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## INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/16659  
DOI URL: <http://dx.doi.org/10.21474/IJAR01/16659>



### RESEARCH ARTICLE

#### LATE UROLOGICAL COMPLICATIONS OF PELVIC RADIOTHERAPY PRESENTING TO A TERTIARY CARE INSTITUTE

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#### Manuscript Info

##### Manuscript History

Received: 10 February 2023

Final Accepted: 14 March 2023

Published: April 2023

##### Key words:-

Pelvic Radiotherapy, Hemorrhagic  
Cystitis, Radiation Complications, Small  
Capacity Bladder

#### Abstract

**Background:** The present study aims to assess various presentations of radiotherapy-induced late urological complications and management done in a tertiary care institute.

**Methods:** A prospective study was carried out in two-year which included 30 patients. Patients who received pelvic radiotherapy anytime in the past and presented with complications related to it were included. Their demographic data, primary malignancy, radiotherapy details, presentations, complications and management done were studied.

**Results:** The mean age and interquartile range of patients was 59.76 yr. (57 – 65 yr.). 23 patients (76.66%) were females. Ca cervix was the most common indication for primary radiotherapy (20 patients) followed by ca prostate (six patients). The mean duration of presentation after radiotherapy was 11.96 year with EBRT being the most common modality. The median dose per fraction (IQR) was 2 (2) Gy per fraction. The median number of fractions (IQR) of radiation therapy was 25 (20 – 31.25) and the median total dose (IQR) was 50 Gy (40 – 70.50 Gy). Radiation-induced hemorrhagic cystitis was the most common complication in 15 patients (50%). Other complications include urethral stricture, ureteral stricture and vesicovaginal fistula. The surgical intervention rate was 63.33%. Cystourethroscopy, clot evacuation and electrocoagulation was the most common procedure done in 23.33%. Other operative intervention includes ileal conduit with or without cystectomy, vesicovaginal fistula repair and transureteroureterostomy.

**Conclusion:** Complications of pelvic radiotherapy can manifest very late, are usually irreversible in nature and frequently needs surgical management. Surgery remains the mainstay of treatment modality for many of the complications.

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#### Introduction:-

Although a non-invasive modality of cancer treatment, the main disadvantage of radiotherapy is the damage that occurs to the surrounding normal tissues. Although complications are classified into acute and late, several late complications represent the continuation and evolution of the same pathologic process. Treatment-related factors that influence the risk of genitourinary toxicity includes cumulative radiation dose, radiation modality, treatment volume and patient factors and comorbidities [1]. The reported rate of major urologic complications ranges from

1.3% to 14.5% at 3 years and increases with duration [2]. Specific urological complications of radiotherapy include radiation cystitis, strictures, fistulas, infertility and erectile dysfunction [3]. These late complications can be challenging to manage; patients tend to be older and frequently requires surgical intervention, the outcome of which is compromised because of reduced local tissue vascularity and poor wound healing [4].

There is the paucity of studies of radiotherapy complications from a urologist perspective. The majority of such studies focuses on a single type of complications like radiation cystitis or fistula. The aim of the present study is to comprehensively assess all the various presentations of radiotherapy-induced late urological complications and management done in a tertiary care institute.

## **Methods:-**

### **Patient population**

A prospective study of patients presented to the urology department between November 2018 to October 2020 was performed. Institutional ethics committee approval was taken before the collection of data. Patients who had received pelvic radiotherapy anytime in the past and presented with complications related to it were included. Radiotherapy complications were defined according to the Radiation Therapy Oncology Group (RTOG) toxicity criteria [5]. The current classification does not involve fistulas and strictures, so we subclassified complications into hemorrhagic cystitis, strictures and fistulas.

### **Data collection**

Data obtained included: age, sex, comorbidities, medications, smoking status, primary malignancy treated by radiotherapy, radiotherapy type (external beam radiation therapy, intensity-modulated radiation therapy, image-guided radiation therapy or brachytherapy), dose in Gray (Gy) and fraction, complications and interventions.

Complications were divided into subcategories (hemorrhagic cystitis, fistula, stricture). Data on management were divided into non-operative and operative. Routine postoperative care was provided to patients who underwent surgical intervention.

## **Results:-**

### **Demographic data**

The mean (IQR) age of patients in the study was 59.76 (57 – 65) years. Out of 30 patients, 23 (76.66%) were females and 7 (23.33) were males.

Ca cervix was the most common indication of radiotherapy in 20 (66.66%) patients followed by ca prostate in six (20%), ca rectum in two (6.66%), ca vulva in one and vaginal rhabdomyosarcoma in one patient (3.33%).

The mean(range) duration of presentation after radiotherapy was 11.96 years (3- 18years). The main mode of radiotherapy was external beam radiation therapy (EBRT) in 28 (93.33%) patients. One patient received EBRT with brachytherapy and one received EBRT with IMRT. The median dose per fraction (IQR) was 2 (2) Gy per fraction. The median number of fractions (IQR) of radiation therapy was 25 (20 – 31.25) and the median total dose (IQR) was 50 Gy (40 – 70.50 Gy). (**table 1 and fig 1 here**)

### **Radiotherapy Complications and management**

The commonest complication was radiation-induced hemorrhagic cystitis which was present in 15 (50%) of patients. Next common complication was a stricture which was present in 10 (33.33%) patients (six patients of urethral stricture and four of ureteral stricture). Five (16.66%) patients had a vesicovaginal fistula.

Nineteen patients (63.33%) required surgical intervention. Some patients required minor procedures like percutaneous nephrostomy insertion and DJ stent insertion before the definitive surgical procedure.

Seven (23.33%) patients underwent cystourethroscopy with clot evacuation and electrocoagulation, which was the most commonly performed procedure. In eight patients, hematuria settled with conservative medical management and bladder irrigation.

Six (20%) patients underwent ileal conduit for the small capacity urinary bladder. Cystectomy with ileal conduit and vesicovaginal fistula repair was performed in three (10%) patients each. Augmentation cystoplasty was done in one of the patients along with VVF repair.

One (3.33%) patient of ureteric stricture underwent boari flap reconstruction which led to the development of ureterocolic fistula in the postoperative period. She was reexplored and transureteroureterostomy with colostomy was done.

(table 2 and fig 2 here)

### **Discussion:-**

Radiotherapy is a common treatment modality for the management of pelvic malignancies. Treatment for prostate, bladder, rectal, and cervical cancers often involve radiotherapy as definitive management with or without surgery and chemotherapy. Although radiotherapy-planning techniques can deliver high-energy radiation directly to the tumor, the surrounding organs like distal ureters, bladder and urethra usually receives some of the doses of radiation. This is responsible for acute and late radiation-related side effects like radiation-induced hemorrhagic cystitis, stricture disease, fistula formation etc. In the present study, we studied the demography, various presentations of radiotherapy related late urological complications and management done in our tertiary care institute over a period of two years.

In our study, 23 patients were female (76.66%) and cervical carcinoma was the most common primary diagnosis in 20(66.66%) patients with a mean age of presentation 59.76 years. This is in contrast to the studies done in western countries where carcinoma prostate was the most common primary diagnosis and the majority of patients were male. In a study by Joyce L. Ma et al [6] the majority of patients were males with a primary diagnosis of carcinoma prostate. The high incidence of cervical carcinoma in India may be responsible for this variation in demographic profile [7].

The mean duration of presentation after radiotherapy was 11.96 years in the present study. It is well documented that radiotherapy changes can remain asymptomatic for a long time. Pellerin et al. [8] studied 39 cases of genitourinary complications after abdominopelvic radiotherapy and found similar findings. The response of the urinary bladder, ureter and urethra to radiation treatment can be classified into acute or subacute reactions that occur within three to six months of treatment and late reactions that occur after six months to many years. Direct urothelial injury is responsible for acute radiation-induced toxicity, while radiation-induced vascular endothelial damage leading to obliterative endarteritis is responsible for late tissue injury. Vascular ischaemia, oedema, and cellular destruction causes the replacement of bladder smooth muscle fibres with fibroblasts and lead to increased collagen deposition and a subsequent decrease in bladder compliance and capacity [9]. Unlike acute toxicities, late pathological changes are chronic and irreversible.

The development of radiation toxicity is directly related to the volume of tissue irradiated, total radiation dose, method of delivery, and fractionation schedule [10]. In the present study, the majority of patients had received EBRT (93.33%) in the past. Historically, conventional radiotherapy delivery techniques lacked precision, delivering a radiation dose to both the tumor site and normal surrounding tissues. Advances in radiotherapy like image guidance and intensity modulation have limited the radiation exposure to surrounding tissue however, the risk is not completely removed and toxicity may still occur. Many patients are cured of their cancer and had received radiotherapy before the introduction of these modern techniques and are at higher risk for radiation-induced surrounding organ complications.

The presentations of radiotherapy related late urological complications can be quite variable. Flannigan et al [11] has described 43 potential complications post-radiotherapy for carcinoma prostate. Fujikawa et al [12] also described various complications of radiotherapy in patients of carcinoma cervix treated with radiotherapy. These complications frequently required surgical intervention. In the present study surgical intervention was needed in 19(63.33%) patients. A similar type of surgical intervention rates ranging from 46.15% to 68% has been reported in various studies of radiotherapy related adverse events presenting in a tertiary care institute [11 – 15].

Radiation-induced hemorrhagic cystitis was the most common complication seen in 15 (50%) patients. It is a urological emergency, patients were admitted and stabilized, started with bladder irrigation via triple lumen foleys catheter and injectable tranexamic acid given. Blood transfusion was given when necessary. With conservative

management hematuria resolved in eight patients (53.33%). In seven (46.66%) patients hematuria didn't resolve with conservative management and cystourethroscopy, clot evacuation with electrocoagulation was done using bipolar cautery; which was the most commonly performed procedure in the present study. The mean amount of bladder clot in the conservative management group was 34 cc while it was 63 cc in the operative management group. One patient with intractable hematuria requiring cystoscopy with clot evacuation and fulguration twice and requiring five blood transfusion over a period of three days underwent cystectomy and ileal conduit. A study conducted by Ma JL et al on radiotherapy related complications showed 70% of patient presenting with radiation-induced hematuria with a 71.4% success rate with conservative management [6]. ( **fig 3, fig 4, fig 6 here**)

Strictures were the second most common complications. Six female patients had a urethral stricture. Three patients underwent ileal conduit because they were having a small capacity bladder and severe local fibrosis. The remaining three are on regular urethral dilatation. Although urethroplasty may have a higher success rate, this is not possible due to radiation-induced urethral damage. One of the patients who underwent supravescical diversion in the form of ileal conduit for small capacity bladder and urethral stricture had an anastomotic leak of bowel and ureteroileal anastomosis. She was reexplored and diversion ileostomy with bilateral PCN was done as there were dense adhesions in the abdomen. She died in the postoperative period due to sepsis.

Four patients had ureteric stricture which was located in the lower ureter. All the patients had malignancy excluded as a cause. They were initially managed with a diversion in the form of PCN insertion or DJ stenting. Two patients underwent ileal conduit as they had a concomitant small capacity bladder. One patient underwent left Boari flap reconstruction as she was having normal bladder capacity and in the postoperative period, she developed a uretero-colic fistula. She was reexplored and a transureteroureterostomy procedure was done. After 4 years she developed ureteric stricture in the contralateral lower ureter for which she is on regular DJ stent exchange. One patient had bilateral lower ureteric stricture for which bilateral retrograde pyelography with bilateral percutaneous nephrostomy was done. She was not fit for any major operative procedure and is on regular nephrostomy tube change. The overall incidence of radiation-induced ureteral stricture is reported to be 1.0%, 1.2%, 2.2%, 2.5%, and 3.3% at 5, 10, 15, 20, and 25 years, respectively with a mean latency period of 16.8 years [16]. In our study average duration of development of ureteric stricture after radiotherapy was 14.75 years. Though ureteric stricture is an uncommon complication of radiotherapy if undetected for a long time can lead to loss of renal function. Surgical treatment in the form of diversion or reconstruction remains the definitive long term treatment option for management [17].

Five patients had Vesicovaginal fistula, two of them underwent successful transabdominal fistula repair, one patient had transabdominal fistula repair with bladder augmentation. Omental interposition was done during fistula repair. Ileal conduit and cystectomy with ileal conduit were carried out in one patient each since they had severe local fibrosis and small capacity bladder. Vesicovaginal fistula is reported in 1- 10 % of patients following pelvic radiotherapy. Fistulas are the most difficult complications to manage due to radiation-induced local tissue damage. Not all patients are suitable for fistula repair. Urinary diversion is recommended when surgical reconstruction is not possible, fails or in the presence of a small contracted bladder [18]. In a study of radiation-induced genitourinary fistula by Bissada NK et al 10 out of 28 patients were suitable for fistula repair and was successful in nine patients. The remaining patients underwent supravescical diversion [19]. In a study by Pushkar DY et al 216 patients of radiation-induced vesicovaginal fistula underwent surgical treatment, cumulative closure rate of 80% was eventually achieved after four or more operations. The success rate was 48% after the first repair, 40 % after the second operation, 52% after the third operation and 35% after the fourth operation. These studies showed that careful assessment, proper patient selection, choice of appropriate surgical procedure is crucial for successful repair [20]. (**fig 5 here**)

Limitation of the present study include the short duration of study and the inclusion of late urological complications which may not reflect the true burden of radiation-induced urological complications; more long-term data are desirable.

### **Conclusions:-**

Complications of pelvic radiotherapy can manifest very late, are usually of irreversible nature and frequently needs surgical management. Radiation-induced hemorrhagic cystitis when severe and requiring multiple blood transfusions can require cystectomy. Ureteroileal anastomosis and bowel anastomosis done during conduit formation are prone to urinary and bowel leak. Ureteric strictures associated with small capacity contracted bladder are best

treated by urinary diversion. Fistula repair is associated with low success rates on a primary repair. Fistulas associated with a small contracted bladder and unhealthy vagina are best managed with an ileal conduit. Special precautions should be taken to deal with postoperative complications in these subgroups of patients.

Figures

Fig 1:- Primary indication of radiotherapy.

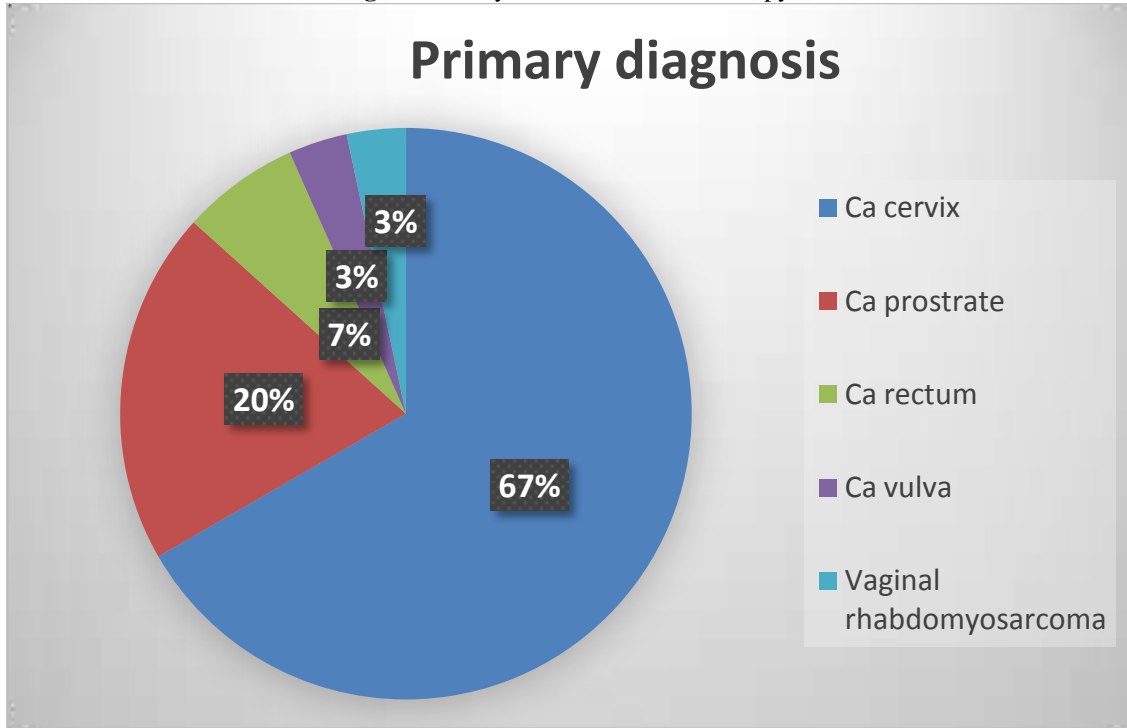
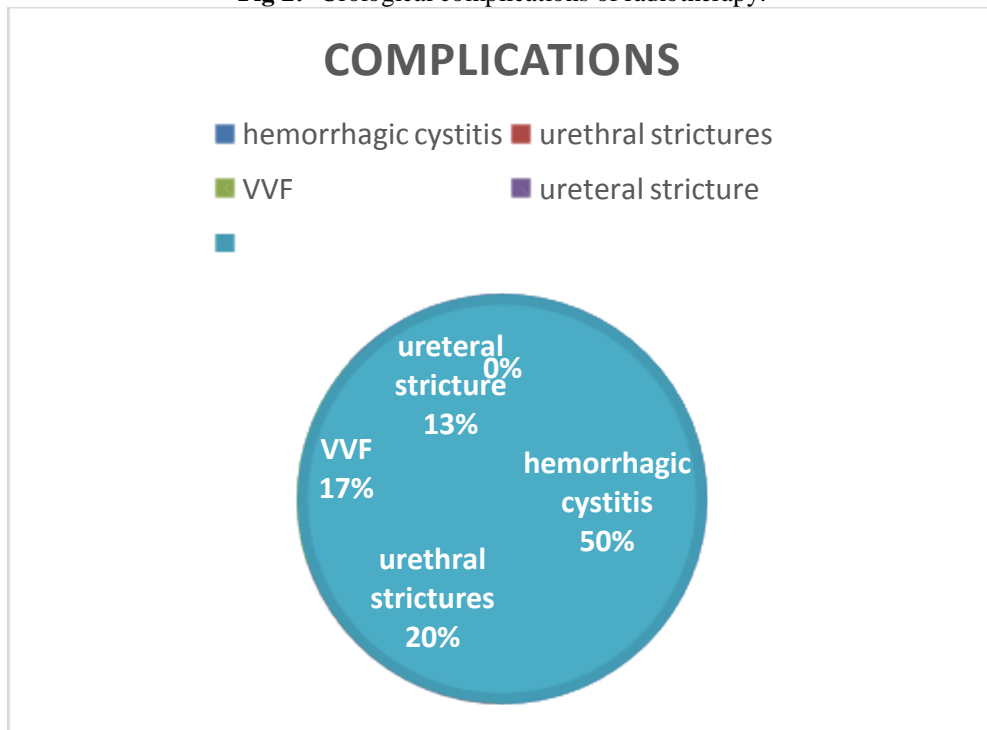


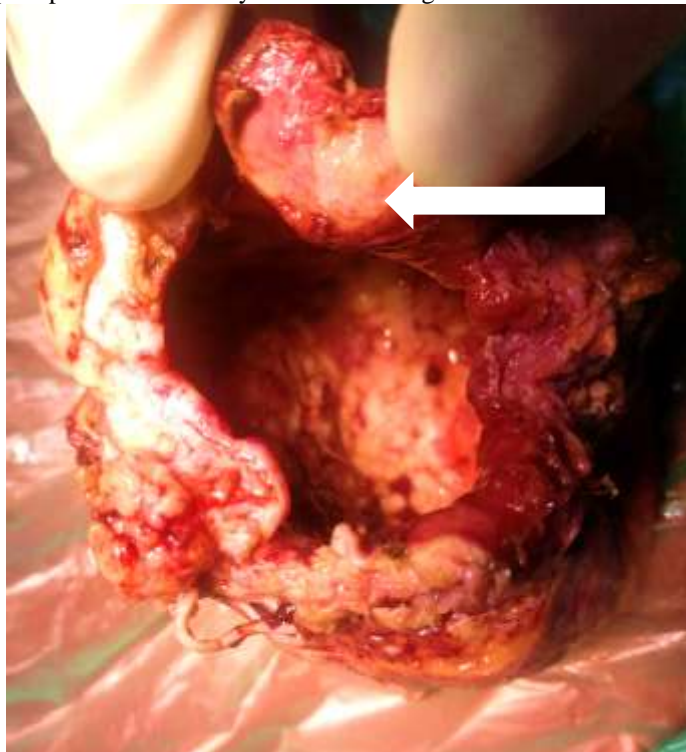
Fig 2:- Urological complications of radiotherapy.

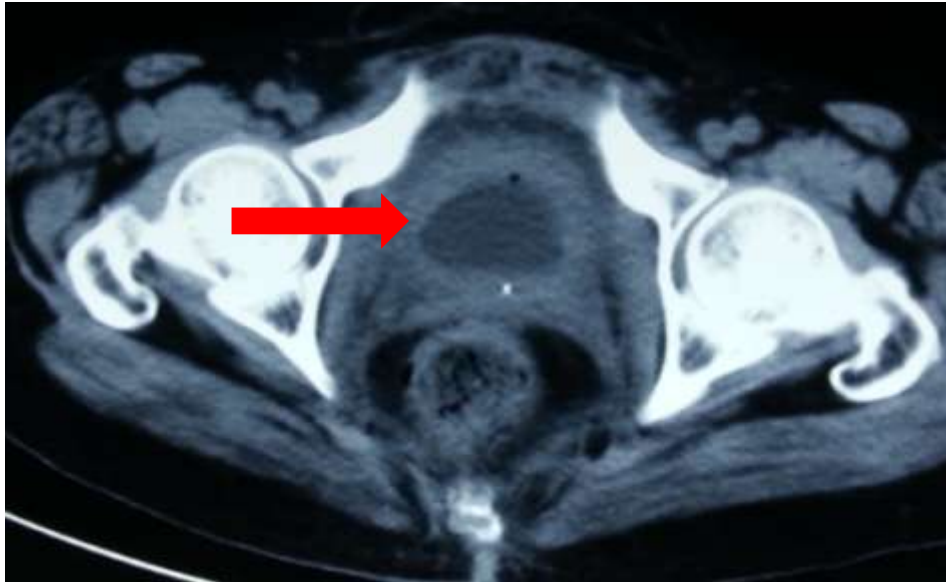


**Fig 3:-** Cystectomy specimen of contracted, low-capacity urinary bladder secondary to radiation induced hemorrhagic cystitis.



**Fig 4:-** Cut open specimen of urinary bladder showing thick and fibrosed wall (thick arrow).



**Fig 5:-** Severe local fibrosis in the area of introitus**Fig 6:-** Axial computed tomography showing contracted, small capacity, thick walled urinary bladder due to radiation (red arrow).**Tables****Table 1:-** Patient demography and radiotherapy details.

Total patients	30
Mean age (IQR), years	59.76 (57 – 65)
Male, n (%)	7(23.33)
Female, n (%)	23(76.66%)
<b>Primary malignancy</b>	n (%)
Ca cervix	20(66.66)
Ca prostate	6(20)
Ca rectum	2(6.66)
Ca vulva	1(3.33)

Vaginal rhabdomyosarcoma	1(3.33)
<b>Modality of radiotherapy</b>	<b>n (%)</b>
EBRT	28(93.33%)
EBRT with brachytherapy	1(3.33%)
EBRT with IMRT	1(3.33%)
Dose per fraction in Gy, median (IQR)	2(2)
No of fraction, median (IQR)	25(20 – 31.25)
Total dose in Gy, median (IQR)	50(40 – 70.50)

IQR = interquartile range, Ca = carcinoma, n = number of patients, EBRT = external beam radiotherapy, IMRT = intensity modulated radiotherapy

**Table 2:-** Radiotherapy induced complications and management.

<b>Complications</b>	<b>n (%)</b>
Radiation induced hemorrhagic cystitis	15(50%)
Urethral stricture	6(20%)
Ureteral stricture	4(13.33%)
Vesicovaginal fistula	5(16.66%)
<b>Management</b>	
Non-operative	11(36.66%)
Operative	19(63.33%)
Cystourethroscopy, clot evac sos coagulation	7(23.33%)
Ileal conduit	6(20%)
Cystectomy with ileal conduit	3(10%)
Vesicovaginal fistula repair	2(6.66%)
VVF repair with augmentation cystoplasty	1(3.33%)
Transureteroureterostomy	1(3.33%)

#### LIST OF ABBREVIATIONS

RTOG	Radiation Therapy Oncology Group
Gy	Gray
Ca	carcinoma
IQR	interquartile range
EBRT	external beam radiotherapy
IMRT	intensity modulated radiotherapy
VVF	vesicovaginal fistula

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