Bacterial Urinary Tract Infection after Transrectal Placement of Fiducial Markers prior to Proton Radiotherapy for Prostate Cancer

William M. Mendenhall, MD[1]; Gabriella Glassman, BS[1]; Christopher G. Morris, MS[1]; Joseph A. Costa, DO[2]; Christopher R. Williams, MD[2]; Stephanie E. Harris, MD[2]; Stephen E. Mandia, MD[2]; Bradford S. Hoppe, MD[1]; Randal H. Henderson, MD[1]; Curtis M. Bryant, MD[1]; R. Charles Nichols, MD[1]; and Nancy P. Mendenhall, MD[1]

[1]University of Florida Health Proton Therapy Institute, Jacksonville, FL, USA
[2]Department of Urology, University of Florida College of Medicine, Jacksonville, FL, USA

Abstract

Purpose: To determine the incidence of a bacterial urinary tract infection (UTI) necessitating hospitalization after transrectal placement of fiducial markers prior to proton radiotherapy (RT) for prostate cancer.

Materials and Methods: Six hundred sixty six patients returning for follow up after proton RT consented to participate in this institutional review board (IRB) approved study. Patients were queried whether they required hospitalization within 1 month of transrectal placement of fiducial markers. Patients were treated with proton RT between August 2006 and December 2014. Median International Prostate Symptom Score (IPSS) was 7. Sixty four patients (9.6%) had diabetes, 9 patients (1.4%) had chronic obstructive pulmonary disease, 6 patients (0.9%) had prior bladder surgery, 7 patients (1.1%) had a transurethral prostatectomy within 3 months, and 549 patients (82.4%) had a course of antibiotics within 6 months. Fifty five patients (8.3%) were taking tamsulosin, 16 patients (2.4%) were taking finasteride, and 62 patients (9.3%) were taking saw palmetto. The interval between the most recent prostate biopsy prior to fiducial placement and fiducial marker placement was less than 6 months in 609 patients (91.4%). No patient had a prior recent rectal culture.

Results: Ten patients (1.5%) developed a bacterial UTI necessitating hospitalization after transrectal placement of fiducial markers. A bacterial UTI occurred in 3 (0.7%) of 440 patients treated from 2006 to 2012 and in 7 (3.1%) of 226 patients treated from 2013 to 2014. Univariate analysis of potential association of a bacterial UTI with the following parameters revealed: IPSS less than or greater than the median ($p=0.3400$), diabetes ($p=0.6099$), tamsulosin ($p=0.9999$), saw palmetto ($p=0.0093$), interval between prostate biopsy and placement of fiducials ($p=0.9999$), year of treatment ($p=0.0363$), and antibiotics within 6 months ($p=0.2233$). A bacterial UTI was observed in 4 (6.5%) of 62 patients who were taking saw palmetto versus 6 (1.0%) of 604 patients who were not taking this medication. The incidence of a bacterial UTI between 2006 and 2012 was 3 (0.7%) of 440 patients and from 2013 to 2014 was 7 (3.1%) of 226 patients. Multivariate analysis revealed that the likelihood of a bacterial UTI was increased in patients taking saw palmetto ($p=0.0044$) and those treated in 2013-2014 ($p=0.0303$).

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Corresponding author:
William M. Mendenhall, MD
2000 SW Archer Rd.
PO Box 100385
Gainesville, FL 32610-0385
Telephone: (352) 265-0287;
Fax: (352) 265-0759
Email: mendwm@shands.ufl.edu

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Conclusion: The incidence of a bacterial UTI requiring hospitalization after transrectal placement of fiducial markers prior to proton RT was 1.5% and was impacted by taking saw palmetto and year of treatment. Patients treated during 2013 and 2014 had a significantly higher risk of a bacterial UTI requiring hospitalization.

Keywords: prostate cancer; fiducial markers; urinary tract infection

Introduction

Transrectal placement of fiducial markers into the prostate prior to image-guided radiotherapy (RT) is frequently employed to optimize beam alignment [1–5]. A potentially serious complication of this procedure is a bacterial urinary tract infection that can result in sepsis requiring hospitalization and, in a worst case scenario, death.

There are relatively few data relating to the risk of this complication after transrectal placement of fiducial markers so that most of the relevant data pertain to transrectal ultrasound guided prostate biopsy [1]. Herein we report our experience in men treated with proton beam RT for prostate cancer at our institution.

Materials and Methods

Between August 2006 and December 2014, 3556 men were treated with proton beam RT for prostate cancer at the University of Florida Health Proton Therapy Institute. With institutional review board approval, patients returning for follow up after completing treatment were asked whether they would be willing to participate in this study. If they consented, they were asked whether they required hospitalization within one month of transrectal placement of the fiducial markers prior to RT. Six hundred sixty six men (18.7%) were included in the study. Patient characteristics are depicted in **Table 1**.

Typically, four fiducial markers were placed into the prostate employing a transrectal approach prior to obtaining treatment planning computer tomography and magnetic resonance imaging [3]. Patients received a 3 day course of levofloxacin 500 mg daily beginning the day before the procedure. They were asked to use an enema three hours before the fiducial placement. No patient had a rectal culture prior to the procedure to direct selection of the optimal antibiotic for infection prophylaxis. The median IPSS was seven. The majority of patients had a prostate biopsy and/or a course of antibiotics within 6 months of

Table 1. Patient characteristics (666 patients).

Parameters	No. of patients (%)
Treatment year	
2006 to 2010	202 (30.3%)
2011 to 2012	238 (35.7%)
2013 to 2014	226 (34.0%)
No. of fiducial markers	
3	25 (3.8%)
4	638 (95.8%)
≥5	3 (0.4%)
International Prostate Symptom Score	
Median, 7	
<Median	332 (49.8%)
≥Median	334 (50.2%)
Interval between prostate biopsy and fiducials	
<6 months	609 (91.4%)
≥6 months	57 (8.6%)
Antibiotics within 6 months	549 (82.4%)
Diabetes	64 (9.6%)
Chronic obstructive pulmonary disease	9 (1.4%)
Tamsulosin	55 (8.3%)
Finesteride	16 (2.4%)
Saw Palmetto	62 (9.3%)

Table 2. Univariate analysis of urosepsis (666 patients).

Parameters	P-value
International Prostate Symptom Score: < vs ≥ median	0.3400
Diabetes: yes vs no	0.6099
Tamsulosin: yes vs no	0.9999
Saw Palmetto: yes vs no	0.0093
Interval between biopsy and fiducials: < vs ≥6 mo	0.9999
Antibiotics within 6 months: yes vs no	0.2233
Time period: 2006 to 2012 vs 2013 to 2014	0.0363

fiducial placement. A small subset of patients were taking tamsulosin, finasteride, and/or saw palmetto. Six patients (0.9%) had prior bladder surgery and 7 patients (1.1%) had a transurethral prostate resection within 3 months.

Results

Ten (1.5%) of 666 patients developed an apparent bacterial UTI requiring hospitalization after fiducial marker placement. The time interval between fiducial marker placement and hospitalization was 1 day (2 patients), 2 days (5 patients), 3 days (2 patients), and 7 days (1 patient). Urine cultures revealed a bacterial infection in 7 patients, negative in 2 patients, and no data in 1 patient. Blood cultures were positive in 4 patients, negative in 4 patients, and no data was available in 2 patients. The offending organism was *Escherichia coli* (E. coli) in 7 patients and *Klebsiella pneumoniae* in 1 patient. Resistance to the following antibiotics was observed: ampicillin, 6 patients; ciprofloxacin, 4 patients; levofloxacin, 3 patients; trimethoprim/sulfamethoxazole, 2 patients; gentamicin, 1 patient; cefazolin, 1 patient; cefepime, 1 patient; ceftriaxone, 1 patient; and ceftazidime, 1 patient. The results of a univariate analysis of parameters that could impact the likelihood of developing a bacterial UTI is depicted in **Table 2**. Multivariate analysis of these parameters is shown in **Table 3**. The incidence of a bacterial UTI was 6 (1.0%) of 604 patients not taking saw palmetto versus 4 (6.5%) of 62 patients who were taking saw palmetto. The incidence of a bacterial UTI was 3 (0.7%) of 440 patients between 2006 and 2012 and increased to 7 (3.1%) of 226 patients during 2013 and 2014.

Because some patients may develop a bacterial UTI after returning home after placement of the fiducial markers, we do not have reliable data pertaining to results of blood or urine cultures that may have been obtained or the identity of offending organism in all 10 patients.

Discussion

Although the transrectal placement of fiducial markers allows for more precise beam alignment, and thus more conformal fields when treating patients with prostate cancer with RT, there is a modest risk of a major complication including a bacterial UTI that may result in sepsis. The risk of bacterial urinary tract infection after transrectal fiducial placement as well as after transrectal prostate biopsy is depicted in **Table 4 and 5** [6–18]. The incidence of a bacterial UTI has been rising in recent years likely due to the increasing prevalence of E. coli resistant to flouroquinolones (FQ) that may be detected in rectal cultures in 13% to 22% of patients [15, 19–22]. Indeed our data indicate that the risk of a bacterial UTI resulting in hospitalization increased in 2013-2014 compared with patients treated from 2006 to 2012. There are data indicating that patients who have

Table 3. Multivariate analysis of urosepsis (666 patients).

Parameters	P-value
International Prostate Symptom Score: < vs ≥ median	0.2806
Diabetes: yes vs no	0.2758
Tamsulosin: yes vs no	0.2444
Saw Palmetto: yes vs no	0.0044
Interval between biopsy and fiducials: < vs ≥6 mo	0.6337
Antibiotics within 6 months: yes vs no	0.1647
Time period: 2006 to 2012 vs 2013 to 2014	0.0303

Table 4. Incidence of bacterial UTI after transrectal fiducials.

Author	Institution	No. of patients (dates)	Antibiotic prophylaxis	UTIs
Berglund et al [6]	Cleveland Clinic	50 (2008-2010)	Cipro	10%
Langenhuijsen et al [7]	University of Nijmegen	209 (2001-2005)	Cipro	1.9%
Igdem et al [8]	Istanbul Bilim University	135 (2005-2008)	Cipro	2.2%
Linden et al [9]	Jefferson University	98 (2003-2006)	Quinolones	0%
Brown et al [10]	Princess Alexandra Hospital	20 (2007)	Trimethoprim	5%
Thompson et al [11]	Peter McCallum Cancer Center	28 (2007)	Cipro	0%
Kably et al [12]	University of Miami	75 (2010-2013)	Cipro	2.7%
Loh et al [13]	Calvary Mater Newcastle Hospital	285 (2012-2013)	Quinolones	2.8%*

Abbreviation: UTI, urinary tract infection.

*Required hospitalization.

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had a prior prostate biopsy may be at an increased risk of developing this complication [1]. Thus, essentially all patients undergoing transrectal placement of fiducial markers are at an increased risk because all have had at least one transrectal ultrasound guided prostate biopsy to diagnose prostate cancer. Additionally, a recent course of antibiotics may increase the risk of urosepsis [1]. Because patients undergoing a transrectal prostate biopsy usually receive prophylactic antibiotics, a substantial proportion of patients undergoing placement of fiducials would have received antibiotics within 3 to 6 months of the procedure.

The reasons that saw palmetto might impact the likelihood of developing a bacterial UTI are unclear. One might postulate that patients with more urinary obstructive symptoms might have larger prostates and be more inclined to take this drug and that prostate volume might be related to this complication. However, we observed no difference in the risk of a bacterial UTI and IPSS.

There are several strategies that may be employed to reduce the risk of a severe bacterial UTI after placement of fiducial markers. These include empiric changes in the prophytactic antibiotic regimen, rectal cultures obtained prior to the procedure to direct the antibiotic prophylaxis, and deployment of the fiducuials through the perineum rather than rectal wall [1]. We have chosen to obtain a rectal culture at the time of initial consultation. If the culture reveals FQ resistant E. coli, the sensitivity of the bacteria to various antibiotics is determined and the prophylactic antibiotic regimen is modified accordingly. Patients who do not have FQ resistant E. coli receive a 3 day course of levofloxacin as previously described and intramuscular gentamicin 80 mg on the day of the procedure. We have also begun to employ the hydrogel SpaceOAR in eligible patients to reduce the RT dose to the anterior rectal wall. Eligible patients are those with low- and intermediate-risk prostate cancers and a prostate less than 100 cc. The SpaceOAR is deployed via the transperineal route and, during the procedure, the fiducial markers are placed into the prostate also using the transperineal route. These patients receive ciprofloxacin 500 mg twice daily for two days beginning the day before the procedure and undergo an enema 3 hours prior to deploying SpaceOAR and placement of fiducial markers.

Weaknesses of our study include that it is retrospective and the study population represents a subset of the overall patient population treated during that period. Patients included in the study were those who returned for a follow up evaluation so that those who elected not to return, or were unable to do so because of age or infirmity, would not have been included. These

Table 5. Incidence of bacterial UTI after transrectal prostate biopsy.

Author	Institution	No. of patients (dates)	Antibiotic prophylaxis	UTIs
Sanders and Buchan [14]	Christchurch Hospital	1421 (2010-2011)	Cipro	2.8% required hospitalization
Carignan et al [15]	Universite de Sherbrooke	5798 (2002-2011)	Cipro	0.83% sepsis
Campeggi et al [16]	Henri Mondor	3000 (2006-2009)	Quinolones	0.67% required hospitalization
Edhaie et al [17]	MSKCC	403 (2011-2012)	Quinolones +/- Gentamicin	3.2% required hospitalization
Patel et al [18]	The Prostate Centre- London	316 (2008-2010)	Cipro, Gentamicin, Metonidazole	5% required hospitilization

Abbreviation: UTI, urinary tract infection; MSKCC, Memorial Sloan Kettering Cancer Center.

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patients may have a different likelihood of developing urosepsis, possible higher, than the study population. Patients who were hospitalized often had returned to their community and hospitalized there and results of blood and/or urine cultures were not always available.

Conclusion

The incidence of a bacterial UTI necessitating hospitalization after transrectal placement of fiducial markers is low but is likely increasing due to development of multidrug resistant E.coli. Strategies to decrease the risk of developing this complication include empirical changes in the prophylactic antibiotic regimen, rectal culture and directed changes in the prophylactic antibiotics, and changing from transrectal to transperineal placement of fiducial markers. Although the transperineal approach should reduce the risk of a bacterial UTI there are not convincing data that support this assumption. However, a caveat is that most of the relevant data are 10 to 15 years old before the apparent increased risk of harboring FQ resistant E. coli in the rectum.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of interest: The authors have no conflicts of interest to disclose.

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