The Incidence, Management and Outcomes of Stage IIIB Cervical Cancer in a Middle-Income Setting

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INTRODUCTION

Cervical cancer is the fourth most common cancer among women globally and the fourth leading cause of cancer death in women with an estimated 604000 new cases and 342000 deaths worldwide in 2020 according to Globocan data [1]. Approximately 90% of new cases and deaths worldwide in 2020 occurred in low- and middle-income countries with the highest regional incidence and mortality found to be in sub-Saharan Africa. This is due to limited access to preventative measures resulting in diagnosis of advanced stage disease [1]. The incidence of cervical cancer in developing countries remains high due to a combination of the absence of effective screening programmes, limited access to health services, poor awareness about preventative measures including human papillomavirus (HPV) vaccination and screening, poverty and low socioeconomic status [2, 3].

In an upper middle-income setting, like South Africa, the incidence of cervical cancer is much higher in comparison with Western countries. In South Africa, cervical cancer is the second most common cancer and the leading cause of cancer-related deaths [4]. This is largely owed to infection with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), which is known to increase the risk of HPV acquisition. Women are typically of younger age and present with more advanced disease by the time they are diagnosed [5].

There were 6268 new histologically diagnosed cervical cancer cases in South Africa during 2018, which made up 15% of all cancers diagnosed in women in South Africa that respective year. Cervical cancer ranked as the second highest incidence, with breast cancer having the highest incidence with 23% [6]. The Groote Schuur Hospital (GSH) Gynaecological Oncology Unit's 2018 annual report reflects a continuous increase in cervical cancer incidence over the years, with a total of 174 new cases diagnosed at Groote Schuur in 2018. This represented a 20% increase in incidence when compared to 2007. The proportion of early-stage disease has increased from 60 new cases in 2007 to 80 in 2018 while the proportion of advanced stage disease has remained stable. Stage III disease is still the most common presenting stage representing 43.7% of all newly diagnosed cervical cancer cases [7].

Cervical cancer is staged clinically, and The International Federation of Gynaecology and Obstetrics (FIGO) staging is preferred, as it is less resource intensive, is more sensitive in detection of locally advanced disease and identification of patients that are poor surgical candidates [8]. In 2018 FIGO revised the staging system of cervical cancer with the goal of improving prognostication and planning of treatment [9]. Stage III cervical cancer was previously subcategorised into stage IIIA, where disease extends into the lower third of the vagina, and stage IIIB, where disease either extends into the pelvic sidewall (PSW) or there is hydronephrosis (HN) or a non-functioning kidney. Revised staging incorporated stage IIIC1 and IIIC2, which now includes radiological detection of pelvic and para-aortic lymph nodes respectively [9].

The ureters are in close anatomical proximity to the cervix. Tissue from malignant cervical tumours can compress the urinary outflow or directly invade the ureter or result in ureteral scarring or stricture [10, 11]. Hydronephrosis is a frequent complication in advanced disease, which is present in almost 50% of patients with advanced cervical cancer and is associated with worse outcomes [12]. Hydronephrosis, which may be unilateral or bilateral, can result in renal dysfunction and thus limit use of concurrent radio-sensitising chemotherapeutic agents like Cisplatin, which is of proven survival benefit [13, 14]. Numerous studies have concluded that the presence of hydronephrosis is a negative prognostic factor

for cervical cancer, with mean survival of patients with unilateral hydronephrosis being significantly larger compared to that of patients with bilateral hydronephrosis [15]. However, it remains unclear whether placement of ureteral stents or percutaneous nephrostomies are of any benefit and improve survival outcomes for these patients with bilateral hydronephrosis [15].

While the outcomes of patients with stage IIIB cervical cancer presenting with hydronephrosis have been studied at length, data is limited on those patients with pelvic sidewall involvement without hydronephrosis and having normal renal function. It stands to reason that there may be a difference in survival outcomes between these two groups of patients that fall within the same clinical stage of IIIB, with the premise that patients without hydronephrosis have a more favourable outcome.

There is also very limited data on management and outcomes of women with stage IIIB cervical cancer in low- and middle-income settings. Groote Schuur Hospital (GSH) is one of two tertiary level hospitals in Cape Town, South Africa. This study specifically focuses on the management and care of stage IIIB cervical cancer at GSH, and hence provides a snapshot of a middle-income setting.

This retrospective review aims to evaluate the management and outcomes, specifically overall survival and disease-free survival, in patients with stage IIIB cervical cancer in a public hospital within a middle-income country setting.

METHODS AND MATERIALS

This retrospective descriptive audit was conducted in the Department of Radiation Oncology at Groote Schuur Hospital in Cape Town, South Africa. The study reviewed the clinical data of a cohort of patients who received treatment for stage IIIB cervical cancer at Groote Schuur Hospital in 2017 and 2018. Data was collected by reviewing clinical files as well as using the electronic patient database at GSH and Gynaecological Cancer Research Centre (GCRC) database (HREC RO16/2013), which is based at the University of Cape Town and is aimed at programmes that address challenges faced by patients with a gynaecological cancer diagnosis. Criteria necessary for inclusion was histologic confirmation of cervical cancer – both squamous cell carcinoma and adenocarcinoma were included, and stage IIIB disease by FIGO 2009 classification. Patients found to have stages I, II, IIIA and IV were excluded, as well as those patients who had pre-existing renal dysfunction at diagnosis. Renal dysfunction was defined as a serum creatinine of more than 90umol/L according to the National Health Laboratory Service (NHLS) at Groote Schuur Hospital. The treatment protocol used for stage IIIB cervical cancer at the time of the study comprised of definitive concurrent chemoradiation: external beam radiotherapy (EBRT) delivered by volumetric modulated arc therapy (VMAT) technique to a total dose of 46Gy in 2Gy fractions (delivered to cervix, uterus and elective lymph nodes) with concurrent Cisplatin/Carboplatin at 40mg/m2 given once weekly, followed by intracavitary brachytherapy (28Gy delivered in four 7Gy fractions prescribed to Point A).

The records of patients meeting the above criteria were reviewed to obtain the following information: age, HIV status, comorbidities, baseline haemoglobin and creatinine at the time of diagnosis, presence or absence of pelvic sidewall involvement, presence or absence of hydronephrosis, whether renal dysfunction was present at commencement of treatment or developed during treatment, treatment

intent and type of treatment offered, whether patients were referred for nephrostomy or developed nephrostomy complications, and whether patients completed treatment.

The hypothesis is that patients diagnosed with stage IIIB cervical cancer presenting with hydronephrosis, irrespective of pelvic sidewall involvement, have a worse prognosis than patients presenting with pelvic sidewall involvement only, and that the prognosis of patients with hydronephrosis improves with early urinary diversion. The primary objectives of the study were to determine the overall survival and disease-free survival of patients with stage IIIB cervical cancer with specific attention to those patients with hydronephrosis, determine the incidence of unilateral hydronephrosis and bilateral hydronephrosis in patients diagnosed with stage IIIB cervical cancer, determine how many patients with hydronephrosis were offered percutaneous nephrostomies and reasons why others were not, describe the treatment offered and outcomes of the women who were offered percutaneous nephrostomy, describe any complications that arose by inserting nephrostomies, and to determine how many patients with hydronephrosis received concurrent chemo-radiation (CCRT). Secondary objectives were to determine the overall incidence of stage IIIB cervical cancer seen at a single institution between from January 2017 until December 2018, and to determine whether there are any additional demographic factors which may significantly influence outcomes of patients.

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 29. Statistics for numerical data included measures of central tendency. A cox regression was run to determine associations between overall survival and age, HIV status, and comorbidities, as well as between disease-free survival and age, HIV status and comorbidities. Statistical significance was accepted at $p \leq 0.05$.

Application for permission to perform the study were obtained from the Departmental Research Committee, hospital management and the Human Research Ethics Committee of the Faculty of Health Sciences at University of Cape Town. A waiver of informed consent was also obtained because data was collected retrospectively. Data was deidentified by allocating participant numbers to each patient included in the study to preserve their privacy. This study is in keeping with the Declaration of Helsinki (2013) [16].

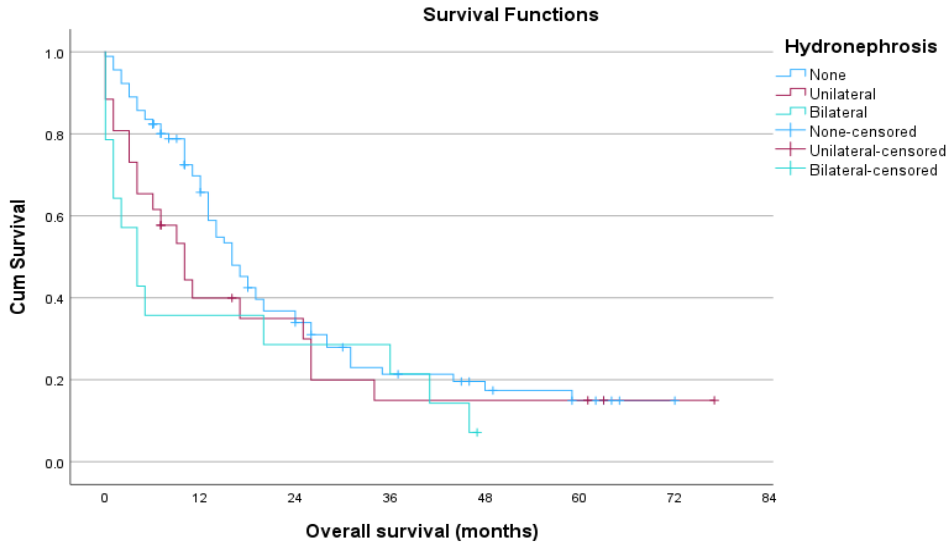
RESULTS

The overall incidence of cervical cancer seen at GSH between January 2017 and December 2018 was 350, of which 137 were staged as IIIB (39%). A total of 132 patients were eligible and were analysed in our study. The reasons for exclusion were upstaging to stage IVA due to presence of bladder involvement (n=2), and patients who relocated back in Eastern Cape and did not commence treatment at GSH (n=3).

The age of the study population ranged from 24 to 92, and mean age at diagnosis was 52 with a standard deviation of 13.2 years. There was no statistically significant association between both overall survival and disease-free survival with age and comorbidities. However, HIV was found to have a statistically significant unique contribution to both overall survival (OS) ($p=0.05$) and disease-free survival (DFS) ($p=0.03$). The hazards ratio for OS and DFS were 0.598 and 0.451 respectively. A total of 45 patients (34%) were found to be co-infected with HIV at the time of diagnosis. HIV status did not affect

the treatment intent of patients. Patients found to be virally unsuppressed were referred to their local HIV clinic to initiate antiretroviral treatment (ARV's) prior to starting CCRT.

Of the 132 patients, 96 had died (73%) over a period of 5 years. The median overall survival was 15.00 (95% CI, 11.96 to 18.04) months. The cumulative survival 3 years (36 months) after the date of diagnosis was 0.20 (20%) and 0.14 (14%) at 5 years (60 months). Table 1 shows how overall survival varied in patients with no hydronephrosis, unilateral hydronephrosis and bilateral hydronephrosis. The log rank results showed that the overall survival between presence and absence of hydronephrosis was not statistically significant, $\chi 2(2) = 3.66$, p=0.16. A trend was noted towards poorer survival in women with bilateral hydronephrosis, however, this was not statistically significant.



p-value: 0.16

Figure 1: Kaplan-Meier estimate of overall survival according to the hydronephrosis group.

Overall Survival	Total	Died	Median OS (months)	Cumulative survival at 3 years	Cumulative survival at 5 years
No HN	92	63	16	0.21 (21%)	0.15 (15%)
Unilateral HN	26	20	10	0.15 (15%)	0.15 (15%)
Bilateral HN	14	13	4	0.21 (21%)	0.07 (7%)
Total	**132**	**96**	**15**	**0.20 (20%)**	**0.14 (14%)**

Table 1: Relationship between overall survival and hydronephrosis

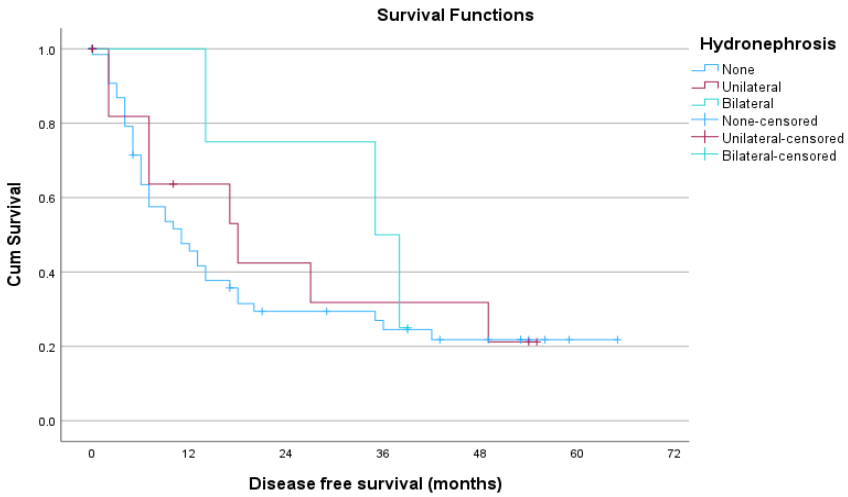
There was a greater propensity toward radical treatment using CCRT in patients with no hydronephrosis, which can be seen in Table 2. Five patients with bilateral hydronephrosis were treated with radical intent, however, only 4 patients completed treatment. Three patients were referred for percutaneous nephrostomy. Normal renal function and poor performance status were the reasons for the remaining 2

patients to not be referred for nephrostomy. One patient received concurrent chemoradiation, and remains alive with a complete response to treatment, while the other 2 received radiotherapy (RT) alone and are both deceased. Cause of death was sepsis and progressive disease in these patients. The reason for omission of concurrent chemotherapy was not documented but can be accounted for by a change in treatment protocol at the time.

	Type of treatment	Frequency	Percent
No HN	CCRT (radical)	47	51.1%
	RT only (radical)	16	17.4%
	Palliation	29	31.5%
	Total	**92**	**100%**
Unilateral HN	CCRT (radical)	10	38.5%
	RT only (radical)	4	15.4%
	Palliation	12	46.1%
	Total	**26**	**100%**
Bilateral HN	CCRT (radical)	2	14.3%
	RT only (radical)	3	21.4%
	Palliation	9	64.3%
	Total	**14**	**100%**

Table 2: Treatment modalities split by hydronephrosis.

There was a total of 82 patients who completed radical treatment (CCRT or RT only), of which 50 relapsed or died (61%). The median disease-free survival in the group of patients who completed radical treatment was 13.00 (95% CI, 9.15 to 16.86) months. The cumulative disease-free survival 3 years (36 months) after the first follow-up after completing radiotherapy was 0.27 (27%) and 0.21 (21%) at 5 years (60 months). Table 3 shows how disease-free survival varied in patients with no HN, unilateral HN and bilateral HN. The log rank results showed that the disease-free survival between presence and absence of hydronephrosis was not statistically significantly different, $\chi 2(2) = 0.98$, $p = 0,61$.



p-value: 0.61

Figure 2: Kaplan-Meier estimate of disease-free survival according to the hydronephrosis group

Disease-free Survival (DFS)	Total	Relapse/died	Median OS (months)	Cumulative DFS at 3 years	Cumulative DFS at 5 years
No HN	65	39	11	0.25 (25%)	0.22 (22%)
Unilateral HN	13	8	18	0.32 (32%)	0.21 (21%)
Bilateral HN	4	3	35	0.25 (25%)	0.25 (25%)
Total	**82**	**50**	**13**	**0.27 (27%)**	**0.21 (21%)**

Table 3: Relationship between disease-free survival and hydronephrosis

DISCUSSION

The high incidence of stage IIIB cervical cancer corroborates much of what has been found at our institution in previous years [7]. Comparative studies, both locally and abroad, have not specified the proportion of stage IIIB cancers specifically in relation to all cervical cancer cases, however, it confirms a significantly lower incidence of advanced disease in high-income countries compared to higher incidence in low- and middle-income countries [7, 11, 17-19] . This highlights the disparity between the extent and burden of disease of middle- and high-income countries, which often relates to better access to healthcare, screening programmes with interventions and education.

The mean age at diagnosis was 52 years, which aligned with studies in USA, Brazil, and South Africa where mean age ranged between 49 and 53 years old [5, 12, 20]. While we are aware that there is a higher incidence of cervical cancer amongst HIV positive patients [5], this study has also highlighted an association between HIV and worse OS and DFS (p value = 0.03). The study was not powered, and this association may not be reliable. However, these findings are in keeping with a similar study conducted in

Kenya [21]. This highlights the importance of voluntary counselling and testing within our communities and ensuring women are started, and are compliant, on antiretroviral treatment. By doing so we may be able to reduce the incidence of cervical cancer and improve overall survival by diagnosing and successfully treating early-stage disease.

A study in India showed a survival benefit in patients who received CCRT compared to RT only, however, this study excluded HIV positive patients, patients with abnormal renal function and patients with known para-aortic nodes [18]. Our assumption is that patients with hydronephrosis tend to have worse outcomes following radical treatment, however, our study has demonstrated no statistically significant difference in overall survival or disease-free survival when comparing patients with and without hydronephrosis. This outcome may be because of a generally high mortality rate for stage IIIB disease, as the surviving fraction of patients with PSW involvement only was found to be 22%. Another consideration may be that these patients could have had pelvic or para-aortic nodal disease but was not documented, as the 2009 FIGO staging did not make provision for radiological upstaging for pelvic or para-aortic node involvement. Similar studies carried out in Brazil, Taiwan, Turkey and USA showed that patients with hydronephrosis had lower overall survival and progression-free survival when compared to those without hydronephrosis, identifying hydronephrosis as a negative predictive indicator [8, 12, 20, 22, 23].

A significant limitation to our study is the few patients referred for nephrostomies. Only patients with bilateral hydronephrosis considered for radical treatment were candidates for referral, which excluded 87% of patients upfront. Of the 5 eligible candidates 2 were further excluded due to normal renal function and poor performance status. During our study period we also saw a change in the treatment protocol for stage IIIB patients from radiotherapy only to including weekly concurrent cisplatin, which is a confounding factor. As a result, we have found that only 1 patient referred for nephrostomy received concurrent chemoradiation and, incidentally, is the only patient who remains alive and in remission. This, too, explains the high rate of patients without hydronephrosis that received radiotherapy only, as depicted in Table 2. Comparative studies abroad showed varying outcomes – *Nobrega et al* showed that urinary diversion had no impact on overall survival or progression-free survival [12], *van Aardt et al* showed an improvement in overall survival [5], and *Pergialiolis et al* states it is unclear whether treatment of obstruction may be of any benefit [15]. Unfortunately, our study was not powered to determine an association between urinary diversion and treatment outcome.

Hydronephrosis can be relieved by either percutaneous nephrostomy or by ureteral stent placement. Percutaneous nephrostomies are the first choice in patients with more severe hydronephrosis, ureteral obstruction >3cm in length, or bladder infiltration, as ureteral stent placement has a lower success rate [10]. Our institution follows the same practice of percutaneous nephrostomy over ureteral stent placement in the acute setting. The rationale for this is based on the above reason, as well as financial constraints that encourage cost-saving strategies in our daily practice. Stents are more expensive, and its insertion cannot be justified if the patient deteriorates and is no longer a candidate for radical treatment, nor if the stent migrates while on radiotherapy treatment due to tumour response. We do, however, offer patients stents on follow-up visits if they are found to have ureteric fibrosis or stenosis. *Horan et al* recommends careful consideration of candidates who will likely require urinary diversion prior to starting radiotherapy to prevent disruptions and delays during treatment [14].

Palliation, as demonstrated in Table 2, included palliative radiotherapy and best supportive care. Patients with very advanced or bulky disease, advanced age or having multiple comorbidities with baseline renal dysfunction were treated with palliative radiotherapy, the dose and fractionation dependent on their performance status. Patients with poor performance status were considered for best supportive care where our focus was adequate symptom control and support to the patient and their family. Locally advanced disease typically has a high symptom burden from diagnosis and often persists during treatment. *Rhadhakrishna* has challenged our treatment approach to consider a patient centric one by ensuring early integration of palliative care in combination with radical treatment [24]. Based on the data of this study it appears appropriate to adopt this approach to ensure that patients are treated holistically and have the necessary channels of support at their disposal early on in their treatment journey, irrespective of their treatment intent. Further consideration can also be given to patient selection for radical treatment where additional factors like age and burden of disease can help steer the decision whether to treat radically or not. Certain patients may benefit more from a shorter palliative radiotherapy course for local control and improvement in quality of life rather than concurrent radiotherapy.

Radiological staging for patients with locally advanced disease may be beneficial to identify appropriate candidates for radical intent prior to embarking on treatment, especially when image-guided adaptive brachytherapy (IGABT) is available to ensure that a total dose of 80-90Gy can be delivered. A higher brachytherapy boost has proven to be a critical component of treatment to maximise the probability of local control and overall survival [25]. Further studies, using a larger cohort, comparing outcomes of patients who underwent urinary diversion followed by definitive chemoradiotherapy is recommended.

LIMITATIONS

Limitations of our study are attributed to its retrospective nature, which was conducted at a single institution. Our study population, specifically patients with bilateral hydronephrosis, was small. Furthermore, many of these patients were not candidates for radical treatment and was thus not referred for nephrostomies. Our study period saw a change in our radical treatment protocol for stage IIIB from RT only to CCRT, resulting in a treatment plan that was not standardised between patients. Our data looked at patients staged using 2009 FIGO staging, which did not make provision for radiological upstaging and may affect the interpretation of the results seen.

CONCLUSION

Hydronephrosis was not found to have a statistically significant impact on overall survival or disease-free survival. There remains a place for percutaneous nephrostomies in the acute setting and is preferred over ureteral stents in a resource-constrained setting, but patient selection and timing is of paramount importance. Further prospective studies comparing outcomes of patients who underwent urinary diversion followed by definitive chemoradiotherapy is recommended. In our cohort factors that impacted overall survival included HIV positivity but were not significantly linked to hydronephrosis. Further research using a larger cohort of patients is recommended to determine if any significant association exists.

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