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ORIGINAL ARTICLE

Incidence, management, and sequelae of ureteric obstruction in women with cervical cancer

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Abstract

Purpose Hydronephrosis due to ureteric obstruction (UO) is stage-defining at cervical cancer presentation but may occur after primary staging. We aimed to determine the incidence and review the presentation and management of UO in women with cervical cancer attending our center. Particular attention was paid to the evolving role of interventional radiology (IR) in management.

Methods Women with a new diagnosis of cervical cancer between January 2012 and December 2016 formed the cohort that was retrospectively reviewed from the oncology database and patient records.

Results There were 310 women diagnosed with cervical cancer; 240 were stages I/II and 70 were stages III/IV. Primary treatments were chemoradiotherapy ($n = 168$; 54.2%), surgery ($n = 121$; 39.0%), and palliative care alone ($n = 21$; 6.8%). UO occurred in 74 (23.9%); present at primary staging in 53 (71.6%) and arising after staging in 21 (28.4%). Primary interventions for hydronephrosis were IR ($n = 50$; 67.6%), cystoscopic stenting ($n = 19$; 25.7%), bowel urinary conduit construction ($n = 2$; 2.7%), and none ($n = 3$; 4.1%). For those who attended IR, the mean number of IR procedures was 2.2, range 1–7. Maximum serum creatinine was 303 μmol/L for women with UO at primary staging compared with 252 μmol/L for UO after staging ($P = 0.267$). Thirty-eight women experienced substantial morbidity related to UO. Stage-adjusted mortality risk was 2.3 times higher for UO cases compared with those without UO.

Conclusions UO is associated with substantial morbidity and survival disadvantage in cervical cancer and may present after primary cancer staging. We recommend renal biochemistry during routine follow-up. A majority of cervical cancer-associated UO cases are managed with IR in our center.

Keywords Neoplasms · Ureteric obstruction

Introduction

Cervical cancer remains the sixth most common malignancy in European women and the second most common among women of reproductive age [1]. Ureteric obstruction (UO) is a common complication of cervical cancer. It occurs due to extrinsic compression of the ureter by tumor and replacement of part of the ureter by tumor (usually the parametrial portion), from ureteric ischemia and fibrosis resulting from the inflammatory response to the disease or its treatment and less frequently as a result of surgical injury to the ureter. Cervical cancer is staged clinically using the FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) staging system [2]. Newly diagnosed cervical cancer that presents with hydronephrosis is at least stage IIIB, a classification which also includes disease extending to the pelvic side wall without UO. The FIGO staging does not distinguish between stage IIIB cases with and without hydronephrosis. UO can also arise after diagnosis and staging of cervical cancer, even in early-stage disease. An incidence of up to 11% is quoted for patients following pelvic radiotherapy [3–5].

This common complication of cervical cancer has been infrequently addressed in the gynecological oncology literature. Most studies that previously examined hydronephrosis were confined to women with at least stage III cervical cancer, even though UO may occur subsequent to cancer diagnosis in

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women with early-stage disease at initial cancer presentation [6–8]. Hydronephrosis has been reported to impact on performance status and possibly on survival [6]. Adverse events related to the stents themselves are more common when ureteric stents are inserted in cervical cancer patients compared with women without cancer [9].

Intervention to achieve effective drainage of the urinary system is undertaken in the setting of hydronephrosis associated with cervical cancer in order to relieve symptoms of obstruction and maintain or restore renal function and reduce long-term sequelae. Relief of obstruction is often essential prior to commencement of systemic treatment. The management of UO has evolved in recent years with the advent of interventional radiology (IR) techniques, and these have been described in detail by Thornton [10]. Traditionally, primary retrograde ureteric stenting was attempted at cystoscopy under general anesthesia. The distortion and elevation of the trigone by disease often rendered that impossible so that antegrade stenting via nephrostomy is now the preferred option for many patients. Repeat ureteric stenting is often necessary and can be lifelong in the setting of cervical cancer [9]. This is associated with a burden on patients' health and a demand on healthcare resources. In our center, the standard of care retrograde stent exchange has been moved from the operating theater to IR.

In this study, we describe our IR technique of retrograde ureteric stent exchange and retrospectively review the incidence, presentation, management, prognostic implications, and complications of UO arising in patients with a diagnosis of cervical cancer.

Materials and methods

The study was undertaken at a university teaching hospital serving large urban and regional populations. The gynecological oncology unit is staffed by four gynecological oncologists and doctors in training. It is approved as a center for sub-speciality (fellowship) training in gynecological oncology. There is close collaboration with the hospital's pathology, medical oncology, radiation oncology, and IR departments. Cancer staging and management are determined by multidisciplinary team consensus. In addition to clinical staging, all patients had pelvic magnetic resonance imaging (MRI) scans and positron emission tomography–computerized tomography (PET-CT) scans to supplement minimal staging requirements.

An electronic patient record (EPR) system and cancer database are in operation in the hospital. Women who were recorded as having a new diagnosis of cervical cancer between 01 January 2012 and 31 December 2016 formed the study group. They were identified from the oncology database and their details were extracted from patient records. In cases with UO, the diagnosis of hydronephrosis was confirmed radiologically by ultrasonography, MRI, or CT or a combination of these modalities.

Data collected included details of cancer diagnosis, cancer treatment modalities, timing of UO in the disease pathway, and interventions for hydronephrosis. Serum creatinine levels and estimated glomerular filtration rates (eGFR) at cancer diagnosis and subsequently in the disease pathway and details of morbidity arising in relation to hydronephrosis were recorded. The hospital's biochemistry laboratory calculates eGFR using the Modification of Diet in Renal Disease four-variable equation [11]. Chronic kidney disease was defined in line with international nephrology guidelines as eGFR < 60 mL/min/1.73 m^2 [12]. Survival data were recorded.

The technique for retrograde stent exchange utilized in the IR department facilitates stent exchanges as day-case procedures without general anesthesia [13]. To summarize the technique, the patient is placed in the supine position and a urinary catheter is inserted. The urinary bladder is distended with contrast, and the procedure is performed under fluoroscopic guidance. A hydrophilic guidewire is subsequently inserted into the bladder via a Foley catheter, which is then removed over the wire. A sheath is inserted into the bladder over the wire, and a snare device is passed into the bladder, in order to grasp the distal portion of the stent. The existing stent is withdrawn beyond the urethral meatus, and then, the hydrophilic wire is inserted through the stent and advanced into the intrarenal collecting system. A new stent is then placed by advancement over this wire and deployed.

Data were analyzed using a statistical analysis program (*SPSS*, IBM, Armonk, USA). Comparison of mean values for tests of renal function in women with and without hydronephrosis was performed with two-sample *t* tests. The Kaplan-Meier curves were plotted to calculate survival rates and 31 December 2017 was the censoring point. Log-rank test was used to compare the survival distributions. Cox regression analysis was performed to adjust survival data for cancer stage (with stage I used as reference). A p value < 0.05 was considered statistically significant. The study was approved by the Institutional Research Office (reference number 4991).

Results

Three-hundred ten women had a new diagnosis of cervical cancer during the 5-year study period: 240 had stage I or II and 70 had stage III or IV disease. Their mean age at diagnosis was 47 years (SD = 15, range 22–93 years). Primary cancer treatment was surgery for 121 (39.0%), chemoradiotherapy for 168 (54.2%), and palliative care only for 21 (6.8%). Seventy-four (23.8%) developed hydronephrosis as a result of UO. The incidence of UO arising subsequent to primary cancer staging was 8.8% (n = 21) in women with stage I and II cervical cancer. Hydronephrosis was

diagnosed at either primary cancer staging or subsequent to staging in 75.7% ($n = 53$) of women with stage III and IV disease ($\chi^2 = 130.86$, $p < 0.001$). Across all stages, 74 women had hydronephrosis, 39 (52.7%) had unilateral, and 35 (47.3%) had bilateral ureteric obstruction.

Twenty-one women with stage I or II disease developed hydronephrosis after initial cancer diagnosis and staging, and they accounted for 28.4% of the entire cohort with UO ($n = 74$) (Table 1). Hydronephrosis arose in the interval between staging and treatment in two (9.5%), during treatment in two (9.5%), and subsequent to completion of treatment in 17 (81.0%).

Eight women who did not have hydronephrosis at presentation with stage III or IV disease developed obstruction prior to commencement of chemoradiotherapy ($n = 1$), during treatment ($n = 4$), and subsequent to completion of treatment ($n = 3$).

In all, 29 patients developed hydronephrosis after their initial cancer diagnosis, clinical and radiological staging: two were detected on their radiotherapy-planning CT scan; five were detected on imaging to investigate a rise in serum creatinine on serial biochemistry while undergoing primary chemoradiotherapy; one was detected on imaging to investigate apparent progression of disease while undergoing chemoradiotherapy; 21 women developed obstruction during post-treatment surveillance at intervals ranging from 6 to 41 months (mean 16.7 ± 8.7 months) after diagnosis. Eighteen (85.7%) of these 21 women developed hydronephrosis at an interval less than 24 months following primary treatment. Of these 21, 19 (90.5%) had received either postoperative or primary radiotherapy, and hydronephrosis was associated with recurrence of disease in 14 (66.7%) patients. Disease recurrence was asymptomatic and was detected following investigation of a rise in serum creatinine in 5 of these 14 women. Nine women had symptoms or disease detected by clinical pelvic examination. UO without recurrence of cancer ($n = 7$) was revealed by a rise in serum creatinine in six cases and during investigation of vesicovaginal fistula in one patient.

Table 1 Incidence of hydronephrosis identified at any point in the disease pathway classified according to FIGO stage for women diagnosed with cervical cancer, 2012–2016 ($n = 310$)

Stage	Incidence %, number of patients (n)	
	Hydronephrosis	No hydronephrosis
I ($n = 175$)	8.6 (15)	91.4 (160)
IA1	0.0 (0)	13.1 (23)
IA2	0.5 (1)	5.1 (9)
IB1	6.4 (11)	53.1 (93)
IB2	1.7 (3)	20.0 (35)
II ($n = 65$)	9.2 (6)	90.8 (59)
IIA	0.0 (0)	13.8 (9)
IIB	9.2 (6)	76.9 (50)
III ($n = 49$)	77.6 (38)	22.4 (11)
IIIA	2.0 (1)	4.1 (2)
IIIB	75.5 (37)	18.4 (9)
IV ($n = 21$)	71.4 (15)	28.6 (6)
IVA	47.6 (10)	9.5 (2)
IVB	23.8 (5)	19.0 (4)
Total	23.9 (74)	75.8 (236)

Fédération Internationale de Gynécologie et d'Obstétrique cervical cancer staging, 2009; since the presence of hydronephrosis is stage-defining (i.e., at least stage III), those with hydronephrosis identified here as stages I/II developed hydronephrosis following primary cancer staging

First-line interventions for the 74 women with hydronephrosis were with IR for 50 (67.6%) women, cystoscopic retrograde stent insertion for 19 (25.7%), and bowel urinary conduit construction for two (2.7%), and three (4.1%) women had symptom control only for disease progression. No patient had renal dialysis. Seventeen of the 50 women managed primarily with IR had primary antegrade ureteric stenting performed at their first procedure. Primary ureteric stenting was not progressed immediately if there was any evidence of infection. The remaining 33 women managed primarily with nephrostomy underwent successful interval antegrade ureteric stenting in 24 (72.7%) cases and urinary conduit construction in two (6.1%) cases, and seven (21.2%) retained their nephrostomies until death from progressive cancer.

Forty-nine patients had an ongoing requirement for stent and 40 (82%) exchanges were performed in IR. Of the 41 patients managed primarily with IR antegrade stenting, 32 (78.0%) women had subsequent retrograde stent changes by IR, two (4.9%) required cystoscopy under general anaesthetic, and seven (17.1%) women died before interval stent change. Of the 19 women initially managed with retrograde ureteric stent at cystoscopy, eight had retrograde stent changes with IR, seven had stent changes via cystoscopy under general anesthesia, three women died before scheduled stent change, and one underwent bowel urinary conduit construction. IR exchange of ureteric stenting was repeated between one and seven (mean 2.2) times in the 40 patients.

The mean creatinine level at initial diagnosis of cervical cancer was 150 μmol/L (95% confidence interval ± 59.7 μmol/L) and 64.1 μmol/L (95% confidence interval ± 3.3 μmol/L) for women with and without hydronephrosis at cancer presentation, respectively ($p = 0.005$). Table 2 shows no significant difference in the maximum creatinine level and minimum eGFR for women diagnosed with hydronephrosis at presentation with cervical cancer compared with women who developed hydronephrosis subsequent to primary cancer staging.

Morbidity or major interventions occurring in relation to UO and its sequelae affected 38 (51.4%) of the 74 women with hydronephrosis. These events were recurring urinary tract infection ($n = 12$, 16.2%), chronic kidney disease ($n =$

Table 2 Comparison of mean values for tests of renal function in women with cervical cancer diagnosed with hydronephrosis at primary staging and subsequent to staging, 2012–2016 ($n = 74$)

Parameter	Group A[b] ($n = 45$)		Group B[c] ($n = 29$)		P
	Mean	CI[d]	Mean	CI	
Creatinine at cancer diagnosis (μmol/L)	205.6	± 97.9	67.6	± 4.8	0.003
eGFR[a] at cancer diagnosis	50.3	± 8.3	82.6	± 4.1	< 0.001
Highest creatinine (μmol/L)	302.8	± 107.8	252.4	± 123.7	0.267
Lowest eGFR	32.0	± 6.8	37.8	± 8.4	0.139

[a] Estimated glomerular filtration rate, mL/min/1.73 m^2

[b] Group A—hydronephrosis diagnosed at primary cervical cancer staging

[c] Group B—hydronephrosis after primary cancer staging

[d] 95% confidence interval

8, 10.8%), stent-associated pain ($n = 6$, 8.1%), urinary diversion by bowel conduit ($n = 4$, 5.4%), secondary hypertension due to chronic kidney disease (n = 4, 5.4%), nephrectomy for non-functioning kidney with recurring urinary tract infection ($n = 3$; 2.7%), renal artery embolization ($n = 2$; 2.7%), and persistent hematuria, perinephric hematoma, and arterio-ureteric fistula involving the left internal iliac artery ($n = 1$; 2.7%). The patient with arterio-ureteric fistula presented with heavy hematuria at the time of retrograde stent placement with IR. Cystoscopy revealed pulsatile bleeding from her left ureter. Fistula formation between the left ureter and the left internal iliac artery was diagnosed at angiography. An endovascular-covered stent was inserted into the affected segment of artery, and an antegrade ureteric stent was placed through the fistulized segment of ureter. Subsequent retrograde ureteric stent exchange under fluoroscopy was successful.

Analysis of survival revealed the following: 214 (90.7%) of the 236 women without hydronephrosis and 42 (56.8%) of the 74 women with hydronephrosis were alive at the censoring point. Hazard ratio for mortality for women who developed hydronephrosis at any time point was 5.8 (95% confidence interval 3.4–9.9) times higher than for those who did not. This relationship remained significant when adjusted for cancer stage, with hazard risk for mortality being 2.3 (95% confidence interval 1.1–4.9) times higher for women who developed hydronephrosis (Fig. 1).

Discussion

We found that a substantial proportion, almost a quarter of women with cervical cancer develop hydronephrosis at some point in the course of their disease and this supports previous published reports. Hydronephrosis is stage-defining for advanced cervical cancer and more than three quarters of patients with stage III/IV disease had UO in this series. However, it was a not uncommon occurrence in patients with stage I/II disease at primary staging, with one in 12 patients developing UO subsequent to their initial staging. Previous reports confined to women with stage III disease include the study by Chao et al. [8] which found 26.2% of 297 patients treated for cervical cancer between 1959 and 1989 had hydronephrosis; Rose et al. [6] found a rate of 44.2% in 539 women between 1981 and 2000; and Pradhan et al. [14] found a rate of 49% in 143 women between 1990 and 2007. Patel et al. [15] found 23.6% of 279 women with all stages of cervical cancer had hydronephrosis at some point in their disease course and 46% of their patients with hydronephrosis had stage I and II cervical cancer at disease presentation.

With regard to UO arising after diagnosis and staging of cervical cancer, we found it was infrequent in the interval between staging and radiotherapy-planning CT. It was more likely to arise during primary chemo-radiotherapy, and the majority of these cases were detected by a rise in serum creatinine. Two thirds of cases arising after the completion of treatment had recurrent disease and 90% had received radiotherapy. Hydronephrosis arising after surgery alone was always with relapse of disease. Recurrences were asymptomatic and detected by a rise in serum creatinine in more than one third of patients with relapse of cancer. Rising serum creatinine was also the harbinger of UO in six of seven isolated obstructive uropathies, all of which arose within 2 years of diagnosis. Routine renal biochemistry, therefore, is useful in detecting obstruction of ureters and relapse of disease. We recommend renal biochemistry at surveillance visits for at least 2 years. Most women who developed hydronephrosis following treatment had received either primary or post-operative radiotherapy. This raises the possibility that in order to minimize the risk to glomerular function, interval, perhaps quarterly renal ultrasonographic assessment in this subgroup of women for the first 2 years following radiotherapy might be of value. Further prospective work would be needed to investigate this.

Traditionally, UO was treated by retrograde stenting at cystoscopy, usually under general anesthesia, and this intervention was often unsuccessful due distortion of the bladder trigone and parametrium by disease and/or fibrosis. The

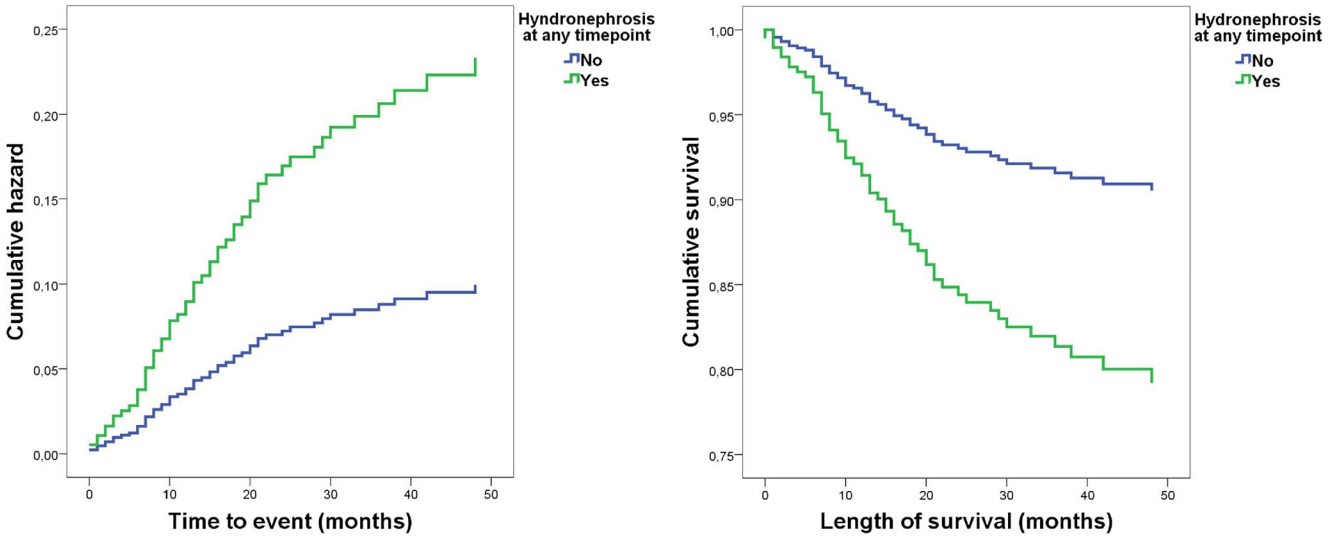

Fig. 1 Survival (left) and mortality (right) plots according to hydronephrosis status developed at any time point, adjusted for cancer stage at diagnosis

introduction of antegrade stenting via nephrostomy resulted in a major improvement in the rates of successful primary ureteric stenting, and patients then returned for interval retrograde stent exchange via cystoscope. Fluoroscopically guided stent exchange has now become the standard of care in our center [10]. Forty women had repeated stent exchanges in IR; only a small minority could not tolerate stent exchange without anesthesia. This represents a valuable saving of hospital resources as well as the reduction of risk to patients by avoidance of hospitalization and general anesthesia for interval stent exchange. Reducing the morbidity risk and more efficient use of healthcare resources associated with IR techniques are particularly relevant for women with recurring requirement for ureteric stent exchanges. The successful management of these women by IR also leaves only a small minority needing urinary diversion by bowel conduit. We recommend that gynecological oncologists should actively involve interventional radiologists in their management of UO.

We found that the impact of UO on renal function was substantial, regardless of whether hydronephrosis was diagnosed at presentation with cancer or arose later in the disease pathway and one in ten patients developed chronic renal impairment. More than half of the patients had major morbid events including recurring infections, pain, chronic renal impairment, secondary hypertension, and bleeding including an arterio-ureteric fistula. Surgeries arising included nephrectomy and urinary diversions via bowel conduit. The psychological and social burden of repeated stent changes for management of hydronephrosis was not measured. Patel et al. [15] found that hydronephrosis was associated with morbidity, with 26.2% of patients experiencing notable morbidity including pain, local infections, and urinary tract bleeding. Rose et al. [6] found that hydronephrosis was associated with worse performance status. Goldfarb et al. [9] reported that rates of urinary system symptoms were three- to tenfold higher in women with cervical cancer who required ureteric stenting compared with those without cancer, but the method of stent insertion was not reported.

Arterio-ureteric fistula is an uncommon condition, with less than 200 cases reported in the literature [16–18]. Risk factors include previous abdominal or pelvic surgery, radiation, and chronic ureteric stent placement. Mortality from massive hemorrhage is reported in 7–23% of cases [17]. Clinicians should be mindful of the condition when patients present with substantial hematuria, particularly in the presence of risk factors.

We found that the presence of hydronephrosis had an impact on survival whether it was diagnosed at presentation with cancer (i.e., late-stage disease) or subsequently in the disease pathway in women with early-stage disease at cancer diagnosis. Adjusted for stage of disease, the hazard ratio for mortality was 2.3 times higher for cervical cancer patients who developed ureteric obstruction. Rose et al. [6] found that hydronephrosis was a significant but not independent prognostic factor; Pradhan et al. [14] found that hydronephrosis was associated with poor prognosis, with a hazard ratio for death of 2.4, and this remained significant when controlled for radiation, chemotherapy, and performance status; and Patel et al. [15] found that hydronephrosis was associated with worse survival in landmark univariate analysis.

Our study has limitations. Its retrospective nature meant that we could not determine with accuracy the impact of hydronephrosis on quality of life; therefore, overall morbidity related to the condition may be under-reported. While all women with a diagnosis of cervical cancer underwent standardized radiological staging at presentation with cancer, after cancer presentation, radiological imaging was determined by

clinical need and not as a routine. Therefore, we may have underestimated the incidence of delayed diagnosis of hydronephrosis in our population. We are unable to comment on the causal effect of cancer treatment modalities on the risk of subsequent hydronephrosis owing to the retrospective nature of our review.

In summary, hydronephrosis has a negative impact on morbidity and survival in women with cervical cancer. IR can manage the primary relief drainage, antegrade stenting, and subsequent retrograde stent exchanges in the majority of cases of UO associated with cervical cancer. The impact on renal function is as substantial in women with stage I or II cervical cancer who develop hydronephrosis subsequent to primary staging as it is in those with hydronephrosis at diagnosis of cancer. Women undergoing clinical follow-up for both early- and advanced stage cervical cancer should have interval serum renal biochemistry performed. Interval ultrasonographic renal assessment for the first 2 years following treatment in the subgroup of women who have received primary or postoperative radiotherapy should be evaluated by a prospective study.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

The study was approved by the Institutional Research Office (reference number 4991).

Conflict of interest The authors declare that they have no conflict of interest.

The authors have full control of the all primary data related to this research and we agree to allow the journal to review our data if requested.

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