



Original Article

The Effectiveness of Urinary Diversion in Patients with Cervical Cancer at Kariadi General Hospital

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Abstract

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Background : Obstructive uropathy and hydronephrosis are common complications of cervical cancer. In order to provide an alternative route due to ureteral obstruction, urinary diversion was performed. Urinary diversion procedures are a therapeutic option for obstructive uropathy but their effectiveness is remain unclear. There is limited data that support urinary diversion as a treatment of ureteral obstruction to improve overall survival and progression-free survival. This study was aimed to determine the effectiveness of urinary diversion in the treatment of obstructive uropathy in cervical cancer patients.

Methods : This study is a cross sectional involved cervical cancer patients with symptoms of obstructive uropathy. Data were obtained from medical records and limited to patients admitted from May, 2020 to May, 2021. Primary outcome was urea level, creatinine level, stage of hydronephrosis and overall survival rate of patients.

Results : A total of 100 patients were included in the study. In both groups, the mean age of study subjects was 52–53 years with stage IIIB being the most widely reported. There was an improvement in post creatinine in the urinary diversion group. There was a significant difference in post creatinine levels between the non-urine diversion and urinary diversion groups ($p=0.039$). The 12-month survival rate, in the non-urinary diversion group had a value of 86% while the urinary diversion group had a value of 94%.

Conclusion : This study shows that urinary diversion procedure is effective in increasing the renal function and increasing the 12-month survival of cervical cancer patients with obstructive uropathy.

Keywords : Cervical cancer, Obstructive uropathy, Urinary diversion

INTRODUCTION

Cervical cancer is the second most common malignant tumor and one of the leading causes of cancer mortality in women. Persistent high-risk *human papillomavirus* (HPV) infection (serotypes 16 and 18) is considered as the main cause.¹ Over the past 30 years, the increase in the proportion of young women with cervical cancer has ranged from 10% to 40%.² In 2018 worldwide with an estimated 570,000 cases and 311,000 deaths, cervical cancer was the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women.³

Advanced cervical cancer patients often present with several life-threatening. Urinary tract obstruction due to cervical cancer mass accounts for about 11–44% of complications. Obstructive uropathy and hydronephrosis are common complications. Obstructive uropathy is usually a late manifestation of advanced disease, resulting from extrinsic compression of the ureter secondary to malignancy. The presence of ureteral obstruction and renal failure have a significant adverse effect on the survival of cervical cancer patients. In order to provide an alternative route due to ureteral obstruction, urinary diversion was performed.⁴

Urinary diversion is a surgical procedure to divert the normal flow of urine out of the body when the flow of urine is blocked. Percutaneous drainage of nephrostomy is associated with promising outcomes in terms of survival, improvement of renal function, pain, uremic symptoms and renal function status. Although urinary diversion procedures can certainly improve the outcomes of cervical cancer patients, current evidence suggests that urinary diversion does not significantly increase the survival rate of cervical cancer patients. This is related to previous studies, most of which were relatively long, involving relatively small cohort studies and many of them were retrospective.⁴

This study aims to determine the effectiveness of urinary diversion in the treatment of obstructive uropathy in cervical cancer patients.

METHODS

Study Design

This study is a cross sectional study. Data were obtained from medical records of cervical cancer patients undergoing urinary diversion for obstructive uropathy in Dr. Kariadi Central Hospital, Semarang. Data collection was limited to patients admitted from May, 2020 to May, 2021. This study has received ethical clearance from the local committee.

Study Populations

This study involved cervical cancer patients with symptoms of obstructive uropathy. Patients were stratified into two groups, those who required diversion

and those who did not. The inclusion criteria were aged ≥ 18 years old, diagnosed with cervical cancer stage IIIb–IVa, had symptoms of obstructive uropathy, and underwent urinary diversion using ureteral stent or percutaneous nephrostomy. Exclusion criteria were diagnosed with kidney failure before the diagnosis of cervical cancer and there were other causes of obstructive uropathy besides cervical cancer.

Outcomes

Primary outcome was urea level, creatinine level, stage of hydronephrosis and overall survival rate of patients. Stage of hydronephrosis, urea and creatinine level were assessed early and after 12 months. This assessment is done to measure obstructive uropathy and patients renal function. Survival rates were assessed at 3, 6, 9, and 12 months after urinary diversion. Survival rates are estimated for each group and considered separately.

Statistical Analysis

Data analysis was performed using SPSS 26.0 series. Univariate analysis was conducted to determine the mean, standard deviation, median value, smallest value, largest value and frequency of patient baseline characteristic. Mann-Whitney U analysis was performed to determine differences in serum urea and creatinine values. The data is significant if $p < 0.05$. Overall survival rate data analysis was conducted using the Kaplan Meier methods.

Ethical Clearance and Informed Consent

All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the Institutional Research Committee at which the studies were conducted (approval number of the Health Research Ethics Committee of Dr. Kariadi General Hospital: No.1280/EC/KEPK-RSDK/2022). Informed consent was obtained from all individual participants included in this study.

RESULTS

Baseline Characteristics of Study Subjects

This study involved 100 patients who were divided into 2 groups, non-urinary diversion ($n=50$) and urinary diversion ($n=50$). There was a significant difference in cervical Ca stage between two groups ($p=0.038$). There was no significant difference in the stage of hydronephrosis at pre and post in the two groups. Urinary diversion does not improve the stage of hydronephrosis.

Comparison of Urea and Creatinine Levels

Creatinine levels were higher in non-urinary diversion group. There was a significant difference in post creatinine levels between the non-urinary diversion and

TABLE 1
Baseline characteristics of study subjects

Variable	Non-Urinary Diversion			Urinary Diversion			p
	n (%)	Mean ± SD	Median (min-max)	n (%)	Mean ± SD	Median (min-max)	
Age (years)	–	53.22±8.53	53 (35–73)	–	53.22±8.53	53 (35–73)	0.530 [§]
Stage of Cervical Ca		–	–		–	–	0.038[#]
IIIB	48 (96)			39 (78)			
IVA	1 (2)			6 (12)			
IVB	1 (2)			5 (10)			
Systemic symptoms		–	–		–	–	–
Anemia	3 (6)			19 (38)			
Fatigue	11 (22)			24 (48)			
Nauseous	17 (34)			18 (36)			
Vomit	14 (28)			9 (18)			
Anorexia	15 (30)			12 (24)			
Comorbidity		–	–		–	–	–
Hypertension	8 (16)			15 (30)			
Diabetes mellitus	4 (8)			12 (24)			
Urological symptoms		–	–		–	–	–
Dysuria	18 (36)			14 (28)			
Low back pain	10 (20)			14 (28)			
Intermittent	14 (28)			24 (48)			
Gynecological symptoms		–	–		–	–	–
Flux	27 (54)			31 (62)			
Fluor	26 (52)			22 (44)			
Hypogastric pain	9 (18)			10 (20)			
Stage of Hydronephrosis							
Pre		–	–		–	–	0.356 [#]
No Hydronephrosis	29 (58)			21 (42)			
Mild	11 (22)			12 (24)			
Moderate	7 (14)			13 (26)			
Severe	3 (6)			4 (8)			
Post		–	–		–	–	0.989 [#]
No Hydronephrosis	19 (38)			21 (42)			
Mild	17 (34)			15 (30)			
Moderate	10 (20)			10 (20)			
Severe	4 (8)			4 (8)			

[§]Independent T test; [&]Mann Whitney U; [#]Fischer Exact; [¥]Chi Square

TABLE 2
Comparison of urea and creatinine levels

Variable		Non-Urinary Diversion		Urinary Diversion		p
		Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Urea	Pre	39.02±30.64	26.5 (11-155)	50.76±42.91	30 (9-156)	0.298 ^{&}
	Post	44.74±22.31	40.5 (18-135)	64.06±58.20	41 (11-240)	0.637 ^{&}
Creatinine	Pre	2.22±1.13	2 (0.8-5.8)	2.81±2.59	2.05 (0.1-12.7)	0.967 ^{&}
	Post	2.53±0.91	2.4 (0.9-5.2)	2.38±1.69	1.7 (0.7-7.6)	0.039^{&}

[&]Mann Whitney U

TABLE 3
The 12-month survival rate

Non-Urinary Diversion			Urinary Diversion		
Period	Status	Survival rate	Period	Status	Survival rate
3 month	Death	100%	3 month	Death	98%
6 month	Death	92%	6 month	Death	94%
9 month	Death	88%	9 month	Death	94%
12 month	Death	86%	12 month	Death	94%

urinary diversion group (p=0.039) (Table 2). The urinary diversion is effective in increasing renal function of cervical cancer patients with obstructive uropathy.

Survival Rate

Within 12 months, in non-urinary diversion group there were 7 subjects died, where 1 subject died at month 4, 2 subjects died at month 5, 1 subject died at month 6, 2 subjects died at month 9 and 1 subject died in month 11. In the urinary diversion group, there were 3 subjects died, where 1 subject died at month 3 and 2 subjects died at month 4.

The 12-month survival rate, in the non-urinary diversion group had a value of 86% while the urinary diversion group had a value of 94%. The urinary diversion is effective in increasing 12-month survival rate of cervical cancer patients with obstructive uropathy.

DISCUSSION

Baseline Characteristics of Study Subjects

In both groups, the mean age of study subjects was 52-53 years with stage IIIB being the most widely reported. Pratiwi SE, *et al.* in their study on the profile of cervical cancer patients at Soedarso Hospital obtained similar results that the highest incidence of cervical cancer occurred in the age range of 41-60 years, where

most of the patients came with stage IIIB (45.4%).⁵ In Indonesia, almost 1.8/1000 population (all ages) suffer from cancer with the peak prevalence at the age of 45-65 years. Meanwhile, in West Kalimantan, 1.5/1000 people suffer from cancer. In the European population, the incidence of cervical cancer begins to increase at the age of 20-29 years and progressively increases until around the age of 45-49 years. In the United States, the chances of developing invasive cervical cancer are also higher in women aged 40 to 59 years.⁶ In India, the peak age for cervical cancer is 40 to 49 years.⁷ In Indonesia, a study conducted in Surabaya from March to August 2016 stated that cancer patients were dominated by ages 41-60, mode was 51 years, and the average was 48 years.⁸

Histological characteristics are significant independent prognostic factors in cervical cancer. Squamous cell carcinoma (SCC) is the most common histologic feature of cervical cancer, accounting for three-quarters of all cases. Age at first sexual intercourse, smoking, suppression of the immune system, use of oral contraceptives, high parity (multiple pregnancies), and human papillomavirus (HPV) infection have all been associated with the development of cervical cancer.⁹

The most systemic symptoms in the non-urinary diversion group were nausea and anorexia, whereas in the urinary diversion group were weakness and anemia. The most frequently reported comorbid by both groups

was hypertension.

Nausea, and vomiting are frequently reported side effects in patients receiving chemotherapy. This side effect has the potential to lead to a patient's refusal to continue the chemotherapy. The incidence and severity of nausea, vomiting and vomiting in patients receiving chemotherapy varies, depending on the type and dose of chemotherapy, drug combination, and individual characteristics. These unpleasant sensations can appear, either as a result of treatment or the disease itself and significantly affect the patient's quality of life and adherence to therapy.¹⁰

Nausea and vomiting are usually more severe in the next cycle, especially in the fourth cycle and a significant predictor in the fifth cycle.¹¹ One study found that in combination therapy (radiation and chemotherapy), patients reported more symptoms of distress than chemotherapy alone.¹² Patients receiving combination therapy with radiation and chemotherapy experienced a significantly higher rate of symptom occurrence than those receiving chemotherapy alone. This suggests that combination therapy is an important factor contributing to the experience of nausea-vomiting symptoms. The stage of the cancer may also be another factor that contributes to the symptoms of nausea and vomiting. The potential causes of nausea and vomiting in cancer patients are numerous, especially in those with advanced or metastatic disease.¹⁰ When cervical cancer progresses to a more advanced stage, symptoms begin to appear. The advanced stage of the disease is a predictor of acute nausea and vomiting. One study found that symptom experience was significantly higher in patients with advanced stages (Stage III and IV) than patients in the early stage group. Previous study involved stage II and III cervical cancer patients without comorbidities. Therefore, the stage of the disease is thought to contribute to the rate of nausea and vomiting.¹²

Anemia is common in cervical cancer patients. Iron deficiency and tumor bleeding are common causes of anemia in cervical cancer. Anemia has a negative prognostic effect, and correction is thought to improve the prognosis. Therefore, most patients will receive transfusion and/or erythropoietin treatment.¹³ Obstructive uropathy increases intrarenal pressure which causes suppression of kidney function. The closer intrapelvic pressure approaches the glomerular filtration pressure (6–12 mmHG), the less urine can be secreted. Glomerular filtration rate and renal plasma flow are reduced, concentrating power is gradually lost, and the urea creatinine concentration ratio of urine is lower than normal kidney. This condition will lead to stages of uremia. Anemia may be found secondary to advanced bilateral hydronephrosis (stage of uremia).¹⁴

Cancer patients usually have several comorbidities.¹⁵ There is evidence that a higher burden of comorbidities is associated with poorer survival for cancer

patients.¹⁶ The prevalence of comorbidities varies between population groups and may contribute to the distribution of cancer survival. These findings are consistent with previous study from New Zealand.¹⁷ Hypertension is very common among adults and is associated with significant morbidity and mortality, including heart attack, stroke, chronic kidney disease and death. Therefore, hypertension remains the most important risk factor for many cardiovascular disorders. Vascular resistance increases with age because vascular walls become less elastic. These changes combined with common age-related conditions such as heart failure that reduce cardiac output result in an increased incidence of hypertension in the elderly.¹⁸

The most frequently reported urological symptom in the non-urinary diversion group was dysuria, whereas in the urinary diversion group it was intermittent. The most frequently reported gynecological symptoms in both groups were flux and fluor.

The clinical presentation of obstructive uropathy is highly variable and often depends on the site of the obstruction.¹⁹ In pelvic malignancies, both acute and chronic presentations of obstructive uropathy may occur, with etiologies ranging from stricture due to pelvic surgery,²⁰ radiation-induced scar tissue formation within the ureter or extrinsically in the retroperitoneum, external ureteral compression from either the primary tumor, recurrent masses, or metastases.¹⁹

Obstruction at the level of the bladder neck, also known as bladder outlet obstruction (BOO), can be caused by a benign process or a malignant process such as invasion of the bladder in or distal to the triangle. Patients often complain of obstructive and irritating voiding symptoms, such as urgency, frequency, decreased power of the stream, and incomplete emptying of the bladder.²¹

Pre-cancerous changes to the cervix usually do not cause pain or other symptoms and are not detected unless a woman undergoes an examination. Symptoms generally do not appear until abnormal cervical cells become cancerous and invade nearby tissues. The most common symptoms are foul-smelling vaginal discharge, abnormal bleeding or inter-menstrual bleeding, postcoital bleeding, postmenopausal bleeding or back pain.²²

The most frequently reported stage of pre-hydronephrosis in the non-urinary diversion group was mild, whereas in the urinary diversion group it was moderate. Urea and creatinine pre-levels were higher in the urinary diversion group, with a mean of 50.76 mg/dL and 2.81 mg/dL, respectively. The most frequently reported stage of post hydronephrosis in the two groups was mild. Post-ureum levels were higher in the urinary diversion group (64.06 mg/dL) while higher post-creatinine levels were found in the non-urinary diversion group (2.53 mg/dL).

Hydronephrosis occurs when an obstruction in the

collecting system of the kidney causes distention of the renal calyces. Women with cervical cancer often develop this complication as a result of a tumor or lymph node disorder, inflammation, or scarring of the pelvic rim. In addition, cervical cancer is often treated with nephrotoxic drugs, which are sometimes dosed or omitted when hydronephrosis occurs in association with renal insufficiency. Such dose changes can compromise cancer treatment and potentially lead to decreased clinical outcomes. Patel K, *et al.* in their study of hydronephrosis in cervical cancer patients stated that the development of hydronephrosis was directly related to advanced cancer stage ($p < 0.0001$), squamous histology ($p = 0.0079$), and non-surgical treatment modality ($p = 0.0039$). Of the 278 patients based on survival data, 221 lived with a median follow-up of 1.5 years (range 0.025-4 years).²³

The presence of ureteral obstruction and hydronephrosis is a sign of advanced disease because it indicates parametrial involvement. This condition may be accompanied by electrolyte and blood urea nitrogen (BUN) disturbances and high serum creatinine levels. Uremia often complicates the case and can lead to a decrease a level of consciousness and even death if left untreated. Previous studies have shown that as the malignancy progresses, patients may develop stage 4 chronic kidney disease and require further treatment. A study investigating the survival of patients treated with radiotherapy found that women with stage T3b cervical cancer (17 patients) and hydronephrosis had a lower 5-year survival rate compared to those without hydronephrosis (26% vs. 41%).²⁴ Goklu *et al.* found that the median survival of patients with unilateral hydronephrosis was significantly greater than that of patients with bilateral hydronephrosis (42.2 vs 29.9 months).²⁵ Patel *et al.* reported that the most prominent symptom of hydronephrosis was urinary tract infection (9 of 17 patients), accompanied by pain (8 of 17 patients). In their series of studies, they observed that 7 patients had renal failure with creatinine levels ranging between 1.7 and 5.6 mg/dL.²⁶

Dienstmann *et al.* investigated the impact of the procedure on 50 patients with recurrent cervical cancer and observed that 60% experienced improvement in renal function and a decrease in mean of creatinine level of 2.7 mg/dL (from 6.4 pre-procedure to 3.7 mg/dL post-procedure). Twenty-nine patients (58%) died of renal failure and median survival was 8.9 weeks.²⁷

Patients presenting with hydronephrosis due to pelvic sidewall disease have previously been shown to have a poor clinical outcome. Urinary diversion procedures can be used to avoid blockages and improve kidney function. Successful use of urinary diversion improves quality of life and survival.²⁸

Survival Rate

At 12 months, more subjects died in the non-urinary

diversion group than in the urinary diversion group. The results of this study are similar to those of Beckta JM *et al.* who assessed urinary diversion as a local management of advanced cervical cancer and found that 79% of non-diverted patients were alive while 60% of patients were alive at the end of 22 months of follow-up. As a result of tumor size Primary or large pelvic lymphadenopathy, 14% to 34.5% of women present with ureteral obstruction at the time of initial diagnosis. This obstruction can lead to hydronephrosis and impaired renal function, which may preclude aggressive treatment with Cisplatin-based chemotherapy. However, renal function may be improved if the ureteral obstruction is removed by insertion of a ureteral stent or percutaneous nephrostomy. Ureteral stent placement is considered first-line therapy for obstructive uropathy, although it is technically difficult to measure the size of a malignant mass. In contrast, in the context of external ureteral compression, percutaneous nephrostomy is a simpler procedure but carries an increased risk of infection and decreased quality of life.²⁹

This study result that the 12-month survival rate, in the non-urinary diversion group had a value of 86% while the urinary diversion group had a value of 94%. Choudhury S, *et al.*³⁰ who assessed the role of urinary diversion in patients with advanced cervical cancer with obstructive uropathy stated that the improvement in kidney function was evidenced by a decrease in serum creatinine levels from an average of 4.98 mg/dl to 2.33 mg/dl. Improved quality of life was seen in 68% of cases. Thus, palliative urinary diversion is effective in patients with obstructive uropathy with complications of advanced cervical malignancy because it results in a significant improvement of renal function as well as quality of life.

CONCLUSION

This study shows that urinary diversion procedure is effective in increasing renal function and 12-month survival of cervical cancer patients with obstructive uropathy.

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