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

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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).
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%)           |
| Finasteride                                    | 16 (2.4%)           |
| Saw Palmetto                                   | 62 (9.3%)           |
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.

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 fluoroquinolones (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

| 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  |

| 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  |
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 prophylactic antibiotic regimen, rectal cultures obtained prior to the procedure to direct the antibiotic prophylaxis, and deployment of the fiducials 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 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.

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

| Author                 | Institution                    | No. of patients (dates) | Antibiotic prophylaxis | UTIs         |
|------------------------|--------------------------------|-------------------------|------------------------|--------------|
| Sanders and Buchanan [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, Metronidazole | 5% required hospitalization |

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

**References**

1. Mendenhall WM, Costa JA, Williams CR, Harris SE, Mandia SE, Hoppe BS, Henderson RH, Bryant CM, Nichols RC, Mendenhall NP. Bacterial Urinary Tract Infection after Fiducial Marker Placement or Prostate Biopsy. *Int J Particle Ther*. 2014;1:745–58.

2. Skarsgard D, Cadman P, El-Gayed A, Pearcey R, Tai P, Pervez N, Wu J. Planning target volume margins for prostate radiotherapy using daily electronic portal imaging and implanted fiducial markers. *Radiat Oncol*. 2010;5:52.

3. Mendenhall NP, Hoppe BS, Nichols RC, Mendenhall WM, Morris CG, Li Z, Su Z, Williams CR, Costa J, Henderson RH. Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2014;88:596–602.

4. Huisman HJ, Futterer JJ, van Lin EN, Welmers A, Scheenen TW, van Dalen JA, Visser AG, Witjes JA, Barentsz JO. Prostate cancer: precision of integrating functional MR imaging with radiation therapy treatment by using fiducial gold markers. *Radiology*. 2005;236:311–7.

5. Wu J, Haycocks T, Alasti H, Ottewell G, Middlemiss N, Abdolell M, Warde P, Toi A, Catton C. Positioning errors and prostate motion during conformal prostate radiotherapy using on-line isocentre set-up verification and implanted prostate markers. *Radiother Oncol*. 2001;61:127–33.

6. Berglund RK, Zaytoun O, Thousand R, Stephans K, Tendulkar R, Klein EA, Jones JS. Early infectious complications with transponder placement for external beam radiation therapy for prostate cancer. *BJU Int*. 2012;110:834–9.

7. Langenhuijsen JF, van Lin EN, Kiemeneij LA, van der Vught LP, McColl GM, Visser AG, Witjes JA. Ultrasound-guided transrectal implantation of gold markers for prostate localization during external beam radiotherapy: complication rate and risk factors. *Int J Radiat Oncol Biol Phys*. 2007;69:671–6.

8. Igdem S, Akpinar H, Alco G, Agacayak F, Turkan S, Okkan S. Implantation of fiducial markers for image guidance in prostate radiotherapy: patient-reported toxicity. *Br J Radiol*. 2009;82:941–5.

9. Linden RA, Weiner PR, Gomella LG, Dicker AP, Suh DB, Trabulsi EJ, Valicenti RK. Technique of outpatient placement of intraprostatic fiducial markers before external beam radiotherapy. *Urology*. 2009;73:881–6.

10. Brown S, Lehman M, Ferrari-Anderson J, Glyde A, Burmeister E, Nicol D. Assessment of prostatic fiducial marker introduction: patient morbidity, staff satisfaction and improved treatment field placement. *J Med Imaging Radiat Oncol*. 2011;55:417–24.

11. Thompson A, Fox C, Foroudi F, Styles C, Tai KH, Owen R, Laferlita M. Planning and implementing an implanted fiducial programme for prostate cancer radiotherapy. *J Med Imaging Radiat Oncol*. 2008;52:419–24.

12. Kably I, Bordegaray M, Shah K, Salsamendi J, Narayanan G. Single-center experience in prostate fiducial marker placement: technique and midterm follow-up. *J Vasc Interv Radiol*. 2014;25:1125–32 e1.

Mendenhall et al. (2016), *Int J Particle Ther*
13. Loh J, Baker K, Sridharan S, Greer P, Wraatten C, Capp A, Gallagher S, Martin J. Infections after fiducial marker implantation for prostate radiotherapy: are we underestimating the risks? *Radiat Oncol.* 2015;10:38.

14. Sanders A, Buchan N. Infection-related hospital admissions after transrectal biopsy of the prostate. *ANZ J Surg.* 2013;83:246–8.

15. Carignan A, Roussy JF, Lapointe V, Valiquette L, Sabbagh R, Pepin J. Increasing risk of infectious complications after transrectal ultrasound-guided prostate biopsies: time to reassess antimicrobial prophylaxis? *Eur Urol.* 2012;62:453–9.

16. Campeggi A, Ouzaid I, Xylinas E, Lesprit P, Hoznek A, Vordos D, Abbou CC, Salomon L, de la Taille A. Acute bacterial prostatitis after transrectal ultrasound-guided prostate biopsy: epidemiological, bacteria and treatment patterns from a 4-year prospective study. *Int J Urol.* 2014;21:152–5.

17. Ehdaie B, Vertosick E, Spaliviero M, Giallo-Uvino A, Taur Y, O’Sullivan M, Livingston J, Sogani P, Eastham J, Scardino P, Touijer K. The impact of repeat biopsies on infectious complications in men with prostate cancer on active surveillance. *J Urol.* 2014;191:660–4.

18. Patel U, Dasgupta P, Amoroso P, Challacombe B, Pilcher J, Kirby R. Infection after transrectal ultrasonography-guided prostate biopsy: increased relative risks after recent international travel or antibiotic use. *BJU Int.* 2012;109:1781–5.

19. Steensels D, Slabbaert K, De Wever L, Vermeersch P, Van Poppel H, Verhaegen J. Fluoroquinolone-resistant *E. coli* in intestinal flora of patients undergoing transrectal ultrasound-guided prostate biopsy—should we reassess our practices for antibiotic prophylaxis? *Clin Microbiol Infect.* 2012;18:575–81.

20. Minamida S, Satoh T, Tabata K, Kimura M, Tsumura H, Kurosaka S, Matsumoto K, Fujita T, Iwamura M, Baba S. Prevalence of fluoroquinolone-resistant *Escherichia coli* before and incidence of acute bacterial prostatitis after prostate biopsy. *Urology.* 2011;78:1235–9.

21. Liss MA, Peeples AN, Peterson EM. Detection of fluoroquinolone-resistant organisms from rectal swabs by use of selective media prior to a transrectal prostate biopsy. *J Clin Microbiol.* 2011;49:1116–8.

22. Qi C, Malczynski M, Schaeffer AJ, Barajas G, Nadler RB, Scheetz MH, Zembower TR. Characterization of ciprofloxacin resistant *Escherichia coli* isolates among men undergoing evaluation for transrectal ultrasound guided prostate biopsy. *J Urol.* 2013;190:2026–32.