppression as indicated by the CD4 count as well as with the presence of concomitant infections and neoplastic disorders (59).

It is uncertain whether HIV infection in patients with cervical cancer and VTE impacts survival.

1.5.3 Management of venous thromboembolism

Pain, swelling, leg oedema, tenderness and erythema are usually present in patients with a deep venous thrombosis of the limb (32). At CMJAH, patients with clinical symptoms and signs of a deep vein thrombosis are referred for a doppler ultrasound of the involved limb to confirm the diagnosis. The technique of colour doppler ultrasound consists of real time ultrasound compression technique with duplex colour doppler imaging. The diagnosis of a deep vein thrombosis is made if there is incomplete compressibility of a vessel is found, or absence of flow is noted on colour doppler. Reported sensitivities and specificities for Duplex ultrasonography are between 82% to 96% and 97% to 100% respectively (60).

Once the diagnosis of a deep vein thrombosis is confirmed, the patient is admitted for anticoagulation. This is done in accordance with clinical guidelines (61). Patients are anticoagulated with enoxaparin 1mg/kg twice daily and warfarin is initiated on day 3 of anticoagulation. The dose of warfarin is adjusted until the international normalised ratio (INR) is within the therapeutic range which is between 2 and 3. Only patients symptomatic of a pulmonary embolus are investigated using either a CT pulmonary angiogram or ventilation – perfusion scan. Patients are referred to the anticoagulation clinic for monthly monitoring and dosage adjustments of the warfarin on discharge from the ward. No changes to the chemotherapy and radiation treatment plan are made if patients are diagnosed with a venous thromboembolism.

1.6 Justification of the study

Venous thromboembolism has been identified as an independent prognostic factor in patients with cervical cancer (30,53,55). The published studies in the literature have shown that VTE confers a poorer prognosis in patients with cervical cancer.

Despite the high incidence of venous thromboembolism found in patients with cervical cancer, patients are not routinely screened for the presence of venous thromboembolism. There are no recommendations for this in published guidelines. (62). Furthermore, there are no recommendations for the prophylactic use of low molecular weight heparin in specifically in patients with cervical cancer. There is, therefore a need to study VTE in patients with cervical cancer.

This study was intended to provide useful prognostic information regarding patients with cervical cancer and venous thromboembolism in the South African setting.

1.7 Study objectives

The objective of the study was to investigate the outcomes and survival of patients with cervical cancer and venous thromboembolism. A secondary aim of the study was to investigate if there was any difference in survival between HIV positive and HIV negative patients with cervical cancer.

Chapter 2

Methods

The study period extended from the 01 January 2015 to 30 September 2018 to have at least 2 years of follow up. The records of patients with cervical cancer who were diagnosed with a venous thromboembolism at Charlotte Maxeke Johannesburg Academic Hospital during the period 01 January 2015 to 31 December 2016 were identified. Criteria for inclusion in the study were patients with cervical cancer and a diagnosis of VTE during the specified time period, irrespective of age, stage, or treatment received. Patients with VTE and other malignancies were excluded from the study. The data obtained from the records were recorded on an excel spread sheet and included, age, HIV status and CD4 count, the date of diagnosis of venous thromboembolism, FIGO stage, histology, chemotherapy treatment received and the details of the radiation treatment received. 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 cancer. The diagnosis of a deep vein thrombosis was determined by duplex doppler ultrasound which confirmed the laterality of the DVT and extent. The date of the doppler study was taken as the date of diagnosis of the DVT.

For the purposes of the statistical analysis patients with stage IIB proximal and IIB distal were grouped together as stage II since they were treated with a similar total dose and fractionation of radiotherapy and a similar chemotherapy regimen. Patients with stage IIIB disease were classified as stage III. Patients with stage IVA disease and patients with metastatic disease namely stage IVB disease were grouped as stage 4 as they were treated with palliative radiotherapy.

2.2 Statistics

Data was imported from Microsoft Excel (Microsoft Corporation, Redmund, WA, USA) and was subsequently analysed using SPSS for Microsoft Windows,25.0 (SPSS, Chicago, IL, USA) . Univariate and multivariate analyses were performed using the Cox proportional hazards regression model and survival from the time of diagnosis of venous thromboembolism and the 12 and 24 month overall survival rates were calculated using the method of Kaplan and Meier (62). The OS survival

period was calculated from diagnosis of cancer to date of death. Multivariable 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 and a p value of < 0.05 was considered statistically significant.

2.3 Ethics

Approval to conduct the study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand. (Clearance certificate number: M181019 (Appendix 1)) Permission to collect data from patient records was obtained from the CEO of Charlotte Maxeke Johannesburg Academic Hospital.

Chapter 3

Results

There were a total of 598 patients with cervical cancer who were admitted to the radiation oncology ward of Charlotte Maxeke Johannesburg Academic hospital during the study period. Fifty two patients were identified as having a concomitant, confirmed diagnosis a deep vein thrombosis on a doppler ultrasonography. Forty seven patients had adequate stored data (Fig 3.1).

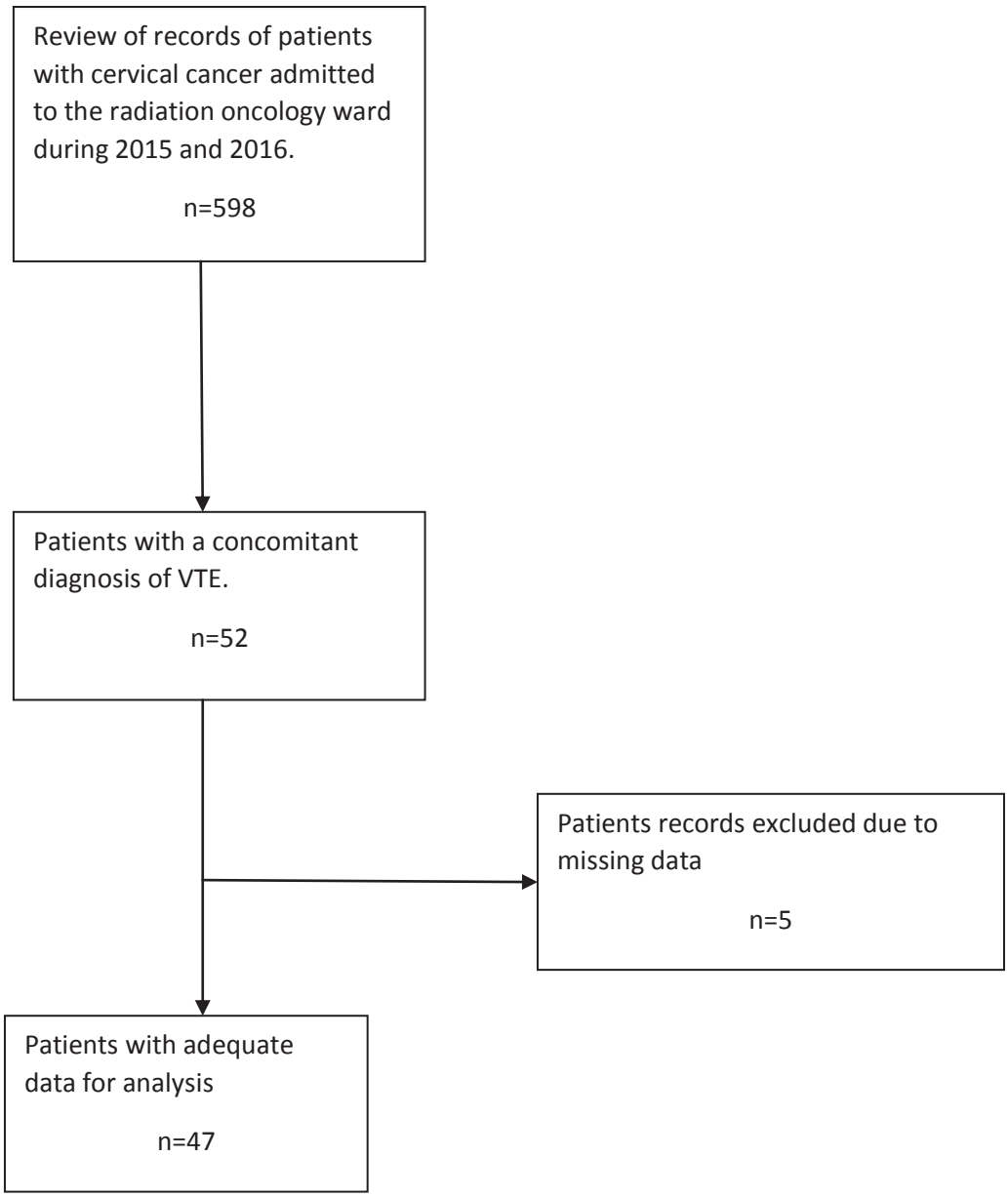


Figure 3.1 Flow diagram indicating the patient record selection process

The clinicopathologic characteristics of the patients with venous thromboembolism are shown in Table 3.1. The histological subtype in the majority of patients (92%, n= 43) was squamous cell carcinoma. Only 1 patient had an adenocarcinoma of the cervix. Two patients had adenosquamous carcinomas of the cervix and 1 patient had a small cell neuroendocrine carcinoma of the cervix.

The frequencies of the different stages of cervical cancer in the cohort were as follows: stage IIB proximal (9%, n=4), IIB distal (17%, n=8), IIIB (62%, n=29), IVA

(6%, n=3) and IVB (6%, n=3). Fifty five percent of patients were below the age of 50 years and the remaining 45 % were above 50 years.

Sixty percent (n=28) of the patients were HIV positive and 40% (n=19) of patients were HIV negative. Of the patients that were HIV positive, the mean CD4 count was: 420 cells/mm^3. Twenty six percent of patients had a CD4 count below 200 cells/mm^3. Fifteen percent (n=4) patients had a CD4 count between 200 and 350 cells/mm^3, and 59% (n=16) patients had a CD4 count of greater the 350 cells/mm^3. The majority of patients, 93% (n=25), were on antiretroviral therapy (ART) and the remaining 7% (n= 2) of patients were not on ART at the time of admission.

Concurrent chemoradiation with cisplatin at a dose of 80mg/m^2 every 3 weeks was administered to 32% (n=15) patients whilst 68% of patients were treated with radiotherapy alone.

One patient was diagnosed with a concomitant pulmonary embolism. One patient had an upper limb DVT. The remaining 46 patients had lower limb deep venous thromboses. Two patients had bilateral lower limb deep venous thromboses.

Thirty four percent of patients (n=16) were diagnosed with a DVT before or during treatment with radiotherapy. The remaining 66% of patients (n= 31) were diagnosed with a DVT after treatment with radiotherapy.

Seventy nine percent (n= 37) of patients had successfully completed their course of radiation therapy, whilst 21 % (n= 10) had initiated but did not complete the prescribed course of radiation therapy. Of the ten patients that did not complete the prescribed course of radiation, 6 had died during the course of radiotherapy and the remaining 4 were lost to follow up.

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 that 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.

Table 3.1 Clinicopathologic characteristics of patients with cervical cancer and venous thromboembolism

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	26	55%
	≥ 50	21	45%
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	-
Diag. of DVT relative to RT	Before /during RT	16	34%
	After RT	31	66%

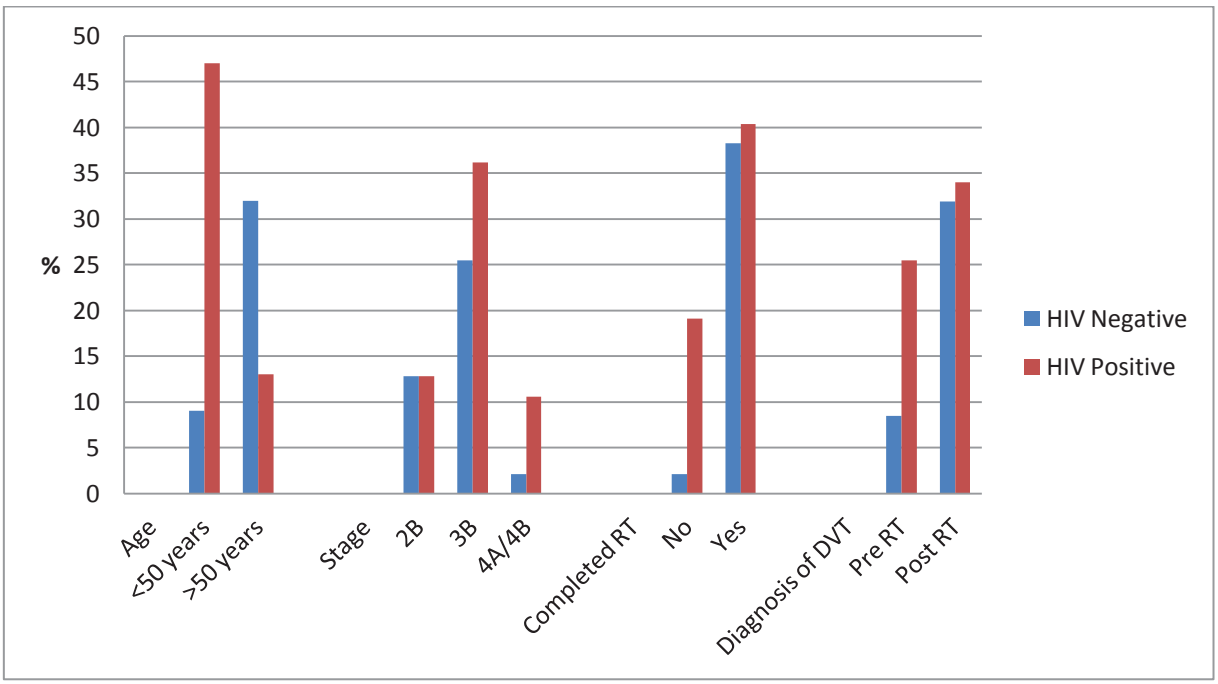


Figure 3.2 Bar chart indicating the clinical characteristics of patients by HIV status

The study period extended over a period of 45 months. The median survival from diagnosis of DVT was 2.77 months (IQR: 0.97 – 6.93 months) and survival at 12 months was 17%. (Fig 3.3)

The 24 month overall survival for the cohort was 29.89% (median 14.3 months, 95% CI, 8.39 – 20.27 months). (Fig 3.4)

The overall survival of the cohort was 55.3% at 12 months (median not reached) and 29.8% at 24 months (median 14.3 months, 95% CI, 8.39 - 20.11 months).

The 12 month survival from diagnosis of DVT in patients < 50 years was 19.2%, (median 3.0 months, 95% CI 2.0 – 4.0 months). For patients above the age of 50 years the 12 month survival from diagnosis of DVT was 14.3 % (median 1.93 months 95% CI, 0.0 – 3.98 months. There was no statistically significant difference in survival between the two age groups, p =0.846. (Fig 3.5)

The 24 month survival for patients less than 50 years of age was 30.8% (median: 12.63 (months, 95% CI, 1.05 – 24.21 months), and for patients aged 50 years and older the 24 month survival was 28.6% (median 14.3 months, 95% CI, 7.75 – 20.90 months). (Fig 3.6)

The 12 month survival from diagnosis of DVT for patients with stage II cervical cancer was 25% (median 2.63 months, 95% CI, 2.23 – 3.04 months), for stage III, 17.2% (median 3.27months, 95 % CI, 1.78 – 4.78 months and for stage IV, 4,7% (median 0.6 months, 95 % CI, 0 – 1.52 months), p= 0.149. (Fig 3.7)

The 24 month survival according to stage was 33.3% and 34.5% for patients with stages IIB and IIIB respectively. The median survival was 16.37 months (95% CI, 10.15 – 22.58 months) for stage IIB patients and 14.3 months (95% CI, 8.217 – 20.38 months). No patients who were stages IVA or IVB were alive at 2 years, p= 0.002. (Fig 3.8)

The 12 month survival from diagnosis of DVT in the HIV negative group was 21.1%, (median 4.0 months, 95% CI, 1.41 - 6.73 months) and 14.3% in HIV positive group, (median 2.57 months, 95% CI, 1.09 – 4.05 months), p =0.466. (Fig 3.9)

At 24 months the survival was 36.8 % and 25.09 % in the HIV negative and positive groups respectively, p = 0.141. The median OS in the HIV negative group was 17.10 months (95% CI, 2.23 -15.63 months) and the median OS in the HIV positive group was 8.93 months (95%, CI 11.61 – 22.59 months). There was, however no statistically significant difference between HIV positive and negative patients in terms of OS, p = 0.141. (Fig 3.10)

The 12 month survival from diagnosis of DVT for patients who were diagnosed with a DVT before or during radiotherapy was 18.5% (median 2.77 months, 95% CI, 0 - 5.79 months). The survival from diagnosis of DVT for those who were diagnosed after radiotherapy was 16.1% (median 2.63 months, 95% CI, 1.17 – 4.09 months). There was no significant between the two groups, p= 0.755. (Fig 3.11)

On multivariate analysis patients who were diagnosed with a DVT before or during the course of radiation had a much shorter overall survival compared to patients who developed a DVT after radiation, p= 0.004.The median survival was 12% at 24 months for patients who were diagnosed with a DVT before or during radiotherapy versus 38.7% at 24 months for patient who developed a DVT after radiation. The median OS for patients diagnosed with a DVT before or during radiotherapy was 5.47 months (95% CI, 1.47 - 9.47 months) vs. 16.73 months (95% CI, 10.40 – 23.05 months) for patients who were diagnosed with a DVT after radiotherapy. (Fig 12 and Table 3.3)

There was no significant difference between HIV positive and negative groups when analysed with the following strata: age, stage, and whether the diagnosis of a DVT was made before or during radiotherapy versus after radiotherapy. (Appendix 1 - Supplementary Tables 1 & 2)

Table 3.2 Survival rates from diagnosis of DVT

12 month survival from diagnosis of DVT								
		%	Median (months)	95 % CI	Log rank test	p value (log rank test)	Hazard ratio	P value (Cox Model)
Overall		17.00%	2.77	1.910-3.67				
Age					0.34	0.846	-	-
	<50 yrs	19.2%	3.00	2.00 – 4.00				
	≥50 yrs	14.30%	1.93	0.0 – 3.989				
Stage					3.81	0.150	-	-
	2BProx/ 2BDistal	25.00%	2.63	2.23 - 3.04				
	3B	17.20%	3.27	1.78 - 4.78				
	4A/4B	17.00%	0.60	0.00 - 1.52				
Diag. of DVT relative to RT					0.097	0.755	-	-
	Pre RT	18.80%	2.77	0.00 - 5.79				
	Post RT	16.10%	2.63	1.17 - 4.09				
HIV Status					0.53	0.466	-	-
	Positive	14.32%	2.57	1.09 - 4.05				
	Negative	21.10%	4.07	1.41 - 6.73				

Table 3.3 Overall survival rates

24 month overall survival (OS)									
		%	Median (months)	95 % CI	Log Rank Test	p-value	Hazard Ratio	95% CI	p-value (Cox model)
Overall		29.80%	14.30	8.39-20.27					
Age					1.629	0.443	-	-	-
	<50 yrs	30.8 %	12.63	1.05 - 24.21					
	≥50 yrs	28.6%	14.3	7.75 - 20.90					
Stage					12.420	0.002	-	-	-
	2BProx/ 2BDistal	33.30%	16.37	10.16 - 22.58					
	3B	34.50%	14.30	8.22 - 20.38			1.02	0.44 – 2.36	0.970
	4A/4B	0.00%	4.33	2.93 - 5.73			3.91	1.17 – 13.08	0.027
Diag. of DVT relative to RT					10.476	0.001			
	Pre RT	12.50%	5.47	1.47 - 9.47					
	Post RT	38.70%	16.73	10.40 - 23.05			0.36	0.17 – 0.72	0.004
HIV Status					2.165	0.141			
	Negative	36.80%	17.10	2.23 - 15.63					
	Positive	25.09%	8.93	11.61 - 22.59			1.39	0.653 – 2.96	0.393

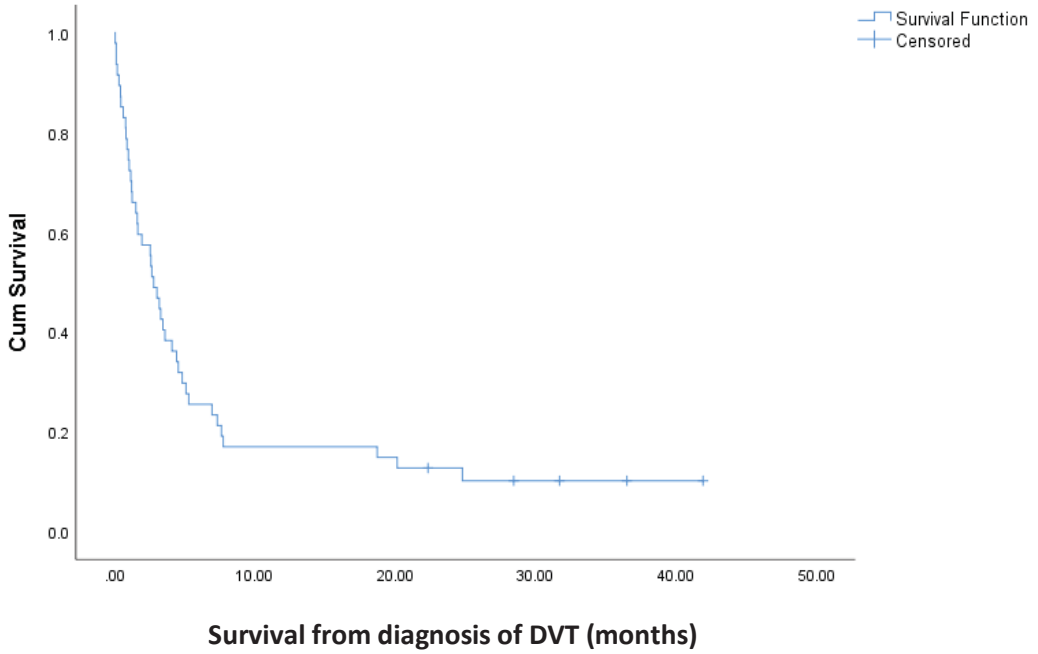


Figure 3.3 Survival from diagnosis of DVT

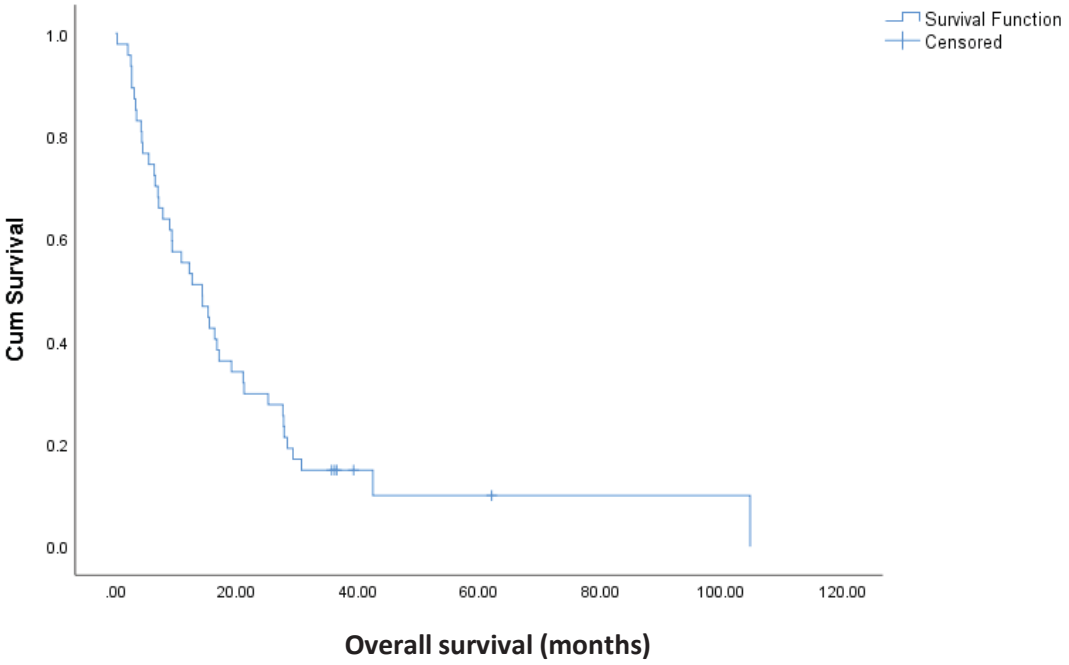


Figure 3.4 Overall survival

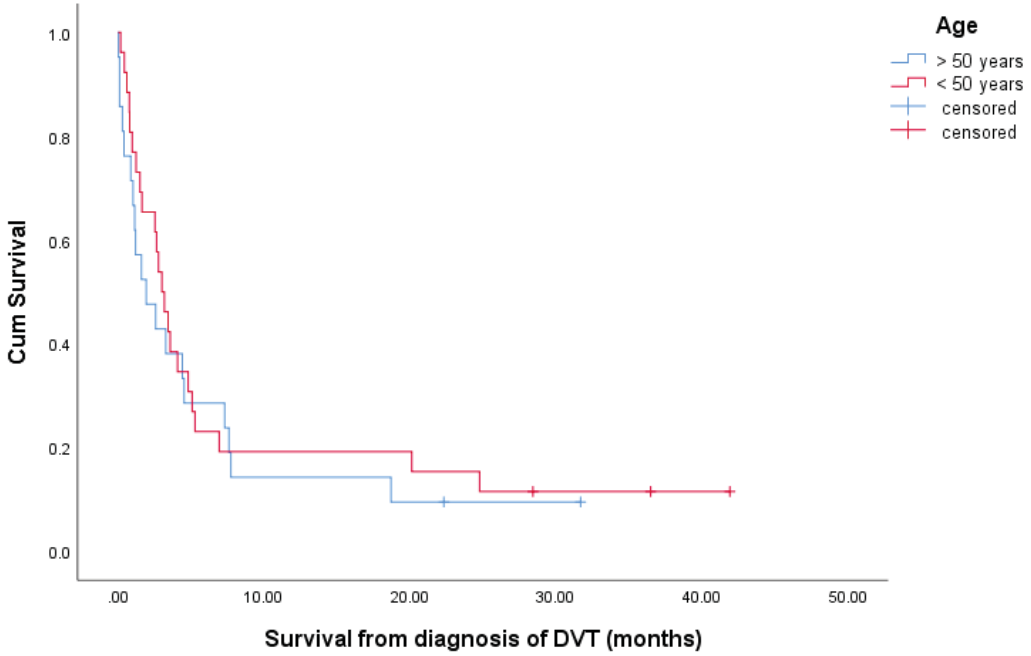


Figure 3.5 Survival from diagnosis of DVT by age category

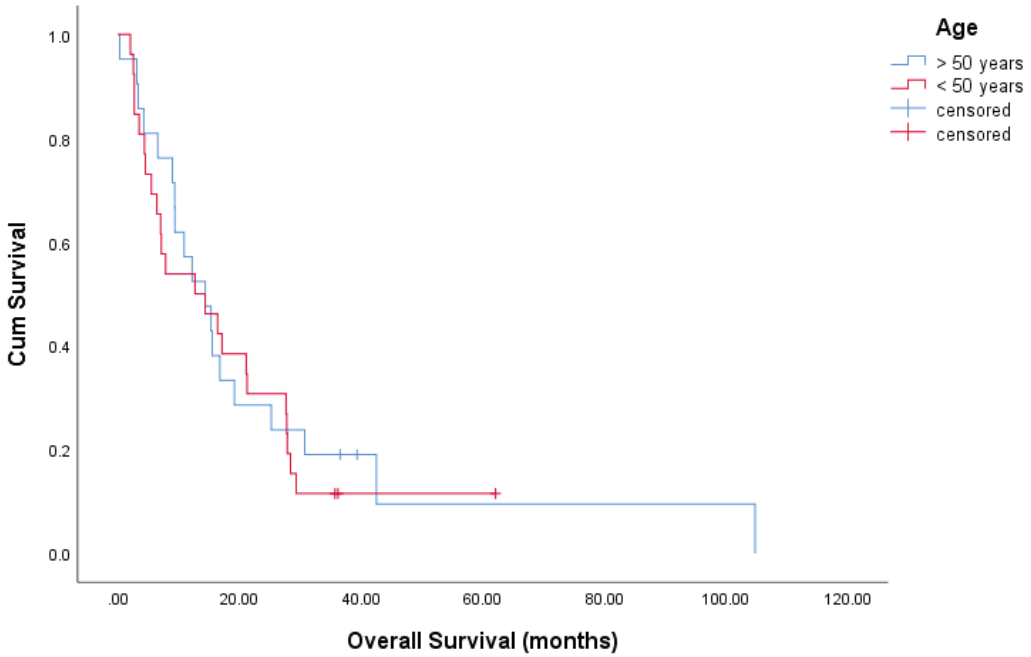


Figure 3.6 Overall survival by age category

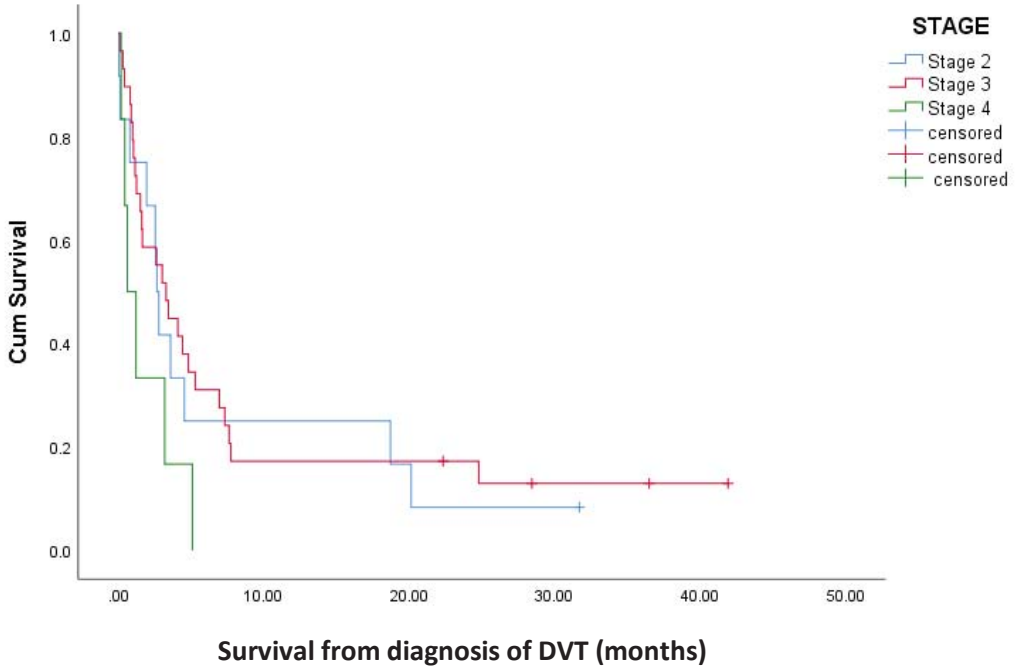


Figure 3.7 Survival from diagnosis of DVT by stage

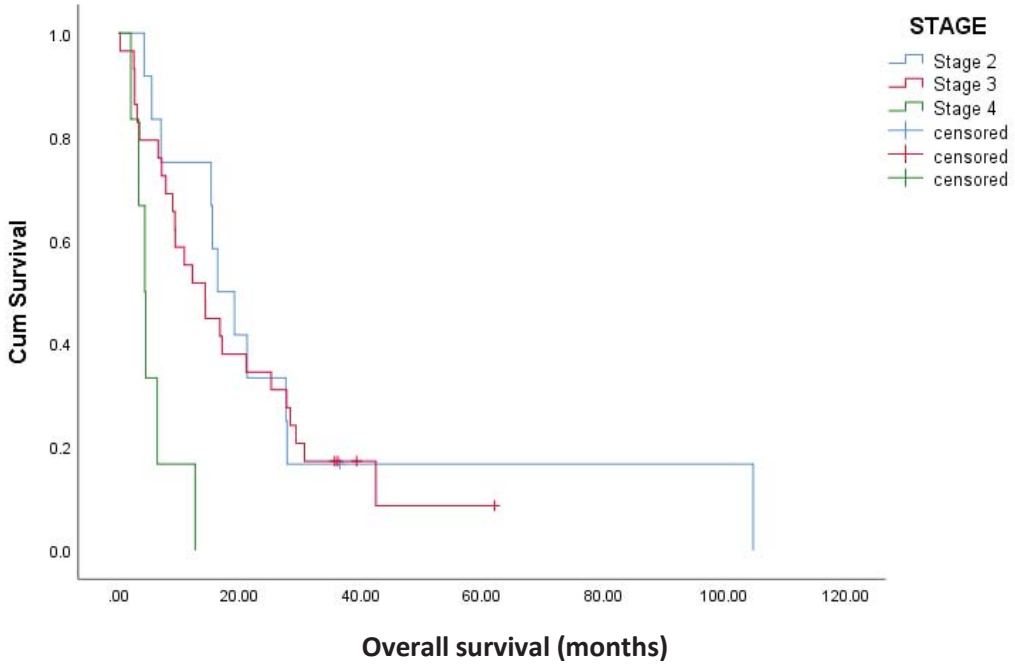


Figure 3.8 Overall survival by stage

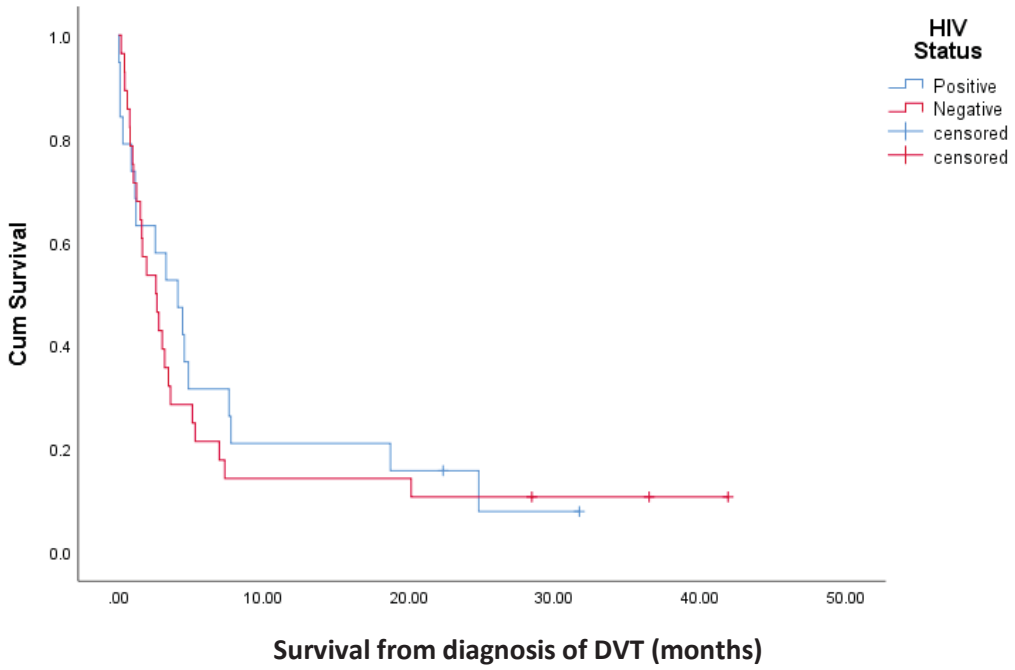


Figure 3.9 Survival from diagnosis of DVT by HIV status

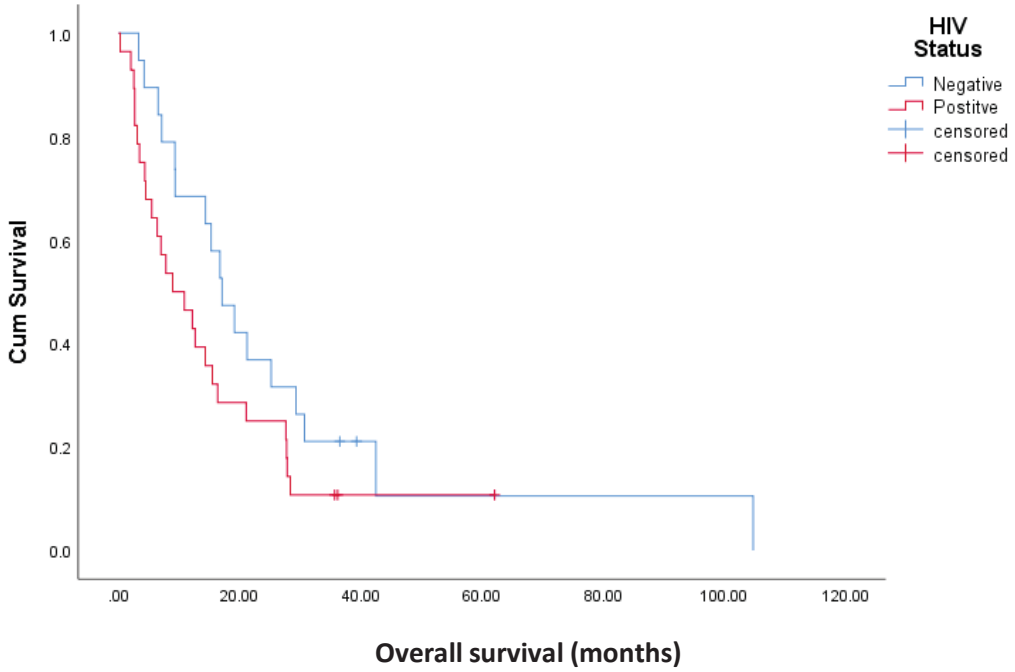


Figure 3.10 Overall survival by HIV status

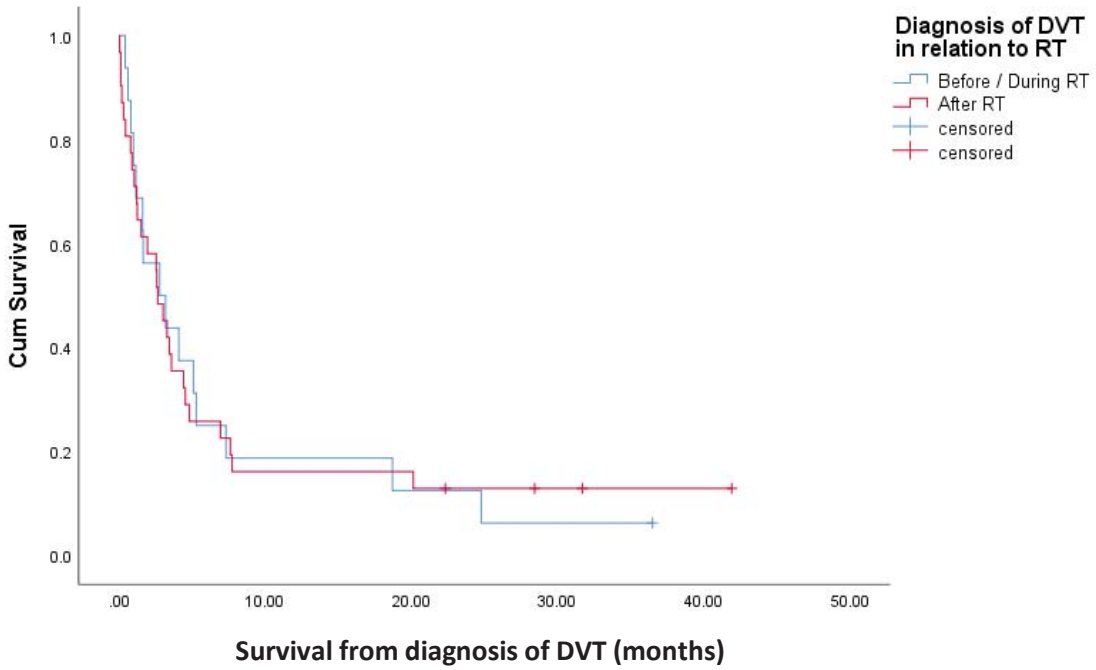


Figure 3.11 Survival from diagnosis of DVT as affected by the timing of the diagnosis of DVT in relation to radiotherapy

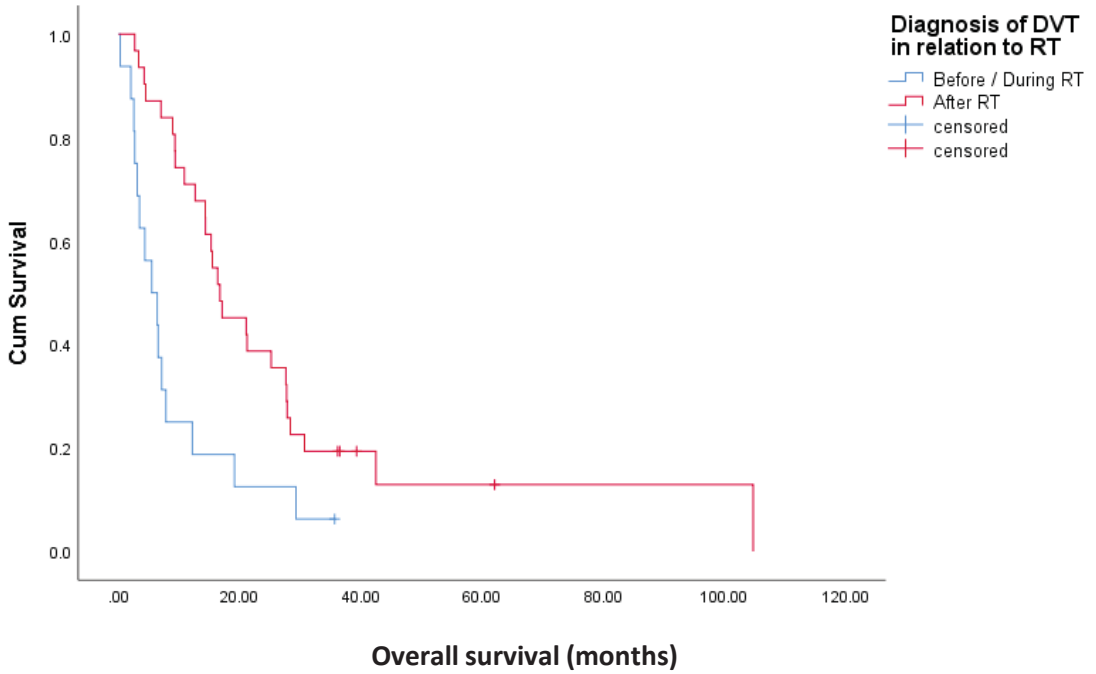


Figure 3.12 Overall survival as affected by the timing of diagnosis of DVT in relation to radiotherapy

Chapter 4

Discussion

This study shows that the short term survival for patients with cervical cancer and VTE is extremely poor. At 12 months from the time a DVT was diagnosed the survival was only 17%. The 2 year overall survival was 29.80%. The median survival of patients in this cohort from the diagnosis of a DVT was only 2.77 months. The poor survival observed in this cohort is worse than that reported in other studies which have investigated VTE in cervical cancer and is markedly reduced compared to reported survival rates in patients with cervical cancer in general.(52,56).

Table 4.1 Studies investigating VTE in cervical cancer

Series	No of patients with cervical cancer and VTE	5 year survival rates: Cervical cancer with VTE vs. cervical cancer without VTE
Morgan et al (56)	21	20% vs. NR*
Jacobson et al (55)	98	40% vs. 80%
Matsuo et al (53)	51	55.1% vs. 90%

*Not reported

4.1 VTE as a poor prognostic marker in cervical cancer

In the univariate analysis, parameters of age, stage, HIV status and the timing of the diagnosis of VTE in relation to radiotherapy did not confer prognostic significance. The implications of these results are that once a DVT is diagnosed, other variables proven to affect survival have no independent effect.

The majority of patients in this cohort had stage IIIB disease. At the time of the study, patients with stage IIIB disease did not routinely receive chemotherapy, and as the number of patients in this cohort was small, meaningful comparisons could not be drawn regarding the effect of chemotherapy on survival. Whether patients with stage IIIB disease are more likely to develop venous thrombosis is uncertain. A possible

mechanism may be due to pelvic sidewall extension and bulky nodal disease which increases the risk of venous stasis and predisposes to thrombosis. Stage IIIB disease also has a greater propensity for loco-regional recurrence, distant nodal and metastatic disease (9). This could explain the reason for a greater number of patients with stage IIIB disease noted in this cohort, as venous thrombosis is known to occur with a greater frequency in patients with metastatic disease compared to patients with non-metastatic disease(34). 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 (53).

The survival of patients with metastatic disease is known to be unfavourable (9). Only 3/47 patients in this group were staged as IVB at the outset before treatment with radiotherapy was initiated. FIGO staging based only on clinical examination has limitations and patients could have been under - staged. Nevertheless, compared to other studies, the survival of this cohort is extremely poor. 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 or magnetic resonance imaging (MRI) scans before treatment is initiated. Information regarding local recurrence or metastatic disease at the time of admission was not always documented as imaging studies are also not routinely ordered to prove metastases 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 sixteen patients had metastatic disease at the time of admission. Frequent sites of metastases were lung, nodal and bone. Eleven patients had other complications with renal failure and sepsis being the most common.

It is not known whether the increased incidence of VTE in patients with cervical cancer is a result of the biology of the tumour, or whether local disease in the pelvis causes compression of the veins in the pelvis, which in turn can cause sluggish flow within the deep venous system in the lower limbs and thereby predisposes to the development of venous thromboses.

The study investigated overall survival and not disease specific survival. With recurrent disease being documented in some patients, progressive disease is more

likely to explain the poor survival. Matsuo et al reported no deaths directly from VTE in their study (53). VTE may therefore be an indicator of aggressive tumour behaviour or having underlying metastatic disease. Most studies however report mortality based on clinical data, which may not necessarily be accurate. Post mortems studies are infrequently performed on cancer patients. In one such published study, however, the incidence of PE in cancer was 26% (63). It is unlikely however that VTE was directly responsible for a large number of deaths in this cohort.

A variable that affected survival in this group was the timing of the diagnosis of the deep venous thrombosis. Patients who were diagnosed with a DVT before or during the course of radiation had a much poorer survival compared to patients who developed a DVT after completing their course of radiotherapy, p =0.001. This remained significant when adjusted for age, stage and HIV status, p = 0.004. 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. The longer OS in patients who were diagnosed with VTE after radiotherapy is largely as a result of the survival, prior to the development of a VTE.

Simonds et al recently reported differences in survival between HIV positive and HIV negative patients (30). There was no significant difference in this cohort, however. It is to be noted that almost all patients were on ART. There was no difference amongst HIV positive patients when stratified by CD4 count either. At the time of this study viral loads were not routinely measured in the clinic.

4.2 Primary thromboprophylaxis in patients with cervical cancer

Whether thromboprophylaxis is likely to reduce mortality or alter the prognosis of patients with cervical cancer is uncertain.

In a Cochrane review of 9 trials investigating the use of thromboprophylaxis in ambulatory cancer patients, thromboprophylaxis with low molecular weight heparin (LMWH) reduced the incidence of symptomatic VTE. 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. Of note was that one-year mortality differences between the LMWH and control groups were 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.(64) The bleeding risk associated with cervical cancer probably outweighs the benefit of thromboprophylaxis in this patient population. Cancer patients, in general, with a concomitant venous thromboembolism tend to have higher risks of bleeding complications than patients without cancer (41,42,65). Bleeding is particularly problematic in patients with active local disease in cervical cancer (40,41,66).

4.3 Treatment of VTE in patients with cervical cancer

Five major open label, multicentre, randomised controlled trials have established that LMWH is the agent of choice in the treatment of venous thromboembolism in cancer.(65,67–70). LMWH is considered the standard of care for the treatment of cancer associated venous thromboembolism (71). Despite recommendations being published in major guidelines supporting the use of LMWH over vitamin K antagonists (VKA) or warfarin, many cancer centres internationally continue to use warfarin in up to 50% of patients (72). At CMJAH, it is routine to anticoagulate the majority of patients with warfarin. The reasons are usually due to the ease of administration of an oral agent for prolonged anticoagulation. Other factors include avoidance of pain at the injection site, bruising, adherence to therapy and cost. Major bleeding is a frequent complication in cancer patients who also receive anticoagulation. Table 4.2 summarizes the risks of major bleeding in patients with cancer. The results of these trials need to be viewed with caution as the majority of these trials had limited numbers of patients with cervical cancer.

The duration of anticoagulation in patients with cancer is unclear. The guidelines generally recommend that anticoagulation be continued as long as there is evidence of active cancer.

Based on the poor survival from diagnosis of DVT in this cohort, it is reasonable to anticoagulate patients with LMWH. Further clinical trials are required to establish the rate of bleeding complications observed in patients with cervical cancer with these agents to make firm recommendations regarding the use of LMWH agents in this population over warfarin. LMWH may be particularly more appropriate where access to a monitoring service is unavailable and in patients with extremes of weight, e.g. <50 kg and >150kg (72). The choice between warfarin and LMWH can be made based on individual patient characteristics e.g. co morbidities, suitable route of administration, need for monitoring, concomitant medication and convenience (72).

Table 4.2 Rates of major bleeding between VKA and LMWH

	Major Bleeding Rates			**Mortality**		
Trial	VKA	LMWH	p value	VKA	LMWH	p value
CANTHANOX(70)	16%	7.0%	0.09	22.7%	11.3%	0.07
LITE (65)	7.0%	7.0%	-	47.0%	47.0%	-
ONCENOX (67)	2.9%	9.0%	NR	32.4	32.8%	-
CLOT (73)	4.0%	6.0%	0.27	39%	41%	0.53
CATCH (69)	2.4%	2.7%	0.77	32.2%	34.7%	0.54

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 in gynaecological malignancies. More research is particularly needed in patients with locally advanced disease managed without surgery due to the high associated morbidity and mortality. Frequently, trials exclude patients with an increased bleeding risk and may therefore not be representative of those with progressive cancer. An urgent need for an updated evidence base is required for the management of these patients.

Further well defined larger studies are required to better understand the magnitude and risk factors associated between cervical cancer and VTE. Further studies are also required to evaluate whether asymptomatic patients should actively be screened for venous thromboses using doppler ultrasonography. Clinical trials evaluating the safety and effect of thromboprophylaxis need to be conducted to effectively guide the future management of patients with cervical cancer and venous thromboembolism. Clinical trials are also required to establish which therapeutic agent is most effective for secondary prevention in cervical cancer patients diagnosed with VTE.

Chapter 5

5.1 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 upfront, 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.

As this is a group of hospitalized patients, concomitant acute illness which also could have contributed the extremely high mortality in this cohort must be kept in mind. This is in line with other studies that have investigated the mortality of hospitalized cancer patients and VTE(48).

Socioeconomic, demographic and medical variables are known to be associated with poor survival (17). However, in this study, these factors were not documented. The highest number of deaths occurred in the 40 – 60 age group which may reflect the higher number of cases in this group. However this is in accordance with the epidemiology of the mortality of cervical cancer patients in South Africa (17).

The majority of patients in this cohort had stage IIIB cervical cancer. This may account for the poor survival of this cohort. At the time, patients with stage IIIB disease were not offered concurrent chemotherapy. This cohort also did not have any patients with stage I cervical cancer, as these patients are usually treated and followed up by the gynaecology oncology department of the hospital. Whether patients with stage I disease who are managed exclusively with surgery, have a better prognosis from the diagnosis of VTE is uncertain.

The cause of mortality cannot always reliably be ascertained in all patients without post mortem studies. It is therefore often difficult, if not impossible to determine whether patients had died as a direct result of venous thromboembolism, progressive disease or other causes. Cause specific survival for this cohort could therefore not be determined.

Bleeding complications were not recorded in all patients as frequently patients attended their local hospitals rather then returning to CMJAH after treatment.

5.2 Recommendations from this research

Patients with locally advanced cervical cancer and venous thromboembolism have a higher likelihood of having metastatic disease and it may be necessary to use more advanced imaging methods to exclude metastatic disease before curative chemoradiotherapy or radiotherapy is initiated.

LMWH, instead of warfarin is recommended for secondary prophylaxis in patients with cervical cancer and VTE. This can potentially prevent a prolonged admission to hospital usually required to optimize the INR in patients with the use of warfarin.

Due to poor survival associated with cervical cancer and VTE, early focus on symptom management and palliative measures must be instituted in conjunction with definitive treatment for the cancer depending on the cancer stage.

5.3 Conclusion

The presence of a DVT or 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. Further research is required to better understand the risk factors and pathophysiology of VTE in cervical cancer. Research is also required to guide the optimal management of these patients.

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SUPPLEMENTARY INFORMATION

Supplementary tables. Survival by HIV status by strata

Supplementary Table I: 12 month survival from diagnosis of DVT by HIV status and strata (median – months)

	HIV Negative		HIV Positive		Overall	p value / Fishers Exact test
	%	median, 95% CI	%	median, 95% CI		
Stage						0.678
Stage II	33%	2.53 (0.0-7.85)	16.7%	2.63 (1.62-3.64)	25 %	
Stage IIIB						
	16.7%	4.07 (2.15 -5.99)	17.6%	2.57 (0.69 -4.45)	17.2%	
Stage 4A/4B	0	1.20	0	0.60 (0.24 -0.97)	0	
Age						0.225
< 50 years	25%	4.07 (1.84-6.29)	18.2%	3.0 (2.0- 4.54)	17.2%	
≥50 years	20%	3.27 (0-7.39)	0	1.6 (0.52-2.68)	14.3%	
Diagnosis of DVT in relation to RT						0.449
Pre - RT						
	50 %	4.07	8.3%	1.63 (0.00 -5.79)	18.8%	
Post RT	13.3%	3.27 (0.00 -7.31)	18.8%	2.57 (1.20 -3.94)	16.1%	

Supplementary table II: 24 month overall survival (OS) by HIV status and strata (median - months)

	HIV Negative		HIV Positive		Overall	p value / Fishers Exact test
	%	median, 95% CI	%	median, 95% CI		
Stage						0.444
Stage II	33%	19.13 (11.98 – 26.28)	33%	15.47(4.24 – 26.72)		
Stage IIIB	41.7%	16.73 (12.02 - 21.43)	29.4%	10.87 (5.04 – 16.71)		
Stage 4A/4B	0	3.30	0	4.47 (4.17 – 4.77)	0	
Age						0.061
< 50 years	25%	17.1 (3.25-30.94)	31.8%	7.83 (0 – 16.94)	30.8%	
≥50 years	40%	16.73 (10.67-22.39)	0	8.93 (0 – 18.29)	28.6	
Diagnosis of DVT in relation to RT						0.219
Pre - RT	25%	7.10 (0 – 19.49)	8.3%	3.47 (1.33 -5.61)	12.5%	
Post RT	40%	17.10 (9.58 - 24.62)	37.5%	15.47 (11.41 - 19.53)	38.7%	

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr Preyesh Thakorbhai Given Shiba

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M181019

NAME: (Principal Investigator)	Dr Preyesh Thakorbhai Given Shiba
DEPARTMENT:	Radiation Oncology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	The impact of venous thromboembolism on the outcomes of patients with cervical carcinoma, a retrospective audit from January 2015 to December 2016
DATE CONSIDERED:	26/10/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Vinay Sharma
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	29/10/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **October** and will therefore be due in the month of **October** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 04/11/2018

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 2

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

Plagiarism Report

I Preyesh Thakorbhai Goven Shiba Student number: 0100421K

am a student registered for MMED in the year 2019

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- I confirm that the work submitted for assessment for the above course is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

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https://doi.org/10.1080/20742835.2019.1701257

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South Afr J Gynaecol Oncol
ISSN 2074-2835 EISSN 2220-105X
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RESEARCH

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

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Check for updates

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/m^2 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%.

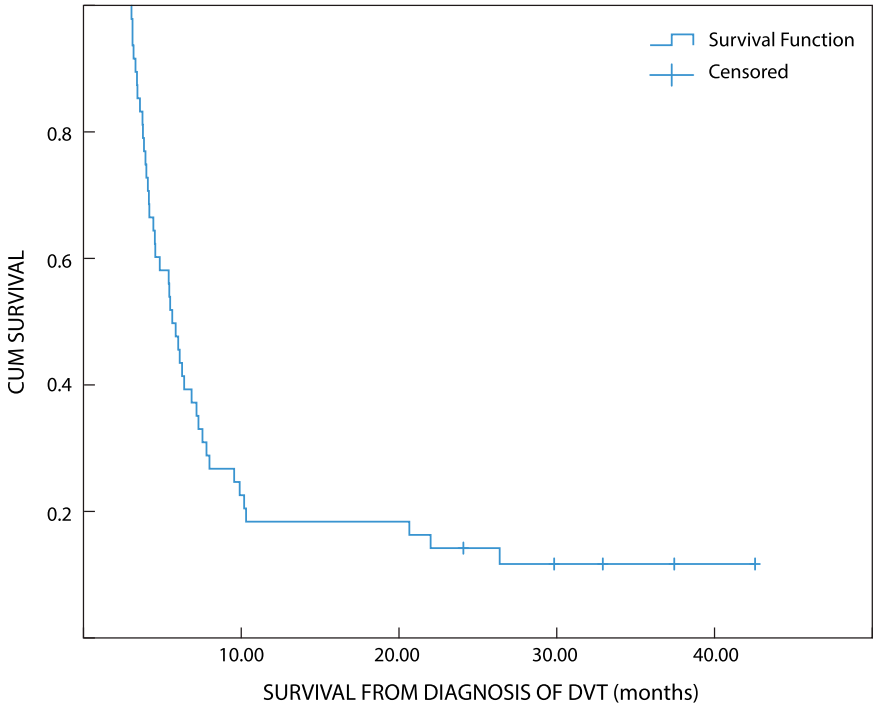

Figure 1: Kaplan–Meier graph indicating survival from diagnosis of DVT/VTE.

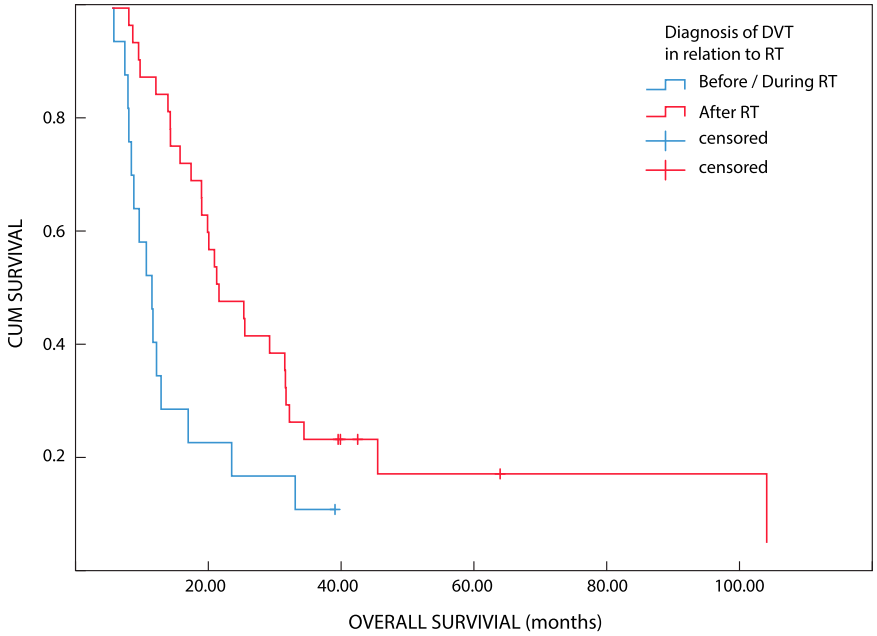

Figure 2: Kaplan–Meier graph indicating overall survival as affected by the timing of the diagnosis of DVT/VTE in relation to radiotherapy.

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 *et al.*[14]	21	20% vs. NR*
Jacobson *et al.*[15]	98	40% vs. 80%
Matsuo *et al.*[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.

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

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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.

Received: 11-11-2019 Accepted: 3-12-2019