Predictive factor for successful retrograde ureteral stent insertion in obstructive uropathy due to advanced cervical cancer

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Abstract

Cervical cancer is the 3rd most common cancer in women. Some of the patients came with kidney failure due to malignant ureteral obstruction. Retrograde ureteral stent insertion as palliative urinary diversion often performed on these patients, but it has high failure rate and often has to be converted to nephrostomy, giving the patient unnecessary burden due to failed procedure. In this study, we evaluate factors that may predict successful ureteral stenting in cervical cancer patients to avoid unnecessary burden to the patient. Data were collected from 2014-2017. We evaluate the clinical, ultrasound and laboratory findings before stent insertion of the patient with successful compared to failed insertion. Comparative study was done using independent T-test and Mann-Whitney U test for nonparametric data. Odds ratio (OR) were calculated using contingency table and P value calculated using Fisher exact test. There were 41 patients diagnosed with cervical cancer performed retrograde ureteral stenting. From 41 patients, 20 (48.7%) were successful and 21 (51.3%) failed. Low hydronephrosis grade (OR=85.8; P<0.0001), low stage (OR=6.0; P=0.0098), radiotherapy (OR=3.7; P=0.04) were strong predictor for successful stent insertion. In bilateral hydronephrosis, more daily urine output (OR=29.2; P=0.002) and normal creatinine level (OR=6.3; P=0.03) were strong predictors for successful retrograde stenting, while bladder infiltration was strong predictor for stent failure (OR=0.0684; P=0.0021). Low hydronephrosis grade, no bladder infiltration, normal creatinine level, more daily urine output, low clinical staging and radiotherapy are predictive factors to predict a successful ureteral stenting in cervical cancer patients.

Introduction

Cancer of the uterine cervix is the 3rd most common gynecologic cancer diagnosis and cause of death among gynecologic cancers worldwide. In the world, there were approximately 500.000 new cases of cervical cancer diagnosed and approximately 250.000 cases of death found for each year.[1] In developing countries including in Indonesia, cervical cancer has higher incidence than developed countries.[2] In Indonesia, about 20,928 new cervical cancer cases are diagnosed annually (estimations for 2012).[3] Cervical cancer ranks as the 2nd leading cause of female cancer and the 2nd most common female cancer in women aged 15 to 44 years.[3] Most patients (66.4%) came in advanced disease (stage 2b-4b) according to the International Federation of Gynecology and Obstetrics (FIGO) and 37.3% in stage 3b (with obstructive uropathy).[4] The cases present in advanced stages of the disease with associated poor prognosis and high mortality rates.[4] In many of them, it is difficult to offer definitive treatment as they present in uremia due to associated obstructive uropathy. This is due to either external compression or malignant involvement of lower ureters. These patients may have large primary advanced/recurrent/post treatment progressive residual disease.

Ureteral obstruction due to malignancy carries a poor prognosis with a resulting median survival of 3-7 months and hence most patients are treated with best supportive care or some palliative diversion procedure.[5] A study by Rasjidi showed a significant longer survival in patients with advanced cervical cancer who underwent percutaneous nephrostomy, even though the median survival was only 203 days.[6] Another study by Lapitan *et al*. showed there was no evidence of an impact on quality of life and the decision to offer diversion surgery might be based solely on a survival benefit,[7] which is modest but potentially important to patients to able them continue their treatment and spent their time with their family. Various method of urinary diversion could be used for palliative urinary diversion. The most common and simple method is percutaneous nephrostomy (PCN).[8] Other methods including the use of various material of ureteral stents.[9] Both procedures has its own advantages and disadvantages. Sometimes ureteral stent insertion failed due to unidentified ureteral opening on cystoscopy and has to be converted to PCN. Even though, endoscopic ureteral stent placement is a simple and safe procedure that can be done under local anesthesia, it may give some burden to the patients including painful procedure and hematuria.[10] Moreover, in some hospital retrograde ureteral stent insertion was done under regional or even general anesthesia, it burdens the patients with impaired renal function and could be avoided if we carefully selected the patients. In this study, we attempt to evaluate factors that may predict successful retrograde ureteral stenting in advanced cervical cancer patients in order to reduce unnecessary PCN conversion in retrograde ureteral stenting.

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Materials and Methods

The design of this study is observational analytics with cross sectional study. This study was approved by Hasan Sadikin Hospital Institutional Review Board for ethical clearance. All patients with attempted retrograde ureteral stenting, either successful or failed, with bilateral or unilateral hydronephrosis were included as subjects. Ureteral stent insertion was done under regional anesthesia. Cystoscopy was done using 20 Fr rigid cystoscope and 30^0 optic lens to identify the ureteral opening. When the ureteral opening identified but stenosis present, ureterorenoscopy then performed to assist guidewire and Double J (DJ) stent insertion. Hydrophilic guidewire then inserted and DJ stent inserted using sliding technique. The procedure was failed if the ureteral opening cannot be identified or either the guidewire or the stent cannot be inserted.

Data included were based on ultrasound findings before stent insertion: Degree of

hydronephrosis, diameter of retrovesical mass and presence of bladder infiltration on ultrasound. Laboratory findings including pre-diversion blood urea nitrogen (BUN) and creatinine level. Clinical findings including clinical stage according to FIGO criteria, daily urine production and previous history of chemoradiation or surgery.

Grade of hydronephrosis was classified according to the Society of Fetal Ultrasound (SFU).[11] We compared the daily urine production, BUN and creatinine level only in patients with bilateral obstruction, with assumption for patients with unilateral obstruction, the unobstructed kidney will biased the urine production, BUN and creatinine level to normal.

We separated the subjects as 2 groups: Those with successful retrograde ureteral stent insertion (group I) and those with failed retrograde ureteral stent insertion attempt (group II). Comparative study was performed using independent T-test for normally distributed parametric data. Alternatively, we used Mann-Withney U test for non-parametric data or parametric data that not normally distributed. We calculated the odd ratios (ORs) of every significantly different characteristic between the two groups using Fisher exact test with 95% confidence intervals (CIs). With calculated OR we hope to find the most reliable predictive factor to predict the successful or failure in DJ stent insertion. The data were analyzed using SPSS version 21.0 for Windows.

Results

We performed retrograde ureteral stenting attempt in 41 patients, either bilateral or unilateral hydronephrosis. Retrograde ureteral stenting was successful in 20 patients (48.7%), and failed in 21 patients (51.3%) and converted to PCN. The mean age of group I was 49.9±8.34 years, and Group II was 47.7±8.33 years. There was no significant difference between mean age of both groups (P=0.427). The reason of failure retrograde stenting was unidentified ureteral opening in 18 cases (85.7%) and unable to slide the guide wire due to severe stenosis in 3 patients (14.3%) (Table 1).

Ultrasound findings

We evaluate the severity of hydronephrosis from ultrasonographic finding of both groups. Hydronephrosis grading was classified according to SFU. In group I, we found the majority of hydronephrosis grade were grade 1 and grade 2, compared to failed stenting group that had a majority of grade 3 and grade 4 hydronephrosis. Using Mann-whitney U test, we found that the hydronephrosis grade was significantly higher in group II than in group I (P<0.0001) (Table 1, Figure 1).

We also identify the retrovesical mass diameter and presence of suspicious bladder infiltration. In group I, the mean mass diameter were 2.38±1.75 cm, with 6 subjects (30%) has no mass infiltration detected. In group II the mean mass diameter were 5.28±1.70 cm. Using independent T-test, we found a significant higher retrovesical mass diameter in group II than in group I (P<0.0001). We found only 2 patients with suspicious bladder infiltration on ultrasound also found significant difference in incidence of suspected bladder infiltration between successful stenting group compared to failed stenting group (2(10%) *vs* 13(61.9%); P=0.001) (Table 1).

Laboratory findings

We compared the BUN and creatinine level between group I and group II with bilateral hydronephrosis, with assumption in subjects with unilateral hydronephrosis, the contralateral unobstructed kidney will

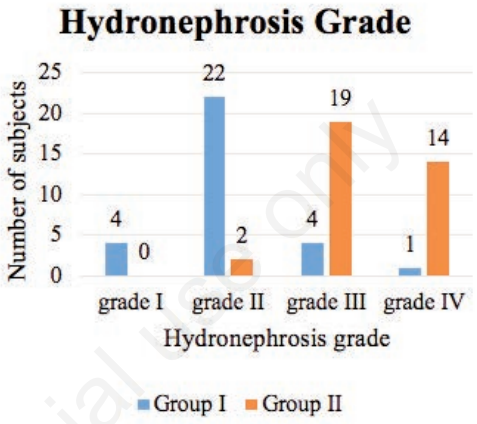

Figure 1. Comparison of hydronephrosis grade.

Table 1. Patient characteristics.

	Success (group I) n=20	Failed (group II) n=21	P value
Age	49.9±8.34	47.7±8.33	0.427[a]
Stenting attempt			
Unilateral	10 (50%)	7 (33.3%)	
Bilateral	10 (50%)	14 (66.7%)	
Ultrasound findings			
Hydronephrosis			<0.0001[b]
Grade I	4 (12.9%)	0 (0%)	
Grade II	22 (70.9%)	2 (5.7%)	
Grade III	4 (12.9%)	19 (54.2%)	
Grade IV	1 (3.2%)	14 (40%)	
Mass diameter	2.38±1.75	5.28±1.70	<0.0001[b]
Presence of bladder infiltration	n=20	n=21	
Yes	2 (10%)	13 (61.9%)	0.001[b]
No	18 (90%)	8 (38.1%)	
Laboratory findings			
Blood urea nitrogen level (bilateral)	41.3±24.68	143.9±72.1	0.004[a]
Creatinine (bilateral)	2.5±1.98	9.4±4.53	0.001[a]
Staging (FIGO)	n=20	n=21	
Stage 3[b]	15 (75%)	7 (33.3%)	0.016[b]
Stage 4	5 (25%)	14 (66.7%)	
Previous therapy			
Previous surgery	2 (10%)	1 (4.76%)	0.76[9b]
Previous chemotherapy	2 (10%)	2 (9.5%)	
Previous radiotherapy	13 (65%)	7 (33.3%)	
Clinical findings	n=10	n=14	
Urine production (bilateral)	1470±494.2	673±343.3	<0.0001[a]

[a]Independent T-test; [b]Mann-Withney U test. FIGO, International Federation of Gynecology and Obstetrics.

compensate the BUN and creatinine level to normal or near normal value. There were 10 subjects in group I with bilateral hydronephrosis with mean BUN level of 41.3±24.68 mg/dl and 14 subjects in group II with mean BUN level of 143.9±72.1 mg/dl. The mean creatinine level in group I was 2.5±1.98 mg/dl, while in group II was 9.4±4.53 mg/dl. Using independent T-test, we found a significant difference between BUN level and creatinine level of the two groups (P=0.004; P=0.001) (Table 1).

Clinical findings

We evaluate urine production of the subjects with bilateral hydronephrosis, with assumption, in unilateral hydronephrosis patients, the contralateral kidney will compensate the function of obstructed kidney. In group I (n=10) the mean daily urine production was 1470±494.2 ml/24 hours, while in group II the mean urine production was 673±343.3 ml/24 hours. Using independent T-test, we found a significantly higher daily urine production in group I compared to group II (P<0.0001) (Table 1).

We compared the clinical staging of the subjects using FIGO classification. The staging was made primarily based on physical examination and ultrasound findings by our colleagues from Gynaecology Department. We found in group I the predominant clinical staging was stage 3b (75%) followed by stage 4 (25%) while in group II, the predominant clinical stage was stage 4 (66.7%) followed by stage 3b (33.3%). Using Mann-Whitney U test, we found a significant difference between the two groups (P=0.016) (Table 1, Figure 2).

We also compared the history of previous therapy of the subjects and divide as previous mass excision surgery (bilateral hystero-salphingo-ovarectomy), radiotherapy and chemotherapy. In group I we found 14 subjects (70%) with previous therapy consists of surgery in 2 (10%), chemotherapy in 2 (10%) and radiotherapy in 13 (65%). In group II, we found 7 subjects (33.3%) with previous therapy, consists of surgery in 1(4.76%) subject, chemotherapy in 2 (9.5%), and radiotherapy in 7 (33.3%) patients. Using Mann-Whitney U test, we found no significant difference between the 2 groups (P=0.769) (Table 1, Figure 3).

Risk analysis for successful stent insertion

Using Fisher Exact test, we analyzed the odd ratio of each variable. In ultrasound findings, we found lower hydronephrosis grade as a strong predictor for successful retrograde ureteral stent insertion (OR=85,8; P<0.0001; CI=15.39-478.45) and presence of bladder infiltration as a strong predictor for failed ureteral stent insertion (OR=0.0684; P=0.0021; CI=0.012-0.378). From laboratory findings, we found normal BUN level (women <20 mg/dl) was not significant as a predictor for successful stent insertion (OR=4.0; P=0.073; CI=0.88-18.2), while normal creatinine level (0.6-1.1 mg/dl) was a strong predictor for successful stent insertion (OR=6.3; P=0.03; CI=1.146-35.0). From clinical findings, we found daily urine production of more than 1000 ml in bilateral hydronephrosis patients (OR=29.2; P=0.002; CI=3.45-247.7), lower clinical staging (stage 3b according to FIGO) (OR=6.0; P=0.0098; CI=1.54-23.3) and history of complete radiotherapy (OR=3.7; P=0.04; CI=1.021-13.51) as a strong predictor for successful stent insertion (Table 2).

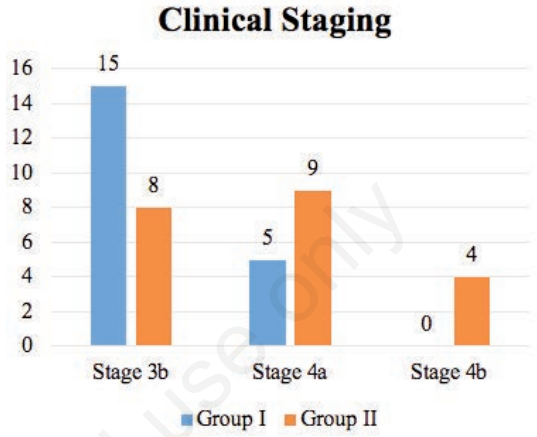

Figure 2. Cervical cancer clinical staging.

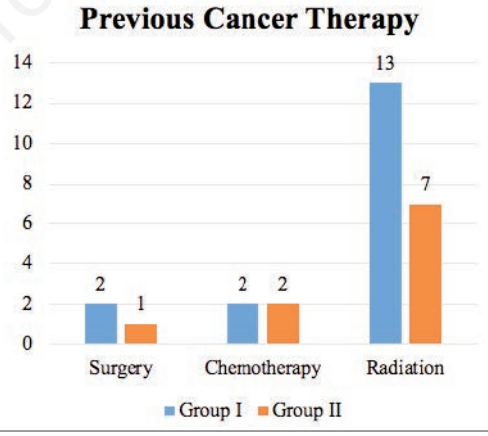

Figure 3. Previous cancer therapy.

Table 2. Risk analysis of successful retrograde stent insertion.

	P-value	OR	95% CI
Ultrasound findings			
Lower hydronephrosis grade	<0.0001	85.8	15.39-478.45
Presence of bladder infiltration	0.0021	0.0684	0.012-0.378
Mass diameter	<0.0001	-	-
Laboratory findings			
Blood urea nitrogen	0.073	4.0	0.88-18.2
Creatinine	0.03	6.3	1.146-35.0
Clinical findings			
Daily urine production	0.002	29.2	3.45-247.7
Lower clinical staging	0.0098	6.0	1.54-23.3
Previous radiotherapy	0.04	3.7	1.021-13.51

OR, odd ratio; CI, confidence interval.

Discussion

Retrograde ureteral stenting use for palliative urinary diversion in malignancy has a high failure rate compared to PCN. In our study, the failure rate was 51.2%. This results similar to a study by Shekarriz *et al*., that found that failure rate of endoscopic stent placement was 51%.[12] In other study, the failure rate of ureteral stent due to malignant compression was 35.7%.[13] Similar to the previous study, the most common reason of this failure was unidentified ureteral opening due to mass compression or infiltration and unable to further slide the guidewire due to mass infiltration to the ureter.[12,13] Due to this high failure rate, preoperative predictive factors that could predict successful stent insertion is an important issue to decrease the failure rate.

We evaluate ultrasonographic characteristics of the patient before diversion. In this study, we found higher hydronephrosis grade in failed retrograde stenting attempt and low grade hydronephrosis as strong predictor for successful stent insertion. This result similar to previous study that found that higher hydronephrosis grade associates with failure rate in retrograde ureteral stent insertion.[14] Higher incidence of suggestive bladder infiltration and larger retrovesical mass diameter on ultrasound also found in failed ureteral stent group. Yossepowitch *et al.* suggested that in patients with extrinsic ureteral obstruction, a higher degree of hydronephrosis was associated with a greater likelihood of stent failure.[15] Another study by Wang *et al*. in 2015 found that degree of hydronephrosis as independent predictors for stent insertion failure in malignant obstruction patients.[16] These findings may related to the pathophysiologic process of advanced cervical cancer, where the spread of cellular infiltration of the parametrial connective tissues over the connective tissues surrounding the ureter resulting stenosis and functional impairment.[17] Pelvic lymphadenopaty also could give a mechanical pressure upon bilateral ureters giving rise to a considerable constriction of their lumina and resulting in various degree of hydronephrosis.[17]

For laboratory evaluation, we compared BUN and creatinine level of the patient with bilateral hydronephrosis, and exclude patients with unilateral obstruction due to compensatory mechanism of unobstructed contralateral kidney may biased the BUN and creatinine level.[18] We found significantly lower level of BUN and creatinine level in patients with successful ureteral stent insertion. This findings may related to degree of ureteral obstruction due to tumor infiltration, as bilateral ureteral obstruction will result in decrease of bilateral renal blood flow and glomerular filtration rate.[19,20] This mechanism will cause elevation of BUN and creatinine level and also reduce the daily urine production, as seen in patient with bilateral hydronephrosis in this study. Unfortunately, various factors influence the BUN and creatinine level other than the obstruction such as dehydration, presence of sepsis condition, history of diabetic and hypertensive renal disease and intrinsic renal disease.[21,22]

There are two criterion for the diagnosis of Stage 3b carcinoma of the uterine cervix in the current FIGO staging system: the tumor fixed to the pelvic side wall or the presence of hydronephrosis not explainable by other factors.[23] Stage 4 of cervical cancer defined as the tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis.[21] In this study, clinical staging according to FIGO criteria in successful stent insertion was significantly lower than in failed group. Bladder infiltration in stage 4 cervical cancer found in 13 patients in this study, while the other 1 included in stage 4 due to distant metastasis. In a study by Wang *et al*., bladder wall invasion was a significant predictive factor for stent failure.[16] Jeong *et al*. reviewed the use of ureteric stents placed for 86 patients with a malignant ureteral obstruction and found that 13 (15%) experienced failure of retrograde stent insertion, and that the risk of failure for stent insertion significantly increased with the presence of bladder invasion.[24] Ganatra and Loughlin analyzed 157 patients with malignant ureteral obstruction who underwent retrograde ureteral stent placement, and found that when invasion into the bladder was noted on cystoscopy, 55.9% developed stent failure.[25]

In previous study by Wang *et al*., prior radiotherapy was shown to be associated with insertion failure on univariate analysis. However, multivariate analysis failed to confirm prior radiotherapy as an independent risk factor for stent insertion failure.[16] On the contrary with study by Wang *et al*., in our study prior radiotherapy present as predictive factor for successful stent insertion in cervical cancer patients. This may related to effect of radiotherapy to shrink the tumor mass that compress the ureter.[26]

Our study did have certain limitations. The study population was retrospectively enrolled from a single center in Indonesia. The sample number was too small to represent the general population in Indonesia and too small for multivariate analysis to be done. Our Hospital was teaching hospital so the stent insertion procedure was done by different surgeon with different experience that can interfere with the success rate of the procedure. In the future, a prospective study should enroll a larger number of patients to determine more precise predictive factors and a scoring should be made to ensure no unnecessary cystoscopy and stent attempt in cervical cancer patients.

Conclusions

From this study, we could conclude that patient with lower hydronephrosis grade, normal creatinine level, lower clinical stage, history of complete radiation and daily urine production more than 1000 cc in 24 hours most likely to be successful in DJ stent placement while patient with bladder infiltration from ultrasound will be not suitable for DJ stent placement candidate. With the use of predictive factor that could predict retrograde stenting successfulness, we could carefully select the patient to reduce the failure rate and avoid unnecessary burden of cystoscopy, failed stenting attempt and anesthesia.

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