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ORIGINAL RESEARCH

A retrospective analysis of the effect of planning tumour volume on survival in cervical carcinoma

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Introduction: Locally advanced stages of invasive cervical cancer (ICC) are associated with poor outcomes; factors influencing survival include increased tumour volume. In resource-constrained settings access to diagnostic imaging with CT and MRI is limited. Alternative methods of establishing tumour volume can be defined with use of the planning target volume (PTV) delineated prior to radiotherapy. The aim of this study is to determine whether increased PTV size impacted on overall survival in a cohort of cervical cancer patients with Stage IIB/IIIB disease who completed radical radiotherapy.
Materials and methods: A retrospective analysis was undertaken of patients with histologically confirmed Stage IIB/IIIB ICC treated with radical radiotherapy. Exclusion criteria included patients who did not complete prescribed radiotherapy and brachytherapy. Demographic and treatment details were collected. Planning target volumes were retrieved. Kaplan–Meier analysis was used to calculate the overall survival rate. A multivariate Cox proportional hazard model was derived to assess associations with all-cause mortality.
Results: A total of 71 patients met the inclusion/exclusion criteria. The median PTV was 653 cc. On univariate analysis factors significantly associated with a lower overall survival included HIV positivity and the presence of hydronephrosis. Increased PTV size paradoxically showed a trend to improved overall survival. On multivariant analysis HIV status, advanced stage, hydronephrosis and a smaller PTV were significantly related to higher all-cause mortality.
Conclusion: It is concluded that, when using planning target volumes, the hypothesis that larger volumes impact on overall survival was disproved. A larger cohort and more accurate methods of determining tumour volume, including PET/CT, will be considered in future prospective studies.

Keywords cervix carcinoma, tumour volume, radiotherapy, survival

Introduction

The National Cancer Registry of 2010 lists invasive cervical cancer (ICC) as the second most common malignancy among females in South Africa.[1] The developing world carries the heaviest burden with 80% of patients residing in these regions. Initial diagnosis is frequently at an advanced stage.

It has long been recognised that more advanced stages of cancer are associated with poor outcomes.[2–5] However, the FIGO staging system is limited in its prognostic and predictive value as known pathological factors, such as histological subtype and tumour size, are not included for all stages. Current staging additionally does not allow for inclusion of cross-sectional imaging findings.[6] Limitations of clinical staging are especially apparent in advanced disease. A more precise and objective method, such as CT or MRI, is preferable.[7]

It was acknowledged that tumour volume influenced prognosis in less advanced cervical cancer (IB–IIA) and therefore the FIGO system was updated to designate differences based on volume greater than or less than 4 cm.[8] It is reasonable to extrapolate that the same might hold true for a more detailed subdivision of locally advanced disease (Stage IIB and IIIB). Unfortunately there is a lack of consistent access to diagnostic CT, MRI and PET-CT in resource-limited settings. In centres with planning CT scans and tumour delineation software there is the potential to use the clinical tumour volume delineated as a surrogate marker for tumour size.

This retrospective review aimed to investigate the effect of the size of planning tumour volume on five-year overall survival for locally advanced cervical cancers (FIGO Stages IIB and IIIB).

Materials and methods

Study design and population

A retrospective analysis of all patients with histologically confirmed Stage IIB and IIIB ICC treated with radical radiotherapy between January 2011 and December 2011 at Tygerberg Academic Hospital in the Western Cape, South Africa was performed. Patient hospital numbers were retrieved from the clinic registry.

Exclusion criteria included patients who did not complete the full course of prescribed radiotherapy and brachytherapy.

Clinical and demographic information was obtained from institutional databases. Data collected included patient age, human immunodeficiency virus (HIV) status, histology, stage of disease, presence of lymph nodes or hydronephrosis. The treatment regimen including external beam radiotherapy (EBRT) and high-dose-rate brachytherapy, dose and fractionation, total number of chemotherapy cycles administered, and overall treatment time was documented. Radiotherapy planning target volume (PTV) was retrieved from the divisional planning system. Size was determined by a computer algorithm calculating the cubic centimetre (cc) volume. The planning system used in this retrospective review was unable to retrieve CTV (clinical target volume) for all patients and therefore necessitated the use of PTV. The CTV included the primary disease, cervix,

uterus and parametria. PTV included the CTV with a 1.5 cm margin in the anterior-posterior plane and 1 cm in all other directions.

Vital status or last follow-up date was retrieved from hospital records and national death registry data.

Treatment

Disease stage was evaluated and confirmed at the weekly multidisciplinary team meeting. Staging was performed according to the FIGO classification and included physical examination, imaging (abdominal ultrasound, chest X-ray) and cystoscopy.

A contrasted planning CT scan was performed for all patients undergoing radiotherapy. The field of view commenced at the bottom of the T12 vertebra to mid-femur with a 5 mm slice thickness. The primary tumour, cervix, uterus, parametria and pelvic lymph nodes (including the common iliacs) were delineated on the planning CT scan.

The standard protocol for patients with Stage IIB to IIIB cervical carcinoma is concurrent chemoradiotherapy. The regimen includes 46–50 Gray (Gy) in 22–25 fractions of EBRT, four to six cycles of weekly chemosensitisation with cisplatin (40 mg/m^2) in those without contra-indications, followed by high-dose-rate (HDR) brachytherapy 20–25 Gy in four to five fractions. The total equivalent dose in 2 Gy fractions to Point A was derived for each patient.

External beam treatment was delivered using a linear accelerator, with 6–18 MV energy beams equipped with a multi-leaf collimator. Treatment was given daily, five days a week. Standard fraction size was 2 Gy, but alternate dosing of 1.8 Gy per fraction was used in cases of HIV-positive patients or patients receiving therapy to para-aortic nodes (PAN). In these cases the PAN field received 45 Gy while the pelvic field received 50.4 Gy.

HDR brachytherapy was commenced in the fifth week of EBRT. The dose was delivered by a Varian GammaMed® machine (Varian Medical Systems Inc, Palo Alto, CA, USA) using a ^{192}Iridium source.

In cases of renal impairment, poor performance status and comorbidity (for example pulmonary tuberculosis) chemosensitisation was not initiated.

Ethics

The study protocol was reviewed and approved by the Health Research Ethics committee of the University of Stellenbosch.

Statistics

Demographic variables were evaluated using frequency statistics. Univariate analysis was performed with chi-squared calculations. Overall survival was calculated by evaluating the time from the end of treatment to the date of last follow-up or death. Kaplan–Meier analysis was used to calculate the overall survival rate from the date of completion of treatment to date of death. Variables identified as significant or showing a trend to significance by univariate analysis were subsequently analysed using the multivariate Cox proportional hazard model to clarify the association between survival and the identified risk factors; $p < 0.05$ was considered to indicate a statistically significant difference. IBM SPSS® version 24 (IBM Corp, Armonk, NY, USA) was used to analyse the data.

Results

Demographics

Of a total of 82 patients with locally advanced cervical carcinoma who were identified during the study time period, a final cohort of 71 patients remained when exclusion criteria were applied.

All patients received a dose of ≥ 66 Gy EQD$_2$ of radiation. The mean EQD2 received was 77.8 Gy (66.7 Gy–85.2 Gy). The overall treatment time for those who completed treatment was equal to or less than 58 days (36–58). Mean overall treatment time was 45 days.

Of the 45 patients who began platinum-based chemotherapy, 40 (88.9%) completed four or more cycles. Chemotherapy was not prescribed in 26 patients, due to poor renal function, poor performance status, CD4 cell count < 200, active pulmonary tuberculosis, or prescription of hypofractionated radiotherapy.

The median age was 48.5 years (23–77 years); eight patients (11%) were HIV-positive and seven (9.8%) patients had hydronephrosis at time of staging. The cohort included 22 Stage IIB patients (31%) and 49 Stage IIIB patients (69%). Table 1 shows the clinical characteristics for the cohort.

The median PTV was 653 cc for the cohort. Stage IIB had a median of 596.97 (iQR 499.87–775.31 cc) and for Stage IIIB the median was 669.2 cc (iQR 509.54–835.81 cc). Large volumes over 1000 cc were in most cases related to the presence of hydrometria. PTV volume was not significantly influenced by stage or HIV status, but a larger volume was significantly associated with suspicious enlarged lymph nodes on ultrasound (Table 2).

Table 1: Clinical characteristics of the cohort

Cohort	Number	Percentage
	***n* = 71**	**100%**
Median age (years)	48.5 (23–77)	
Age:		
< 44	24	34%
44–56	23	32%
> 56	24	34%
Stage:		
IIB	22	31%
IIIB	49	69%
Chemotherapy cycles:		
≥ 4 cycles	40	56%
0–3 cycles	31	44%
HIV status:		
Positive	8	11%
Negative	63	89%
Nodal status:		
Positive/suspicious	12	17%
Negative	59	83%
Hydronephrosis (Stage IIIB only):		
Present	7	14.3%
Absent	42	85.7%

Table 2: Correlation of clinical characteristics and PTV

Factor	PTV ≤ 653 *n* (%)	PTV > 653 *n* (%)	All *n* (%)	*p*-value
HIV status:				
Negative	32 (91.4%)	31 (86.1%)	63 (88.7%)	0.479
Positive	3 (8.6%)	5 (13.9%)	8 (11.3%)	
Nodal status:				
Negative	33 (94.3%)	26 (72.2%)	59 (83.1%)	**0.013***
Positive/ suspicious	2 (5.7%)	10 (27.8%)	12 (16.9%)	
Hydronephrosis (Stage IIIB):				
No	20 (90.9%)	22 (81.5%)	42 (85.7%)	0.348
Yes	2 (28.6%)	5(18.5%)	7 (14.3%)	
Stage:				
Stage IIB	13 (37.1%)	9 (25%)	22 (31%)	0.269
Stage IIIB	22 (62.9%)	27 (75%)	49 (69.0%)	

$p < 0.05$ = statistically significant

Survival

At five years the overall survival for the entire cohort was 59%, 71.1% for Stage IIB patients and 53.1% for Stage IIIB. A planning target volume less than 653 cc had a lower overall survival (OS) of 47.4% compared with 69.3% for those with a larger PTV ($p = 0.135$) (Figure 1).

On univariate analysis the data demonstrated that factors significantly associated with poorer overall survival were HIV status and the presence of hydronephrosis.

A Cox regression model was constructed including age, stage, hydronephrosis, nodal status, HIV status, tumour size and completion of four or more cycles of chemotherapy.

The data from the multivariate analysis demonstrated that the factors which significantly impacted on overall survival in this small cohort include HIV-positivity, Stage IIIB disease, the presence of hydronephrosis and paradoxically small planning tumour volumes (Table 3).

Discussion

In this small cohort study of a subset of cervix carcinoma patients who completed radical radiotherapy, a smaller planning tumour volume was associated with lower overall survival. Additional factors included HIV-positivity, Stage IIIB disease and the presence of hydronephrosis.

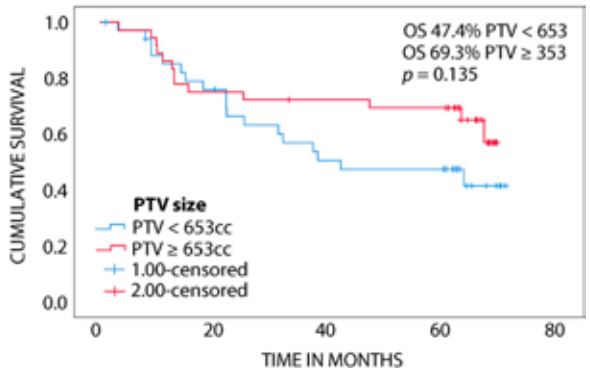

Figure 1: Kaplan-Meier graph comparing overall survival between two tumour volume subgroups.

Evidence suggests that tumour volume should be considered when determining the prognosis in early cervical cancer.[2–5] In advanced cases, very few studies have been performed looking at the effect of tumour volume on overall survival.

Tumour size has generally been determined by pelvic examination. This in itself can be problematic. Clinical examination is not very reliable and understandably differs between observers. The limitations to clinical staging are especially apparent in advanced disease. A more precise and objective method, such as CT or MRI, is preferable.[7] Walsh *et al.* demonstrated that even the use of CT is not entirely accurate in determining tumour volume, as this modality does not provide adequate evaluation of parametrial involvement. This is due to low soft tissue contrast resolution. MRI on the other hand is an imaging method that has several benefits, including improved soft tissue contrast (leading to accurate tumour size measurement and assessment of surrounding soft tissue invasion), improved assessment of depth of stromal invasion and lymph node evaluation.[8] Due to resource limitations no advanced stage patient was imaged with either CT or MRI in our institution during the study period.

Evidence for the effect of tumour volume on overall survival includes studies using many different imaging techniques and methods of determining tumour size and its relation to outcome. Soutter *et al.* investigated pre-treatment tumour volume measurement on MRI as a predictor of survival in early cervical cancer.[9] Results suggest that the size of the tumour, rather than the extent of the disease anatomically, determines outcome. Tumour size > 4 cm as measured on MRI was also found to be a poor prognostic factor by Toita *et al.* from Japan.[10] This finding was in contradiction to their earlier CT-based work, which found that enlarged pelvic nodes was significantly associated with poor outcomes, while tumour size had limited prognostic value.[11] Our small study demonstrates our limitations of using CT-derived PTV alone as a surrogate for tumour volume.

Lee *et al.* found that tumour volume > 33 ml and pelvic lymph node involvement seen on MRI were related to an unfavourable outcome.[12] Kyung *et al.* showed similar results on multivariate analysis for tumour sizes > 4 cm and involved nodes.[13] Limitations of MRI include lack of distinction between metastatic and non-metastatic lymph node hyperplasia as well as difficulty in determining exact tumour size. Tumour is sometimes indistinguishable from normal tissue and some centres use the entire cervical volume when comparing outcomes in patients. The use of a planning CT to delineate tumour size is even more challenging and may have contributed to our negative findings.

Table 3: Prognostic factors for overall survival

Variables	Hazard ratio	95% CI	*p*-value
Age > 50years	1.14	0.54–2.39	0.74
Stage IIIB	5.55	1.71–18.10	**< 0.01***
Positive/suspicious nodes	0.65	0.19–2.31	0.51
Hydronephrosis	4.09	1.24–13.48	**0.02***
HIV-positive	12.95	4.01–41.86	**< 0.01***
PTV < 653 cc	2.77	1.14–6.72	**0.02***
Chemo < 4 cycles	0.92	0.42–2.04	0.84

*$p < 0.05$ = significant.

Functional imaging including positron emission tomography alone or combination PET/CT may assist in this regard. PET/CT can be utilised in many ways—including in the initial evaluation of the primary tumour, metastatic work-up and fusion with the planning scan to assist with tumour/lymph node delineation in radiotherapy planning. The functional information supplied by PET/CT offers greater sensitivity and specificity when compared with CT or other anatomic imaging methods.[14] This method is superior to conventional imaging for detecting metastases. In a study by Grigsby *et al*., tumour volume and lymph node involvement determined by PET/CT predicted overall survival.[15] In more recent years PET/CT has been increasingly performed in our centre for Stage IIIB patients. This is done to detect possible pelvic and para-aortic nodal involvement, metastatic disease and to assist in tumour delineation. Future studies from this institution will include PET/CT information in determining outcomes.

Additional factors related to poor survival outcomes in this cohort included HIV-positivity, advanced stage disease and hydronephrosis. HIV status was considered a poor prognostic factor by Simonds *et al*. in a retrospective trial performed at this institute.[16] This was thought to be partially due to larger tumour volume and interruptions or cessation of treatment in HIV-positive patients. In a prospective study performed by Dryden-Peterson *et al*., analysis showed that HIV infection significantly increased the risk for death among all women with cervical cancer receiving concurrent chemoradiation.[17]

International data on survival by stage include the Vale meta-analysis, which indicated survival benefits in all stages of cervical cancer when comparing radiotherapy alone with concomitant chemoradiation.[18] These effects were modest, but significant. Estimated additional survival benefits were 7% in Stage IIB, and 3% in Stage IIIB at five years. This was confirmed in a meta-analysis from Dutta *et al*., which strictly assessed only primary chemoradiation versus radiation alone in patients who did not undergo surgery.[19] OS benefit was in the order of 7.5%. It is noted the individual studies included in this meta-analysis had small patient numbers but when pooled amount to 2 245 study subjects. The five-year overall survival rates for these stages are 65–75% (Stage IIB) and 35–50% (IIIB) with radiotherapy alone. This corresponds with our observed survival rates per stage (Stage IIB 64%; Stage IIIB 41%) for the HIV-negative patients indicating outcomes comparable to many centres in the developed world. It is noted that completion of chemotherapy did not influence overall survival in our small cohort despite over 40% of patients not completing four or more cycles of chemotherapy.

The limitations of this study include the study design being retrospective in nature and a small sample based at a single institution. This could imply a poor statistical power of all results. It is noted there are wide confidence intervals in the statistically significant results. In addition, if the effect of tumour volume on overall survival is to be studied, a true representation of tumour volume should be obtained; PTV (planning tumour volume) was used as a substitute for this study. This vastly over-estimates tumour volume, especially in cases where hydrometria was present. Five-year progression-free survival or disease-free survival was not evaluated due to the numbers lost to follow-up in our clinical setting. Toxicities secondary to treatment were not considered.

Strengths include a standardised treatment regimen for patients and overall survival rates for chemoradiation in our institution comparable to international studies. Tumour volumes were delineated and planned by the same medical personnel, and therefore inter-observer variation was minimised.

Conclusion

The purpose of this small cohort study was to evaluate the utility of planning target volume as a surrogate marker for survival outcomes in a resource-limited setting.

It is our conclusion that, when using planning target volumes, our hypothesis that larger volumes impact on overall survival was disproved. HIV status and advanced tumour stage did impact on outcome, consistent with international data. A larger cohort and more accurate methods of determining tumour volume, including PET/CT, will be considered in future prospective studies.

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Ethical considerations – No ethical clearance was required for this study.

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