Endourology/Urolithiasis

Predicting Factors for Stent Failure-Free Survival in Patients With a Malignant Ureteral Obstruction Managed With Ureteral Stents

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Purpose: To determine predictive factors for stent failure-free survival in patients treated with a retrograde ureteral stent for a malignant ureteral obstruction.

Materials and Methods: We retrospectively reviewed 71 patients who underwent insertion of a cystoscopic ureteral stent due to a malignant ureteral obstruction between May 2004 and June 2011. Performance status, type of cancer, hydronephrosis grade, location of the obstruction, presence of bladder invasion, C-reactive protein (CRP), serum albumin, and inflammation-based prognostic score (Glasgow prognostic score, GPS) were assessed using a Cox proportional regression hazard model as predicting factors for stent failure.

Results: A univariate analysis indicated that hypoalbuminemia (< 3.5 g/dL; hazard ratio [HR], 2.43; 95% confidence interval [CI], 1.21 to 4.86; p=0.012), elevated CRP (≥ 1 mg/dL; HR, 4.79; 95% CI, 2.0 to 11.1; p=0.001), and presence of a distal ureter obstruction (HR, 3.27; 95% CI, 1.19 to 8.95; p=0.021) were associated with stent failure-free survival. A multivariate analysis revealed that the presence of a mid and lower ureteral obstruction (HR, 3.27; 95% CI, 1.19 to 8.95; p=0.007), GPS ≥ 1 (HR, 7.22; 95% CI, 2.89 to 18.0; p=0.001), and elevated serum creatinine before ureteral stent placement (> 1.2 mg/dL; HR, 2.16; 95% CI, 1.02 to 4.57; p=0.044) were associated with stent failure-free survival.

Conclusions: A mid or lower ureteral obstruction, GPS ≥ 1, and serum creatinine before ureteral stent insertion > 1.2 mg/dL were unfavorable predictors of stent failure-free survival. These factors may help urologists predict survival time.

Keywords: Neoplasm metastasis; Stents; Ureteral obstruction

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INTRODUCTION

Ureteral obstruction caused by metastasis or invasion of malignancy is generally regarded as a sign of poor prognosis and may be due to compression by the primary or metastatic tumor, retroperitoneal lymphadenopathy, or direct tumor invasion. Median survival of patients with a malignant ureteral obstruction is 3.7 to 15.3 months [1-3]. Acute ureteral obstruction associated with renal failure is a urological emergency requiring prompt evaluation and treatment, because renal failure due to a malignant ureteral obstruction is a significant cause of death [4].

Current management options include decompression using retrograde ureteral stent (RUS) placement or percutaneous nephrostomy (PCN). RUS does not usually lead to major complications, is less invasive, better tolerated than PCN, and is considered optimal management for malignant ureteral obstructions [1,2,5]. However, a high stent failure rate is a problem encountered by urologists; there-
fore, PCN has been commonly used as either a primary or secondary procedure in cases of stent failure [6]. Additionally, only a few reports are available that has predicted factors for stent failure-free survival with a malignant ureteral obstruction. Therefore, we reviewed our institution’s contemporary experience with treating malignant ureteral obstruction using RUS and analyzed the predicting factors for stent failure-free survival.

MATERIALS AND METHODS

1. Study population
We retrospectively reviewed patients who underwent insertion of a cystoscopic ureteral stent (Endo-sof, Cook Urological, Spencer, IN, USA) due to a malignant ureteral obstruction between May 2004 and June 2011. Direct ureteral obstruction by urolithiasis, bladder cancer, or prostate cancer and extrinsic ureteral compression from lymphadenopathy caused by urological cancer metastasis were excluded. Patients who had undergone insertion of a cystoscopic ureteral stent due to a ureteral obstruction from nonurological cancer were included. Among 115 patients who underwent insertion of a cystoscopic ureteral stent due to a malignant ureteral obstruction, 71 patients with ureteral obstruction due to nonurological cancer were extracted. This did not include 44 patients who had urological cancer. Stent failure was defined as an increase in serum creatinine of more than twice from naïve and worsening hydronephrosis on an imaging study and an inability to replace the ureteral stent during the replacement procedure. Performance status (Eastern Cooperative Oncology Group criteria), type of cancer, hydronephrosis grade, location of the obstruction, presence of bladder invasion, C-reactive protein (CRP), serum albumin, and inflammation-based prognostic score (Glasgow prognostic score, GPS) were assessed as predictive factors for stent failure. The obstruction level was documented using computed tomography and defined as the upper, middle, or lower ureter as determined by the location above, over, or below the sacroiliac joint. The interval between stent changes was initially planned to be 3 months. In lieu of a formal ethics committee, this study, the principles of the Helsinki Declaration were followed.

2. Measurement of serum CRP
Routine laboratory testing of serum CRP and albumin was performed just before insertion of ureteral stents. Serum CRP was measured by latex turbidimetric immunoassay using a HITACHI 7600 analyzer (Hitachi, Tokyo, Japan). The CRP limit of detection was 0.03 mg/dL, and 1.0 mg/dL was the upper limit of the normal range. Coefficients of variation over the range of measurements were <5%.

Each GPS was assigned as described previously. Patients with both elevated CRP (>1.0 mg/dL) and low albumin (<3.5 mg/dL) received a score of 2, whereas those with only one or none of these biochemical abnormalities earned scores of 1 and 0, respectively [7].

3. Classification of hydronephrosis
The hydronephrosis grade was assessed by preoperative imaging, computed tomography, excretory urography and renal ultrasonography. The cases without caliceal or pelvic dilation were classified as grade 0 hydronephrosis, pelvic dilation only were classified as grade 1, and the cases accompanying mild calix dilation were classified as grade 2. The severe calix dilation was grade 3, and the calix dilation accompanied by renal parenchyma atrophy was classified as grade 4. Mild, moderate and severe hydronephrosis were classified as grade 1, grade 2 and grade 3–4, respectively.

4. Statistics
Statistical analyses were performed with SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA). Parameters subjected to analysis were age, gender, hydronephrosis, serum creatinine, albumin level, CRP, GPS, Eastern Cooperative Oncology Group performance status, bladder invasion, type of cancer, initial symptoms, carcinoma metastasis peritoni, and obstruction level. The time to stent failure and death were counted from the time of the initial stent insertion. The chi-square test was used for categorical variables. Univariate and multivariate analyses using a Cox proportional regression hazard model (stepwise forward procedure) generated an adjusted hazard ratio (HR), representing the effect on stent failure-free survival. Statistical significance was set at p < 0.05 for all analyses.

RESULTS

1. Baseline characteristics
The patient characteristics are shown in Table 1. The median age of the 71 patients was 55 years (range, 19 to 85 years). Forty-six patients (64.8%) were female, and 25 patients (35.2%) were male. Twenty-six patients (36.6%) had a bilateral ureteral obstruction, 29 (40.8%) had a left-sided unilateral ureteral obstruction, and 16 (22.5%) were right sided. Gastric cancer (30, 42.3%) was the most common cause of malignant ureteral obstruction. Other types of cancer that caused ureteral obstruction were colon cancer (13, 18.3%), rectal cancer (10, 14.1%), and cervical cancer (11, 15.5%). Seventeen patients (23.9%) had an upper level ureteral obstruction, 22 (31.0%) had a mid ureteral obstruction, and 32 (45.1%) had a lower ureteral obstruction. Serum creatinine (>1.2 mg/dL) just before insertion of the ureteral stent was elevated in 33 patients (46.5%) and most cases were associated with bilateral obstruction (17, 65.44%, p=0.015, data not shown). Thirty six patients (50.7%) had GPS ≥1. Sixteen (22.5%) and 11 patients (15.5%) had gross hematuria and flank pain, respectively.

In the 71 patients who underwent RUS, the stent failed to indwell in 15 patients (21.1%) at the first visit, and stent failure occurred in 15 patients (21.1%) later. The median periods for stent failure-free survival and overall survival were 5 and 7.7 months, respectively.
TABLE 1. Baseline characteristics

| Characteristic                  | Value          |
|--------------------------------|----------------|
| Age (y)                        | 55 (19–85)     |
| Gender                         |                |
| Male                           | 25 (35.2)      |
| Female                         | 46 (64.8)      |
| Type of cancer                 |                |
| Gastric                        | 30 (42.3)      |
| Colon                          | 13 (18.3)      |
| Rectal                         | 10 (14.1)      |
| Cervical                       | 11 (15.5)      |
| Ovarian                        | 4 (5.6)        |
| Endometrial                    | 1 (1.4)        |
| Pancreas                       | 1 (1.4)        |
| Lymphoma                       | 1 (1.4)        |
| Initial symptom                |                |
| F/U CT                         | 60 (84.5)      |
| Flank pain                     | 9 (12.7)       |
| Hematuria                      | 1 (1.4)        |
| Anuria                         | 1 (1.4)        |
| Carcinomatosis peritoni        |                |
| Yes                            | 25 (35.2)      |
| No                             | 46 (64.8)      |
| Hydronephrosis                 |                |
| Mild                           | 29 (40.8)      |
| Moderate                       | 25 (35.2)      |
| Severe                         | 17 (23.9)      |
| Obstruction level              |                |
| Upper                          | 17 (23.9)      |
| Mid                            | 22 (31.0)      |
| Lower                          | 32 (45.1)      |
| Laterality                     |                |
| Right                          | 16 (22.5)      |
| Left                           | 29 (40.8)      |
| Both                           | 26 (36.6)      |
| Complication                   |                |
| None                           | 44 (62.0)      |
| Hematuria                      | 16 (22.5)      |
| Pain                           | 11 (15.5)      |
| Bladder invasion               |                |
| Yes                            | 10 (14.1)      |
| No                             | 61 (85.9)      |
| ECOG-PS                        |                |
| 0–1                            | 56 (78.9)      |
| ≥2                             | 15 (21.1)      |
| C-reactive protein (mg/dL)     |                |
| ≤1                             | 37 (52.1)      |
| >1                             | 34 (47.9)      |
| Albumin (g/dL)                 |                |
| <3.5                           | 18 (25.4)      |
| ≥3.5                           | 53 (74.6)      |
| Glasgow prognostic score       |                |
| 0                              | 35 (49.3)      |
| 1                              | 20 (28.2)      |
| 2                              | 16 (22.5)      |
| Serum creatinine (mg/dL)       |                |
| ≤1.2                           | 38 (53.5)      |
| >1.2                           | 33 (46.5)      |

Values are presented as median (range) or number (%).

F/U CT, follow-up computed tomography; ECOG-PS, Eastern Cooperative Oncology Group performance status.

2. Stent failure-free survival associated with clinical parameters

A univariate analysis indicated that hypoalbuminemia (<3.5 g/dL; HR, 2.43; 95% confidence interval [CI], 1.21 to 4.86; p=0.012), elevated CRP (≥1 mg/dL; HR, 4.79; 95% CI, 2.0 to 11.1; p=0.001), and presence of a distal ureter obstruction (HR, 3.27; 95% CI, 1.19 to 8.95; p=0.021) were associated with stent failure-free survival, whereas type of cancer and serum creatinine >1.2 mg/dL were not associated with stent failure-free survival (Table 2).

![Table 2](image)

**Table 2. Univariate analysis of factors affecting stent failure-free survival**

| Factor                         | HR (95% CI) | p-value |
|--------------------------------|-------------|---------|
| Age ≤55 y                      | 1.72 (0.87–3.42) | 0.117   |
| Female sex                     | 1.13 (0.53–2.40) | 0.743   |
| Hydronephrosis                 |             |         |
| Moderate to severe             | 1.07 (0.54–2.11) | 0.838   |
| S-Cr >1.2 mg/dL                | 1.57 (0.78–3.14) | 0.200   |
| Albumin <3.5 g/dL              | 2.43 (1.21–4.86) | 0.012   |
| CRP >1 mg/dL                   | 4.79 (2.0–11.1) | 0.001   |
| GPS 1                          | 4.90 (1.90–12.6) | 0.001   |
| GPS 2                          | 6.09 (2.26–16.4) | 0.001   |
| Bladder invasion               | 1.99 (0.81–4.87) | 0.130   |
| Type of cancer                 |             |         |
| Gynecological                  | 2.43 (0.31–19.0) | 0.397   |
| Gastric                        | 1.59 (0.19–13.1) | 0.664   |
| Colorectal                     | 1.68 (0.20–13.9) | 0.627   |
| Initial symptoms               |             |         |
| Flank pain                     | 0.82 (0.30–2.21) | 0.696   |
| Hematuria                      | 3.38 (0.44–25.5) | 0.237   |
| Anuria                         | 0 (0)        | 0.979   |
| Carcinomatosis peritoni        | 1.04 (0.48–2.22) | 0.912   |
| Obstructive level              |             |         |
| Mid                            | 2.46 (0.85–7.10) | 0.094   |
| Lower                          | 3.27 (1.19–8.95) | 0.021   |

HR, hazard ratio; CI, confidence interval; S-Cr, serum creatinine; CRP, C-reactive protein; GPS, Glasgow prognostic score; ECOG-PS, Eastern Cooperative Oncology Group performance status.

![Table 3](image)

**Table 3. Multivariate analysis of factors affecting stent failure-free survival**

| Factor              | HR (95% CI) | p-value |
|---------------------|-------------|---------|
| Obstructive level   |             |         |
| Mid                 | 3.30 (1.12–9.67) | 0.029   |
| Lower               | 4.31 (1.56–11.88) | 0.005   |
| Glasgow prognostic score |           |         |
| 1                   | 6.66 (2.56–17.33) | 0.001   |
| 2                   | 8.77 (3.10–24.84) | 0.001   |
| Serum creatinine >1.2 mg/dL | 2.16 (1.02–4.57) | 0.044   |

HR, hazard ratio; CI, confidence interval.
A multivariate analysis revealed that the presence of a mid or lower ureteral obstruction (HR, 3.27; 95% CI, 1.19 to 8.95; p=0.007), elevated serum creatinine before ureteral stent placement (\(>1.2\) mg/dL; HR, 2.16; 95% CI, 1.02 to 4.57; \(p=0.044\)), and GPS \(\geq 1\) (HR, 7.22; 95% CI, 2.89 to 18.0; \(p=0.001\)) were associated with stent failure-free survival (Table 3).

**DISCUSSION**

Our results suggest that the presence of a mid or lower ureteral obstruction, GPS \(\geq 1\), and elevated serum creatinine before ureteral stent placement were associated with poor stent failure-free survival in patients with a malignant ureteral obstruction.

The management of extrinsic malignant ureteral obstruction is a difficult situation in which the urologist balances patient quality of life, renal preservation and risk of complication in the setting of a poor prognosis. Obstruction of upper urinary tract lesions occurs in both benign and malignant disease, and the focus of treatment is the smooth elimination of urine. Obstruction due to benign diseases was treated by removing the lesions, whereas obstruction due to malignant diseases was treated by relieving the obstruction rather than removing the causative lesions. Ureteral obstruction from malignancy may be due to compression by the primary or metastatic tumor, retroperitoneal lymphadenopathy, or direct tumor invasion; therefore, renal function can be improved in either case and maintained by early detection and appropriate urinary diversion [4].

Experience with ureteral stents was first reported by Gibbons et al. [8] in 1976. Finney [9] and Hepperlen et al. [10] described the technique in 1978, and stents were subsequently used for patients with malignancies that were causing external compression of the ureter [11]. The development of endoscopy tools and techniques occurred in the late 1980s, and the previous treatment concept that surgical treatment for patients with malignant ureteral obstruction had priority was changed in the early 1990s [12-15].

Several studies have reported that predictors of stent failure are baseline serum creatinine, no treatment after RUS, gross tumor invasion noted at cystoscopy, degree of hydronephrosis, type of cancer, and male gender. Izumi et al. [1] reported that male gender and type of cancer are predictors of stent failure and Jeong et al. [6], also showed that baseline serum creatinine and no treatment after RUS are predictors of stent failure. In addition, other studies have revealed that gross tumor invasion noted at cystoscopy and the degree of hydronephrosis are predictors of stent failure [16-18]. Therefore, currently, there is a lack of consensus on the precise predictors of stent failure in malignant obstruction. In the present study, the presence of a mid or lower ureteral obstruction, GPS \(\geq 1\), and elevated serum creatinine (\(>1.2\) mg/dL) before ureteral stent placement were independently associated with stent failure-free survival, whereas type of cancer, male gender, and degree of hydronephrosis were not associated with stent failure-free survival.

Patients with malignancy and weight loss have many reasons for poor baseline renal function and after insidious obstruction, the renal reserve may be insulted and less likely to recover [16]. This mechanism may be associated with poor stent failure-free survival. In the present study, serum creatinine in cases of bilateral obstruction more elevated than unilateral obstruction, therefore, this may be associated with poor stent failure-free survival.

In the previous studies, patients with upper ureteric obstruction had a significantly shorter survival. Jeong et al. [6] suggested that this poor survival time might be due to the extensive metastasis to the retroperitoneum, which results in periureteric metastasis. Also, Chung et al. [16] demonstrated that decreased flow was found to a greater degree in ureters with simulated proximal rather than distal obstruction. Resistance to flow is associated with diameter and length, and if the obstruction is closer its origin resistance to flow is increased. However, in the present study, the presence of a mid or lower ureteral obstruction was associated with stent failure-free survival. Therefore, further studies are needed to identify difference in stent failure-free survival according to the level of ureteral obstruction.

In addition, the systemic inflammatory state characteristic of advanced cancer and reflected in CRP elevation may have bearing on prognosis [19]. Furthermore, serum albumin is frequently low in patients with cancer, fueled by malnutrition and inflammation, so hypoalbuminemia may influence prognosis as well [20]. By combining CRP and albumin determinants as the GPS [7], the independent association of these indices with poor prognosis has been demonstrated in various types of cancer [21]. In the present study, CPR, hypoalbuminemia and GPS were associated with early ureteral stent function failure on univariate analysis, and only GPS was independently associated with short SFFS on multivariate analysis. This was probably due to worsening of ureteral obstruction resulting from rapid progression of malignancy that had systemic inflammation, in line with prior findings. To our knowledge this is the first report that GPS is an independent predictor of SFFS. However, the results should be interpreted carefully because the patient characteristics differed among studies.

Although an intrinsic ureteral obstruction due to benign disease such as stone disease, ureteral stricture, or an ureteropelvic junction obstruction is usually successfully managed in the long term by RUS, the incidence of stent failure is significantly higher in cases of malignant ureteral obstruction [1]. In the present study, the stent success rate was 42%, which was lower than the 72% reported by Donat and Russo [22], and the 92% reported by Rosenberg et al. [2]. This discrepancy may be explained as a result of biocompatibility [6,16] and differences in patient characteristics.

Complications caused by RUS placement may include...
storage symptoms such as increased frequency and nocturia, hematuria, low abdominal pain, and encrustation. In addition, ascending pyelonephritis can occur due to vesicoureteral reflux [23]. However, most of the complications can be managed with conservative treatment. We encountered no serious complications and all complications were managed with conservative treatment. Currently, the limitations associated with conventional treatments for ureteral obstructions highlight the need for a novel treatment that can maintain ureteral patency while minimizing the deterioration of patient quality of life. Several types of metallic stents have been used in the palliative treatment of malignant ureteral obstructions. Goldsmith et al. [24] reported placement of the metallic Resonance stent for malignant ureteral obstruction. Their study identified a 35% rate of failure in patients with malignant ureteral obstruction treated with a metallic stent. This outcome is comparable to the failure rate historically observed with traditional polyurethane based stents for malignant ureteral obstruction. In addition, Kim et al. [25] reported that they assessed the efficacy and safety of insertion of a polytetrafluoroethylene membrane-covered self-expandable metallic stent (UVENTA stent) for palliation of malignant ureteral obstruction. In their study, the UVENTA stents were not obstructed during follow-up, so that the overall patent rate was 100%, but de novo ureteral obstruction developed in 4 ureters. Further studies and long term follow-up would be necessary to assess the role of these stents in the treatment of malignant ureteral obstruction.

The present study had a number of limitations. First, the patients that initially underwent RUS but failed due to severe obstruction were categorized into the stent failure group. As a result, stent failure-free survival may have been shorter. Furthermore, the patient population was relatively irregular, because of the various types of cancer. Second, we did not evaluate poststent systemic therapy because most of enrolled patients were systemic therapy-off state. Finally, cases of removing a ureteral stent due to severe complications were not included. Further studies are needed to identify the predictive factors for stent failure-free survival in a large cohort with malignant ureteral obstructions.

CONCLUSIONS

Ureteral obstruction due to extrinsic malignant compression is a poor prognostic sign and should prompt an open discussion with the patient and family. In the present study, the presence of a mid or lower ureteral obstruction, GPS ≥1, and serum creatinine before ureteral stent insertion >1.2 mg/dL were helpful for predicting poor stent failure-free survival. This information may help urologists guide patient expectations and treatment choices. In addition, PCN and metallic stents are also considered for patients who have these factors.
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