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Management of urethral stricture due to prostate cancer and colorectal cancer radiotherapy: A systematic review

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ABSTRACT

Background: Prostate and colorectal cancer are the second and third most common cancer in male. Radiotherapy is performed as treatment option for both cancers. Thus, lead to the increasing case of radiotherapy-induced urethral stricture. Recurrent stricture post-correction commonly occurs.

Methods: Six relevant English literatures were found throughout online database published between 2011-2017. PICO is used to identify components of clinical evidence to create systematic review. Subjects include 222 radiotherapy-induced urethral stricture patients due to prostate and colorectal cancer who undergone various treatment modality options.

Results: Radiotherapy modality performed in sample population were External Beam Radiotherapy (EBRT) (44.1%), Brachytherapy (BT) (31.5%), EBRT/BT (16.2%), Adjuvant EBRT (6.8%), salvage EBRT (0.9%), and proton beam (0.5%). Strictures were found in bulbomembranous-urethra (64.4%), bulbar-urethra (17.1%), posterior-urethra (10.8%), membranous-urethra (5.4%), vesico-urethra (1.4%), and pan-urethra (0.9%). Known mean onset for urethral-induced radiotherapy is 5.6 years. Treatment options include anastomosis urethroplasty (61.3%), Buccal Mucosa Graft Urethroplasty (23.4%), urolume stent (10.8%), penile island flap onlay (2.2%), Genital fasciocutaneous skin flap (1.4%), and perineal flap urethroplasty (0.9%). Known mean onset for urethral stricture recurrence is 10.8 months.

Conclusion: Urethral strictures commonly occur after radiation therapy for prostate and colorectal cancer. Urethroplasty is the preferable treatment option. The recurrence onset for urethral stricture post urethroplasty is shorter than urethral strictures in general.

Keywords: Prostate cancer, colorectal cancer, urethral stricture, radiation therapy, urethroplasty, stent

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INTRODUCTION

Prostate and colorectal cancer are the second and third most common cancer in male.[1,2] Prostate Cancer (PCa) affects approximately 30% of men with 233,000 new cases in 2014. In the other hand, Colorectal Cancer (CRC) is one of the deadliest cancer in United States, with estimated 70,820 new cases in male in 2016 (8% of all new cancer cases).

Radiotherapy (RT) has been established as a mainstay of treatment alongside surgery for both cancer.[2] RT can be delivered via proton beam therapy, external beam (EBRT) and/or brachytherapy (BT).[3] According to the Surveillance, Epidemiology and End Results database the distribution of these treatment options in men with newly diagnosed PCa is the following: RP, 36%; EBRT, 20%; BT, 10%; EBRT+BT, 4%.4 The 5-years survival rate for PCa patients after these therapies alone or in combination is almost 100% and 37% 5-years survival rate for CRC after EBRT were achieved at Princess Margaret Hospital.[5,7] Side effects associated with each treatment vary significantly, some patients treated with RT may suffer from long-term genitourinary side effects and significant quality of life impact.[6] Development of Urethral Stricture is a delicate problem that occurs in about 2% of patients undergoing EBRT, 4% for BT and 11% of EBRT-BT combination therapy which the bulbomembranous part of the urethra is most commonly involved.[4,8]

Radiation causes ionisation events and production of free radicals resulting in different types of DNA damage.[9,10,11,13] The consequential cell death is generally caused by improperly repaired DNA damage and/or the induction of apoptosis. Moreover radiation activates pro-inflammatory and pro-fibrotic cytokines leading to vascular injury and stem cell damage.[12] The tissue responds with features of failed wound healing like vascular atrophy leading to poorly oxygenated tissue and/or collagen deposition with eventual tissue scarring.[12,13] Pelvic radiation affects genitourinary tracts and presentation of the above mentioned pathophysiologic processes including strictures.[12]

There are several modalities of treatment that has been proposed for radiation-induced urethral strictures. The first decision that needs to be made is whether the stricture is amenable to excision and primary anastomosis (EPA), that found to be appropriate for the majority of radiation-induced

urethral strictures.[8] For more lengthy urethral strictures, substitution urethroplasty with grafts and flaps should be considered.[12] Another alternative option for radiation-induced urethral strictures is insertion of urethral stent that knows to be less invasive procedure for this condition. The recurrence rate after urethroplasty in these patients which has been reported to be as high as 30%, in comparison to the 16% recurrence rate of urethral strictures overall.[8,9] Moreover, due to its specific pathophysiology and high recurrence rate, the treatment of radiation-induced urethral strictures is very complex and demands some operative skills.

METHODS

Search Strategies

The search was performed in July 2019 in several online databases which published between 2011-2017, including ICUrology, Elsevier, American Urological Association Education and Research, Springer, Hindawi using the terms urethral stricture, prostatic cancer radiotherapy, and colorectal cancer radiotherapy. According to the PRISMA statement, titles, and abstract of the records retrieved were screened and the full texts of those considered relevant were analysed. To be included in this work studies had to be clinical trials in humans, present a true control group and report the number of patients who experienced urethral stricture at least 12 months after performing radiotherapy modalities (Brachytherapy, External beam radiotherapy, both brachytherapy and external beam radiotherapy, or proton beam) for prostate cancer and colorectal cancer. The exclusion criteria for this study were patient with non-radio therapy procedure and patient with another pelvic disease.

Data Extraction

Information was collected on the number of patients in each study, the age range, the radiotherapy modalities used for treating prostate cancer or colorectal cancer, the onset of urethral stricture after performing radiotherapy modalities along with the type of urethral stricture, the management used for treating the urethral stricture, and the recurrency onset of the urethral stricture.

RESULTS

Number of patients identified from 6 articles related to radiation-induced urethral stricture due to prostate and colon cancer published between 2011 and 2015 are 222 patients. It is found that 5 out of 6 articles mentioned urethroplasty procedures and only 1 article mentioned urolume stent as treatment. All 6 articles are compared in Table 1. Onset of occurring urethral stricture and its recurrency were mentioned in 5 out of 6 articles.

Hofer et al. recently demonstrated that radiotherapy-induced urethral strictures could be successfully managed with urethroplasty. Thus, they initiated this study in purpose of increased size and followed up in their multi-institutional cohort, and evaluated Excision and Primary Anastomosis (EPA) as treatment for radiotherapy-induced urethral strictures. 64 out of 66 patients identified in this study were radiotherapy-induced urethral stricture patients due to prostate cancer, while the other 2 were radiotherapy-induced urethral stricture patients due to colorectal cancer. Previous radiotherapy treatment performed was EBRT (28 patients), BT (28 patients), Combination of EBRT & BT (9 patients), and proton beam therapy (1 patient). After radiotherapy, 40 patients had urethral stricture on Bulbo-membranous urethra region while the other 26 patients had urethral stricture on Bulbar urethra region. Overall, 66 patients underwent EPA for the occurring radiation-induced urethral strictures and successful (recurrence-free) repair was achieved in nearly 70% at a mean follow up of 3.5 years. Mean onset of the first urethral stricture occurrence post-radiotherapy treatment on targeted population was 6.4 years, while the mean onset of urethral stricture recurrence post-therapy were 10.15 months. Recurrence stricture only affected 30,3% of targeted population.

To determine the success of urethroplasty for radiation-induced strictures, Meeks et al. performed a multi-institutional review of men who underwent urethroplasty for urethral obstruction in 2011. Thirty patients identified in this study were radiotherapy-induced urethral stricture patients due to prostate cancer. Previous radiotherapy treatment performed were EBRT (15 patients), BT (7 patients), and combination of EBRT & BT (8 patients). Urethral stricture on Bulbo-membranous urethra region was found on all patients after radiotherapy. For stricture treatment, 25 patients underwent EPA for occurring radiation-induced urethral strictures, while 3 patients underwent genital fasciocutaneous skin flap, and 2 patients underwent buccal graft urethroplasty as choice of treatment. Mean onset of the first urethral stricture occurrence post-radiotherapy treatment on targeted population was 9.3 years, while the mean onset of urethral stricture recurrence post-therapy was 5.1 months.

In order to report urethroplasty outcomes in men who developed urethral stricture after undergoing radiation therapy for prostate cancer, Glass et al. published their previous study in

Table 1 **Comparison of Radiation-Induced Urethral Stricture Articles and Management**

Author	Sample	Cancer	Age range (in years)	Type of Radiotherapy	Type of US	Onset of US (mean in years)	Management	Onset of Recurrency (mean in months)
Hofer et al. (2014)	66	Prostate: 64 Colorectal: 2	NR	• EBRT 28 • BT 28 • EBR/BT 9 • Proton beam 1	• Bulbar Urethral 26 • Bulmomembranous 40	6.4	• EPA: 66	10.15: 30,3%
Meeks et al. (2011)	30	Prostate: 30	43-79	• EBRT 15 • BT 7 • EBR/BT 8	• Bulbomembranous urethra 30	9.3	• EPA 25 • Genital fasciocutaneous skin flap 3 • BMGU 2	5.1 urethroplasty: 27% graft: 3%
Glass et al. (2012)	29	Prostate: 29	Mean: 69	• EBRT 11 • BT 4 • EBR/BT 7 • EBRT/RP 7	• Bulbar urethra 12 • Membranous urethra 12 • Vesico-urethra 3 • Pan-urethra 2	3.8	• EPA 22 • BMGU 5 • Perineal flap urethroplasty 2	12
Erickson et al. (2011)	24	Prostate: 24	Mean Adjuvan EBRT: (64.2) EBRT+Salvage P: (67.8) BT: (66,6) EBR+BT: (72,8)	• Adjuvant EBRT 8 • Salvage EBRT 2 • BT 8 • EBR/BT 6	• Posterior urethra 24	3.8	• Urolume Stent 24	7.4
Ahyai et al (2015)	38	Prostate: 35 colorectal: 3	Median: 70	• EBRT 24 • BT 8 • EBR/BT 6	• Bulbomembranous urethra 38	NR	• Ventral-onlay BMGU 38	19.3
Rourke et al. (2015)	35	Prostate: 35	43 - 81	• EBRT 20 • BT 15	• Bulbomembranous urethra 35	4,9	• EPA: 23 • BMG onlay: 7 • Penile island flap onlay: 5	NR

*Abbreviation: BT: Brachytherapy, EBRT: External Beam Radiotherapy, EBR/BT: External Beam Radiotherapy + Brachytherapy, RP: retropubic prostatectomy. EPA: Excision and Primary Anastomosis, BMGU: Buccal mucosa Graft Urethroplasty

2011. 29 patients identified in this study were radiotherapy-induced urethral stricture patients due to prostate cancer. Previous radiotherapy treatment performed was EBRT (11 patients), BT (4 patients), combination of EBRT & BT (7 patients), and combination of EBRT & RP (7 patient). Location for occurring stricture post-radiotherapy on 12 patients was found on bulbar urethra region, while 12 patients on membranous urethra region, 3 patients on vesico-urethra, and 2 patients on pan urethra. For stricture treatment, 22 patients underwent anastomosis urethroplasty for occurring radiation-induced urethral strictures, while 5 patients underwent buccal graft urethroplasty, and 2 patients underwent perineal flap urethroplasty as choice of treatment. Mean onset of the first urethral stricture occurrence post-radiotherapy treatment on targeted population was 3.8 years, while the mean onset of urethral stricture recurrence post-therapy was 12 months.

Since prostate cancer treatment has the potential to cause posterior urethral stricture, Erickson et al. reviewed their experience with urolume stent for prostate cancer treatment-related stricture. Twenty-four patients identified in this study were radiotherapy-induced urethral stricture patients due to prostate cancer. Previous radiotherapy treatment performed was adjuvant EBRT (8 patients), salvage EBRT (2 patients), BT (8 patients), and combination of EBRT & BT (6 patients). Location of occurring urethral stricture post-radiotherapy found on all patients was on posterior urethra. Urolume stent was placed on all patients as treatment choice for occurring urethral stricture post-radiotherapy. Mean onset of the first urethral stricture occurrence post-radiotherapy

treatment on targeted population was 3.8 years, while the mean onset of urethral stricture recurrence post-therapy was 7.4 months.

Ahyai et al. performed a research to evaluate stricture-free survival and functional outcomes of buccal mucosa graft urethroplasty in patients with urethral stricture disease post-radiotherapy. 35 out of 38 patients identified in this study were radiotherapy-induced urethral stricture patients due to prostate cancer, while the other 3 were radiotherapy-induced urethral stricture patients due to colorectal cancer. Previous radiotherapy treatment performed were EBRT (24 patients), BT (8 patients), and Combination of EBRT & BT (6 patients). Urethral stricture on Bulbo-membranous urethra region was found on all patients after radiotherapy. All patients underwent ventral-onlay BMGU for the occurring radiation-induced urethral strictures. Mean onset of the urethral stricture recurrence post-therapy on population were 19.3 months, while the mean onset of the first urethral stricture occurrence post-radiotherapy was not recorded.

Due to the fact that bulbomembranous stricture is a significant complication of radiotherapy for prostate cancer, Rourke et al. concluded a study in 2015 which has a purpose to report outcomes of urethroplasty for radiation-induced bulbomembranous urethral stricture. 35 patients identified in this study were radiotherapy-induced urethral stricture patients due to prostate cancer. Previous radiotherapy treatment performed was EBRT (20 patients) and BT (15 patients). Urethral stricture on Bulbo-membranous urethra region was found on all patients after radiotherapy. 23 patients underwent EPA for occurring radiation-induced urethral strictures, while 7 patients underwent Buccal Mucosa Graft (BMG) Onlay, and 5 patients underwent penile flap onlay as a choice of treatment. Mean onset of the first urethral stricture occurrence post-radiotherapy treatment on targeted population was 4.9 years, while the mean onset of urethral stricture recurrence post-therapy was not recorded.

DISCUSSION

Radiotherapy modality performed in 222 sample population were External Beam Radiotherapy (EBRT) (44.1%), Brachytherapy (BT) (31.5%), EBRT/BT (16.2%), Adjuvant EBRT (6.8%), salvage EBRT (0.9%), and proton beam therapy (0.5%). Strictures were found in bulbomembranous urethra (64.4%), bulbar urethra (17.1%), posterior urethra (10.8%), membranous urethra (5.4%), vesico-urethra (1.4%), and pan-urethra (0.9%). Known mean onset for urethral-induced radiotherapy is 5.6 years. Treatment options include EPA or Excision and Primary Anastomosis (61.3%), Buccal Mucosa Graft Urethroplasty (23.4%), urolume stent (10.8%), penile island flap onlay (2.2%), Genital fasciocutaneous skin flap (1.4%), and perineal flap urethroplasty (0.9%). Known mean onset for stricture recurrency is 10.8 months

CONCLUSION

Urethral stricture commonly occurs after radiotherapy in prostate and colorectal cancer. Urethroplasty is the most preferred treatment option. The onset of recurrent stricture is shorter than the previous one.

RECOMMENDATION

We recommend that future studies focused on comparing radiotherapy technique also need to be done to provide more precise data to determine which technique mostly cause radiotherapy-induced urethral stricture as major risk factor. We also recommend to focus on patients treated only with radiotherapy and include complications of radiation-induced urethral stricture management.

CONFLICT OF INTEREST

The author declares there is no conflict of interest regarding publication of current article.

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AUTHOR CONTRIBUTIONS

S.S. conceived of the presented idea, performed data analysis as well as the interpretation, and responsible for the final approval of the version to be published. ;M.A.S.L. developed the theory and drafting the article; K.O.R. performed data collection and verified the analytical methods. All authors discussed the results and contributed to the final manuscript.

REFERENCES

1. Pernar CH, Ebot EM, Wilson KM, Mucci LA. The epidemiology of prostate cancer. Cold Spring Harb Perspect Med. 2018;8(12):pii.a030361.
2. Matthias F. Harner, Jurgen Debus. Radiotherapy for Colorectal Cancer: Current Standards and Future Perspectives. Visc Med. 2016;32(3):172-177.
3. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol. 2014;65:467-79.

4. Herschorn S, Elliott S, Coburn M, Wessells H, Zinman L. SIU/ ICUD Consultation on Urethral Strictures: Posterior urethral stenosis after treatment of prostate cancer. Urology 2014;83(3 Suppl):S59-70.
5. Cummings BJ, Rider WD, Harwood AR, et al. Radical external beam radiation therapy for adenocarcinoma of the rectum. Dis Colon Rectum. 1983;26:30-36.
6. Viswanathan AN, Yorke ED, Marks LB, Eifel PJ, Shipley WU. Radiation dose-volume effects of the urinary bladder. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S116-22.
7. Hudson SV, O'Malley DM, Miller SM. Achieving optimal delivery of follow-up care for prostate cancer survivors: improving patient outcomes. Patient Relat Outcome Meas. 2015;6:75-90.
8. Hofer MD, Zhao LC, Morey AF, et al. Outcomes after urethroplasty for radiotherapy induced bulbomembranous urethral stricture disease. J Urol. 2014;191:1307-12.
9. Elliott SP, McAninch JW, Chi T, et al. Management of severe urethral complications of prostate cancer therapy. J Urol 2006;176:2508-13.
10. Marley AR, Nan H. Epidemiology of Colorectal Cancer. Int J Mol Epidemiol Genet. 2016;7(3):105-114.
11. Mohler JL, Kantoff PW, Armstrong AJ, et al. Prostate cancer, version 2.2014. J Natl Compr Canc Netw 2014;12:686-718.
12. Hofer MD, Gonzalez CM. Management of radiation-induced urethral strictures. Transl Androl Urol. 2015;4(1):66-71.
13. Moltzahn F, Pra AD, Furrer M, Thalmann G, Spahn M. Urethral strictures after radiation therapy for prostate cancer. Investig Clin Urol. 2016;57:309-315.