

Urinary Diversion in the Management of Locally Advanced Cervical Cancer Facilitates the Use of Aggressive Therapy without Adversely Effecting Overall Treatment Time

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Abstract

Objectives: Overall treatment time (OTT) is critical in locally advanced cervical cancer (LACC), with shorter treatment durations leading to improved control of disease. Due to bulky tumors or lymphadenopathy, women may require urinary diversion in order to receive aggressive therapy with chemoradiation. Urinary diversion procedures can cause treatment delays due to complications. This study compares patients treated with definitive radiation therapy (RT) ± chemotherapy that either did or did not receive urinary diversion in terms of their OTT.

Methods/Materials: Women with LACC treated with RT ± chemotherapy from 2006-2015 were identified. Demographics, stage, histology, requirement for stenting, OTT, treatment delays, and receipt of chemotherapy were assessed. Statistical comparisons between non-diverted and diverted groups were done by Wilcoxon signed-rank test for stage, 2-sample t-test for OTT, Fisher's exact test for receipt of chemotherapy.

Results: Of the 82 women, 23% required diversion. The diverted group had higher staged disease compared to non-diverted group ($p < 0.0001$). OTT was 61 days for non-diverted group (range 42-116) compared to 66 days in the diverted (range 51-95) $p = 0.18$. Interestingly, there was no significant difference in rates of chemotherapy use between non-diverted (95%) and diverted (85%) groups ($p = 0.15$). With a median follow up of 22 months (range 1-115), 79% of non-diverted women are alive compared to 60% with diversion ($p = 0.12$).

Conclusions: Women with LACC often require diversion to relieve ureteral obstruction. These procedures allow women with more advanced tumors to receive aggressive therapy with chemoradiation and, despite complications, do not cause significant prolongation of OTT.

Keywords: Cervical cancer; Urinary diversion; Obstructive Uropathy; Cisplatin; Radiation therapy

Introduction

Cervical cancer is a common cause of mortality worldwide and often presents with locally advanced disease. Current standard of care involves concomitant radiotherapy with Cisplatin-based chemotherapy [1-5]. Overall treatment time, from the initiation of chemotherapy

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and radiation to the completion of all therapy, has been shown to be an important treatment parameter, as breaks in treatment result in reduced disease control and higher patient mortality [6,7]. In order to achieve optimal results, practitioners aim to deliver the entirety of therapy within 56 days.

As a consequence of primary tumor size or high volume pelvic lymphadenopathy, as many as 14% to 34.5% of women present with ureteral obstruction at the time of initial diagnosis [8]. This obstruction can lead to hydronephrosis and impaired renal function, which may preclude aggressive treatment with Cisplatin-based chemotherapy. However, renal function can be improved if ureteral obstruction is relieved by ureteral stent (US) or percutaneous nephrostomy (PCN) placement. Placement of US is considered the first-line therapy for obstructive uropathy, though it becomes technically difficult in the setting of bulky, malignant disease [9]. Conversely, in the context of external ureteral compression, PCN is the more simple procedure but carries an increased risk of infection and impairment in quality of life [9].

Improved renal function may permit the use of Cisplatin-based therapy, but both US and PCN can cause delays in treatment due to infection, pain, and/or the need for device exchange. Previous work has shown that urinary diversion procedures performed while undergoing radiation therapy results in significant delays in treatment [10]. Relief of urinary obstruction may allow for more aggressive treatment, but it is unknown if the adverse effects of the procedures prolong the overall treatment time, which may be counterproductive and prove to be contraindicated in the setting of malignant obstruction. This study aims to compare patients with locally advanced cervical cancer treated with definitive radiation therapy with or without chemotherapy that either did or did not receive urinary diversion in terms of their overall treatment time, receipt of chemotherapy, and disease outcomes.

Materials and Methods

Patient Selection

With institutional review board approval, a review was performed of women treated with radiotherapy for cervical cancer between 2006 and 2015. Criteria for inclusion were: biopsy-proven cervical carcinoma, FIGO stage IB1-IVA, and treatment with definitive intent radiotherapy (+/- chemotherapy). Patients with metastatic disease, prior surgery for their cancer, or with incomplete records were excluded from our analysis.

Data collected included patient demographics, primary tumor stage and histology, radiation therapy details (technique, dose, and treatment time), receipt of chemotherapy, and requirement of urinary diversion. The diagnosis of urinary obstruction was made by physicians in the departments of Gynecologic Oncology and/or Radiation Oncology using 3D imaging (PET/CT or CT) in conjunction with serum creatinine measurements. Urinary diversion procedures were performed by the departments of Urology and Interventional Radiology. The primary diversion strategies included US if retrograde stenting was feasible and PCN placement if it was not.

Statistical Analysis

Patients were stratified into two groups, those who required diversion and those who did not. Statistical comparison between diversion and no-diversion groups were done by Wilcoxon signed-rank test for stage, 2-sample t-test for treatment time, and Fisher's exact test for association between use of chemotherapy and group. Significance was set at $p < 0.05$.

Overall treatment time was calculated as the number of days between the start and completion of all radiation therapy. As this study encompasses a large time period, radiotherapy prescriptions varied slightly over time. From 2006-2012 the treatment course consisted of 5-6 weeks external beam radiotherapy (EBRT), a 2 week break, and concluded with 1-2 HDR insertions. From 2012-present, the treatment course consisted of 5-6 weeks EBRT with 3-5 HDR insertions interdigitated over the last several weeks of treatment.

Results

A total of 82 women were treated with definitive radiation therapy between 2006 and 2015. Patients had an average age of 54 years (range: 26-94) and presented with stage IB1-IVA cervical cancer. Histology was predominantly squamous cell (91.4%); followed by adenocarcinoma (6.2%), clear cell (1.2%), and small cell (1.2%). FIGO staging was primarily IIIB (34%); followed by IIB (27%), IB2 (21%), IB1 (11%), IVA (6%), IIA (3.6%), and IIIA (1.2%).

		All Patients		No Diversion	Diversion	P-Value
Total		82		63	19	
Histology	Squamous	96%		96%	95%	NS
Age (years)		48 (22-84)		48 (22-84)	49 (31-78)	NS
FIGO Stage	IB1	9	(11%)	9	0	P<0.0001
	IB2	17	(21%)	16	1	
	IIA	3	(3.6%)	3	0	
	IIB	19	(23%)	17	2	
	IIIA	1	(1.2%)	1	0	
	IIIB	28	(34%)	16	12	
	IVA	5	(6%)	0	5	

Table 1: Patient age, tumor histology and stage of disease.

Of these women, 23% (19 patients) required urinary diversion. Figure 1 shows the initial CT imaging of one of these patients with a large cervical mass causing ureteral obstruction and bilateral hydronephrosis. Figure 2 shows the placement of PCNs bilaterally using antegrade pyelogram with the subsequent relief of hydronephrosis, allowing for definitive therapy with chemoradiation.

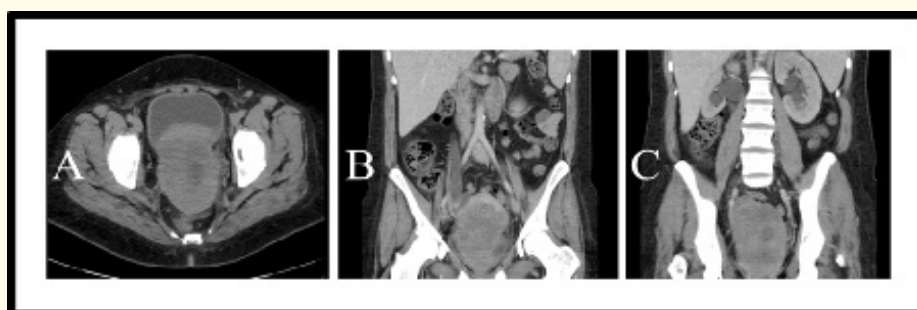


Figure 1: (A) Axial CT showing large cervical mass with extrinsic compression of ureteral orifice. (B) Coronal CT showing clearly dilated right ureter. (C) Coronal CT showing bilateral hydronephrosis.

Notably, the diverted patients had significantly higher staged disease compared to the patients without diversion ($p < 0.0001$). Of these women, 9 received diversion prior to treatment, 4 were diverted during treatment, and 6 needed diversions soon after the completion of treatment. The majority of diversions [17] were performed due to hydronephrosis, with procedures also performed for vesicovaginal fistulas [2] and ureteral stenosis secondary to treatment [1].

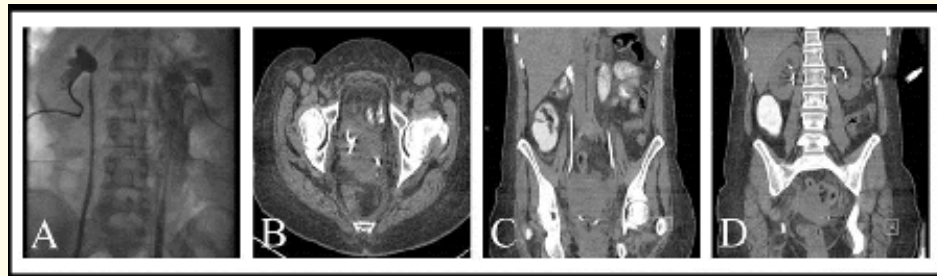


Figure 2: (A) Fluoroscopic image of antegrade pyelogram via percutaneous puncture of the bilateral renal collecting systems with bilateral percutaneous nephroureteral stent placement. (B-D) Axial and coronal CT images showing stent placement with resolution of hydronephrosis.

Six women had ureteral stents placed and 13 others had percutaneous nephrostomies. Of these patients, 9 had bilateral procedures and 10 had unilateral. The average overall treatment time was 61 days in the group without diversion (range: 42-116 days) compared to 66 days in the group with diversion (range: 51-95 days), not significantly different by 2-sample t-test ($p = 0.18$). The average overall treatment time for unilateral diversions was 62 days (range: 51-83) compared to 73 days for bilateral diversions (range: 51-95), also not significantly different by 2-sample t-test ($p = 0.12$). The mean amount of time missed directly related to diversion complications was less than 1 day (0.8, range: 0-4). The primary reason for missed treatments in the diverted group was hospitalization for urinary tract infection, with other delays caused by elevated creatinine, hematuria, and pyelonephritis.

Notably, there was no significant difference in rates of chemotherapy receipt between the diverted vs. non-diverted groups, with 95% of non-diverted patients and 85% of the diverted patients receiving chemotherapy ($p = 0.15$).

		No Diversion		Diversion		P-Value
Chemotherapy	Yes	59	(95%)	17	(85%)	$p = 0.152$
	No	3	(5%)	3	(15%)	
Treatment time (days)		60.8 days (95%CI 57.3-64.4)		65.8 days (95%CI 58.7-72.9)		$p = 0.182$
Overall Survival		79%		60%		$p = 0.139$

Table 2: Receipt of chemotherapy, treatment time and overall survival by group.

While non-diverted patients received LDR brachy therapy at more than twice the rate of HDR treatments (68% vs. 32%), diverted patients were more evenly split with 58% receiving LDR and 42% receiving HDR.

With a median follow up of 22 months (range: 1-115 months), 79% of women without diversion are alive compared to 60% with diversion ($p = 0.12$). There was no significant difference in the average time from treatment completion to death in patients who died due to disease (non-diverted = 526 days vs. diverted = 520 days, $p = 0.97$).

Discussion

To our knowledge, this is the first study to directly examine if adverse effects caused by the use of urinary diversion procedures significantly extend overall treatment time. Previously, it has been shown that, in the setting of cervical cancer, shorter overall treatment time leads to improved control of disease and survival [6,7]. In fact, it is estimated that prolongation of treatment time results in a 0.3% to 1.6% loss of local control per day [11]. This loss of tumor control is theorized to be caused by an accelerated repopulation

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of neoplastic cells which occurs in the downtime between treatments [9]. Our analysis revealed no significant difference in the overall treatment time between those patients who received urinary diversion and those who did not.

Patients who present with hydronephrosis due to pelvic side wall disease have previously been shown to have a poor outcome [12,13]. Urinary diversion procedures can be utilized to circumvent blockage and improve renal function [13]. However, there is controversy over whether or not the routine use of urinary diversion procedures is advisable. One prospective study found that while urinary diversion can be used to alleviate ureteral stenosis, there is no subsequent favorable effect on 12 month survival or quality of life [14]. Conversely, other reports have found that the successful use of urinary diversion improves both quality of life and survival [13-15]. Despite having patients with higher staged disease in the diverted group, we found no significant difference in survival outcomes between the two populations, although this could be due to the relatively small number of women in this study.

Part of the controversy surrounding the use of urinary diversion arises from the myriad of complications potentially caused by these procedures, which include infection (insertion site, UTI, sepsis), catheter failure/obstruction, perforation/hemorrhage, and death. These complications can impair the ability to complete aggressive chemoradiation. Surprisingly, complications from urinary diversion did not cause significant delay in patients in this study. However, it is important to note that cervical cancer patients have many other reasons for missed treatments, including toxicity of therapy, conflicts with work, family, or distance from treatment center, and other challenging social situations.

The standard of care for the treatment of advanced cervical cancer for over a decade has been concurrent radiation (both external beam and brachy therapy) with Cisplatin-based chemotherapy. The addition of chemotherapy to radiation therapy provides an increase in overall survival of approximately 10% [1-5]. However, Cisplatin use is well known to carry a significant risk of nephrotoxicity. This risk is magnified in the setting of decreased renal function and/or obstructive uropathy. Alternative regimens include gemcitabine or carboplatin instead of Cisplatin, both of which have a significantly reduced risk of nephrotoxicity and may be used as radio sensitizers in patients with renal failure. However, there is currently only single-institution data with these agents [16,17]. In our population, diversion allowed for a majority of patients with renal compromise to receive Cisplatin-based chemotherapy.

Notably, our analysis also discovered a difference in the frequency of use of LDR and HDR brachytherapy. This is due to the time-frame from which we acquired our study population. Prior to 2012 the majority of patients were treated with LDR, and from 2012 to 2015 patients received HDR treatment. For this comparison, patients treated with HDR may have an inherent benefit, as HDR generally follows a more condensed treatment plan due to inter digitating the brachytherapy as opposed to waiting until after the completion of the external beam and chemotherapy. In our patient population, the non-diverted patients (with presumably less advanced disease) received LDR therapy more than two times more often than HDR. Conversely, the diverted patients were much more evenly split in regards to brachytherapy modality.

Our report has several limitations. First, it was a relatively small series from a single institution with limited follow up. Furthermore, the assessment of the reason for missed treatments was done retrospectively, rather than in a prospective manner.

Conclusions

In the past, urinary diversion has been used to palliate symptoms in advanced cervical cancer and clinicians have been reluctant to use diversion as a means to pursue aggressive treatment. This study indicates that urinary diversion procedures utilized in advanced-stage cervical cancer does not cause significant delays in overall treatment time, allows for a majority of patients to receive concurrent chemoradiation, and provides a similar expected overall survival. This work adds to the growing body of evidence that procedurally ameliorating obstructive uropathy to facilitate the concurrent use of chemotherapy and radiation is a sound clinical decision.

Conflicts Of Interest

The authors declare no conflict of interest.

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