

Outcome of Obstructive Uropathy After Pelvic Irradiation in Patients with Carcinoma of the Uterine Cervix

K O Lau,*^{MBBS, FRCS}, T N Hia,**^{MBBS}, C Cheng,***^{FAMS, FRCS, M Med (Surg)}, S K Tay****^{FAMS, MD, FRCOG}

Abstract

The natural history and outcome of intervention for obstructive uropathy were studied retrospectively in 20 patients managed at the Department of Urology, Singapore General Hospital between 1991 and 1997. The diagnoses of these strictures were made between 10 months and 21 years after the initial treatment. There were 9 (45%) malignant and 11 (55%) benign strictures. The site of ureteric obstruction was in the lower ureter in 15 patients, in the middle ureter in 3 patients and in the upper ureter in 2 patients. Comparisons between malignant and benign strictures showed that patients with higher original stage of tumour were more likely to have malignant strictures. Besides latency period between primary treatment of the tumour and diagnosis of uropathy, bilaterality and site of strictures showed no discernible difference between benign and malignant strictures. Ureteric stenting provided good outcome in 5 patients with benign strictures and in 3 patients with malignant strictures. Open surgical reconstruction was performed on 2 patients with benign strictures and 2 patients with malignant strictures. All these four patients showed good outcome.

Ureteric stenting is an acceptable treatment of benign ureteric stricture and for selected patients with malignant strictures. Open surgery is recommended in patients with benign strictures who could not be treated successfully on stenting.

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Introduction

Radiotherapy is the mainstay treatment for locally advanced carcinoma of the cervix.^{1,2} It is also administered as an adjuvant therapy to patients deemed at high risk for local recurrence after radical hysterectomy.^{3,4} Organs adjacent to the cervix, such as the ureter, bladder and rectum, are inevitably irradiated to a certain degree. Radiation cystitis and proctocolitis are often encountered during treatment but delayed complications may manifest many years after completion of therapy.

Ureteric stricture was first reported as a complication of radium treatment by Schmitz in 1920.⁵ However, it is believed to have a low incidence between 2% and 3%. It can be asymptomatic with minimal damage to the upper urinary tract or present as severe damage to the kidney with life-threatening consequences. It is important to recognize it early for consideration of appropriate treatment in order to minimise morbidity and mortality.

Recurrence of cancer in the pelvis remains the most common cause of upper tract obstructive uropathy previously treated for cervical cancer. In these cases, the

decision to intervene has to be balanced between the potential for increased survival and the quality of life during the ensuing period of time. For most instances, treatment of obstructive uropathy may be aimed at improving the patients' general health condition in preparation for other mode of therapy such as chemotherapy.

This retrospective study reports on the outcome of treatment of obstructive uropathy after primary treatment of cervical carcinoma.

Patients and Method

The records of 20 consecutive women who presented to the Department of Urology, Singapore General Hospital, with ureteric strictures after radiation treatment for carcinoma of cervix between 1991 and 1997, were analyzed retrospectively.

Patients' hospital records were reviewed and relevant information regarding tumour history, treatment modality, investigations for tumour recurrence, type of uropathy and treatment, and the outcome of treatment were extracted. The patients were divided into 2 groups

* Senior Registrar

** Medical Officer

*** Consultant

Department of Urology

**** Senior Consultant

Department of Obstetrics and Gynaecology

Singapore General Hospital

Address for Reprints: Dr K O Lau, Department of Urology, Singapore General Hospital, 1 Hospital Drive, Singapore 169608.

for analysis. Group 1 consisted of 11 patients with obstructive uropathy related to previous treatment. Group 2 consisted of 9 patients with evidence of recurrent or active cervical cancer after treatment. Study parameters were analysed and compared between these two groups. Statistical tests were performed to evaluate the significance of the observed differences between the groups.

All ureteric strictures were evaluated by combinations of ultrasound scan, intravenous urogram, retrograde or antegrade pyelogram and computed tomographic scan of the genitourinary tract.

Statistical analysis: Significance in the difference in frequency distribution of parameters between benign and malignant strictures was analysed with χ^2 -test. The difference in the latency period for detection of stricture was analysed with Wilcoxon rank sum test.

Results

In group 1, 8 patients were treated with radiotherapy alone and 3 had both surgery and radiotherapy. In group 2, 7 patients were treated primarily with radiotherapy and 2 had combined surgery and radiotherapy.

No statistically significant difference was observed in the mean age of the patients in the two groups (62.5 ± 11.1 vs 54.6 ± 9.4 years). The original staging of the tumour in group 1 patients were: 1 stage I, 5 stage II, 1 stage III and 4 unknown stage. In group 2, 3 patients were stage II, 5 stage III and 1 unknown stage. Other details of the patients are summarised in Table I.

Malignant strictures tend to develop in patients with more advanced initial staging when compared to benign ones (62.5% stage III vs 14.3% stage III).

Latency

The median interval for the development of benign ureteric stricture was 14 years (range 10 months to 21 years). On the other hand, malignant ureteric stricture was diagnosed after a median duration of 3 years (range 1 to 15 years). The difference was statistically significant ($P < 0.01$).

Associated Pathology

Of the 11 patients with benign ureteric strictures, 6 (54.5%) also had other major complications: severe radiation cystitis in 5 (45.5%), and vesicovaginal fistula with a very contracted bladder in 2. These 2 patients were treated by ileal conduit and Martius flap respectively. One patient (9.1%) had vesicocutaneous fistula which was managed by indwelling urethral catheter. Of the 9 patients with malignant stricture, 4 (44.4%) patients also had radiation cystitis, 2 (22.2%) patients had vesicovaginal fistula (which were treated with ileal conduit in one and conservatively in the other due to poor medical condition), 1 (11.1%) patient had rectovaginal fistula (and required a defunctioning colostomy).

Stricture Site

Malignant strictures affected both ureters in 6 (66.7%) patients compared to 3 (27.3%) patients with benign strictures ($\chi^2 = 3.2$ $P > 0.05$). All except 1 benign stricture involved the lower ureter. Similarly, 66.7% of malignant strictures were also found mainly in the lower ureter, 3 (20.0%) strictures were detected in the middle ureter and 2 (13.3%) in the upper ureter.

Management and Outcome

1. Benign strictures

Ten patients underwent ureteric stenting and a 70-year-old patient with asymptomatic benign stricture and normal serum creatinine level was managed expectantly. The renal function on the obstructed side was decreased at the last follow-up 2 years after.

Eight patients (72.7%) were treated with ureteric stents alone, the average duration of stenting was 11.4 months (range 1 to 48 months). Five of these patients showed improvement of hydronephrosis and serum creatinine level. One patient had stent migration and she refused any further intervention. Two patients continued to have reduced renal function and in 1 patient, the deteriorating renal function was treated by reimplantation of the affected ureters using Boari flap. Ureteric stenting was unsuccessful in 1 patient. She also had concomitant radiation cystitis and vesicovaginal fistula. She was treated with ileal conduit surgery successfully. All of these patients had improvement or stabilization of their renal function after surgery. There was no perioperative mortality.

During the last follow-up, 9 patients were still alive with no evidence of recurrent malignant disease. One patient developed metastatic transitional cell carcinoma of the bladder and right kidney and died 3 years after diagnosis of the ureteric stricture. Another patient died of urinary sepsis but renal function remained stable at the time of death.

2. Malignant Strictures

Of the 9 patients with malignant strictures, 3 (33.3%) were treated expectantly because of poor clinical condition and very advanced nature of the cervical cancer at the time of diagnosis of obstructive uropathy. They all died within 6 months of diagnosis.

Four patients (44.4%) were stented for a mean duration of 5 months (range 3 to 9 months). Three of these patients showed improved renal function at follow-up. The other patient died 6 months later with deteriorated renal function.

One patient with concomitant vesicovaginal fistula and a severely contracted bladder was treated with ileal conduit for palliation while another patient underwent ureteric reimplantation using Boari flap. Both of them

TABLE I: PATIENTS WITH URETERIC STRICTURE FOLLOWING TREATMENT FOR CERVICAL CARCINOMA

Pt.	Age (y)	Stage	Latency (Y)	Therapy	Nature	Side	Site	Treatment	Other major complications	Follow up
1	53	II	0.8	Rad/Hyst	Benign	Right	Lower	Stents	Vesicovaginal fistula	6 y, A/NED
2	73	unkn	21	Rad/Hyst	Benign	Left	Lower	Stents	Radiation cystitis, VCF	5 y, D/ICD
3	62	unkn	17	Rad/Hyst	Benign	Bilateral	Upper	Stents	None	1 y, decreased bilateral renal function
4	70	III	8	Rad	Benign	Left	Lower	Observed	Radiation cystitis	2 y, decreased L renal function
5	62	II	5	Rad	Benign	Left	Lower	Stents	None	1.5 y, A/NED
6	55	II	7	Rad	Benign	Right	Lower	Stents	None	1 y, migrated DJ stent, patient refused further intervention
7	38	II	2	Rad	Benign	Left	Lower	Stents	None	1 y, A/NED
8	76	unkn	16	Rad	Benign	Bilateral	Lower	Stents	Radiation cystitis	3 mo, A/NED
9	72	II	14	Rad	Benign	Right	Lower	Stents	None	6 mo, decreased R renal function
10	68	unkn	18	Rad	Benign	Right	Lower	IC	Radiation cystitis, VVF	3 y, A/NED
11	58	I	21	Rad	Benign	Bilateral	Lower	UN	Radiation cystitis	3 y, D/ICD
12	56	III	3	Rad/Hyst	Malignant	Left	Middle	Observed	None	6 mo, D/C, decreased L renal function
13	64	unkn	15	Rad	Malignant	Left	Lower	Observed	Radiation cystitis	2 mo, D/C, decreased L renal function
14	47	III	11	Rad	Malignant	Left	Middle	Stents	None	1 y, Alive with local recurrence, Normal renal function
15	66	III	7	Rad	Malignant	Bilateral	Upper/Lower	Stents	Radiation cystitis	6 mo, D/C, decreased renal function
16	51	II	2	Rad	Malignant	Bilateral	Middle/Upper	Stents	None	3 mo, D/C, improved renal function
17	56	III	1	Rad	Malignant	Bilateral	Lower	Stents	None	3 mo, D/C, improved renal function
18	47	III	3	Rad	Malignant	Bilateral	Lower	Observed	Radiation cystitis, VVF	2 mo, D/C, improved renal function
19	39	II	2	Rad/Hyst	Malignant	Bilateral	Lower	UN	Rectovaginal fistula (colostomy)	6 y, possible systemic recurrence but normal renal function
20	65	II	3	Rad	Malignant	Bilateral	Lower	IC	Radiation cystitis	3 y, local recurrence, normal renal function

A/NED: alive, no evidence of disease; D/C: died of cervical cancer; D/ICD: died of intercurrent disease (unrelated to cervical cancer or treatment); Hyst: total hysterectomy; IC: ileal conduit; L: left; R: right; Rad: radiation; UN: ureteroneocystotomy; Unkn: unknown; VCF: vesicocutaneous fistula; VVF: vesicovaginal fistula

had good renal function at the last follow-up, 3 and 6 years after detection of ureteric strictures. Overall, 6 patients (66.7%) died because of advanced malignancy.

Discussion

Determining the aetiology of obstructive uropathy after treatment for cervical carcinoma is extremely important for planning appropriate treatment. The differentiation between benign and malignant strictures should be based on histology whenever possible. Radiological imaging methods are also useful in excluding malignancy.

A clinical history of a longer latency interval between primary tumour treatment and diagnosis of stricture is indicative but not diagnostic of a benign stricture. Similar to the result in Muram's et al study,⁶ our patients who developed malignant stricture tended to have more advanced clinical stage of cancer at initial presentation (62.5% stage III vs 14.3% stage III). Moreover malignant stricture seemed to affect both ureters more frequently than benign ones (66.7% and 27.3%) but this was not

statistically significant. The majority of ureteric stricture occurred in the lower third ureter (benign 85.7%, malignant 66.7%).

Malignant strictures were more frequently found above the pelvic brim (high stricture) (33.3% malignant strictures vs 14.3% benign strictures).

Different from obstruction secondary to cancer recurrence, radiation-induced ureteric stricture is a rare but well-characterized complication. Both McIntyre et al and Patricia et al^{7,8} reported the risk of radiation-induced stricture to be relatively constant and approximately 0.15% per year for 25 years or more after radiation. Therefore, young patients who were cured of their cervical cancer are exposed to a lifetime risk of ureteric strictures. The actual mechanism of radiation-induced submucosal fibrosis, however, is still poorly understood. It is suggested that radical pelvic radiotherapy results not only in initial acute reaction, but also in more sinister changes in all the treated tissues secondary to release of cytokines,⁹ superimposed bacterial reactions or chronic ischaemia.^{10,11}

The development of radiation-induced ureteric stricture may be related to many other factors such as age, tumour stage, surgical history, diabetes, hypertension and vascular disease.¹² Controversy also exists in whether radiation dosage and type of radiation affect the risk of this complication. We are unable to evaluate any of these relationships because of the small number of patients and no data were available on the precise radiation dosage, the duration of radiation therapy and the exact technique used for radiation.

On the other hand, recurrent tumours cause obstruction either by direct invasion from the primary organ, nodal extrinsic compression or peritoneal seedlings. Like benign strictures, they can also present relatively late, up to 15 years after initial diagnosis in our group of patients. Constant surveillance of all survivors, especially the younger ones, is important in the diagnosis and management of this complication.

Most of the strictures (85.7% benign, 66.7% malignant) were located in the lower third of the ureter. This is expected as this region is the closest to the field of radiation, thus bearing the brunt of radiation damage and exposed to higher risk of tumour invasion. Two of the 14 benign strictures (14.3%), however, occurred above the pelvic brim (high stricture). Taylor et al¹¹ also reported in their series 4 patients who had high strictures which were proven to be the result of radiation damage alone. However, the exact mechanism of these strictures development is uncertain. In a study of 28 patients, Zerbib et al¹³ found high strictures in 7 of 17 cases of cancer recurrences but in none of 11 patients with benign fibrotic strictures. They postulated that high strictures are always secondary to lymph node metastasis. Although high stricture occurred more frequently (33.3%) in malignant obstruction, this is not supported by data in our study.

The treatment for benign strictures should be tailored according to the individual's need. Besides one elderly patient with relatively good overall renal function which was treated expectantly, all our other patients were treated with ureteric stents initially. Stenting gave a fairly good outcome in our patients, though the follow up period was relatively short. Only 45.5% of the patients showed improvement of hydronephrosis and renal function after stenting. None of the patients in this study underwent endoureterotomy but Wolf et al¹⁴ reported poorer long-term result when treating irradiated ischaemic strictures with endoscopic means.

Only 2 patients underwent open surgery after failed stenting but both had the best long-term result. As pointed out by Jones et al,¹⁵ urinary diversion by ileal conduit remains a relatively simple and effective way of dealing with patients who have multiple post radiation complications such as fistula and ureteral obstruction.

The management of patients with malignant ureteric stricture is still controversial. Although patients with recurrent cervical carcinoma sometimes can have a relatively longer survival compared to other pelvic malignancy such as bladder carcinoma,¹⁶ one must take into consideration the quality of life after intervention and the possible complications involved. Patients should be carefully selected before treatment. 44.4% of the patients in our study died of advanced disease within 3 months of diagnosis of obstructive uropathy regardless of the type of palliative treatment. Lau et al¹⁷ supported the proposal that active treatment with nephrostomy should be pursued in patients only if further treatment is available.

In the present study, ureteric stenting was performed in 6 patients with recurrent tumour. Only 3 (33.3%) of them had improved renal function during the follow up. This was probably attributed to disease progression. Although complex reconstructive procedures are usually avoided in patients with advanced malignancy, ileal conduit and ureteric reimplantation were performed in 2 highly selected patients. Both of them had failed stenting and suffered significant morbidity from the local-regional disease. They had normal renal function at the last follow-up at 3 and 6 years after diagnosis.

In summary, obstructive uropathy secondary to benign or malignant stricture after treatment of cervical carcinoma can follow a long time course. The associated morbidity is significant and potentially fatal. Continued surveillance especially for younger women is justified in order to detect the complication early. Factors such as site, bilaterality, latency of stricture and other radiological findings may suggest the underlying aetiology but histology should be obtained, if possible, for prognosis and to assist in the decision of therapy. Patients with benign strictures have potential for long-term survival after stenting. One should not hesitate to perform open surgery for selected patients as it gives the best long-term result.

On the other hand, malignant stricture has a poor outlook. Careful consideration into the quality of life after treatment should be taken seriously.

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