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Biochemical control and toxicity for favorable- and intermediate-risk patients using real-time intraoperative inverse optimization prostate seed implant: Less is more!

G. Shukla[1], A. Sarkar[2], A. Hanlon[3], E. Crockett[2], H.C. Chen[2], J. Martelli-Raben[2], A. Glick[4], B. Benge[4], M. Lobis[4], S. Terranova[4], T. Desperito[4], D. Cozzolino[4], E. Kemmerer[2], F. Mourtada[1,2], A. Raben[2,*]

[1]*Department of Radiation Oncology, Thomas Jefferson University, Philadelphia, PA*
[2]*Department of Radiation Oncology, Helen F. Graham Cancer Center, Newark, DE*
[3]*School of Nursing, University of Pennsylvania, School of Nursing, Philadelphia, PA*
[4]*Brandywine Urology Consultants, Newark, DE*

ABSTRACT

PURPOSE: To report the biochemical control rate and clinical outcomes with real-time inverse planning (inverse optimization prostate seed implant [IO-PSI]) for favorable-risk (FR) and intermediate-risk (IR) prostate adenocarcinoma in a community practice setting. This analysis is an extended followup of our initial report, with favorable early biochemical control rate (biochemical nonevidence of disease) of 97% at 4 years.

METHODS AND MATERIALS: Three hundred fifty-seven evaluable patients with FR and IR prostate cancer underwent real-time IO-PSI (iodine-125/145 Gy or palladium-103/120 Gy) between 2001 and 2013.

RESULTS: With a median followup of 54 months (range, 24−110 months), the absolute biochemical failure free survival of disease was 96%. The 8-year actuarial probability of prostate-specific antigen failure-free survival for FR and IR cohorts was 92.4% and 87%, respectively. Late genitourinary and gastrointestinal toxicity remained low. Late Grade 2 and Grade 3 genitourinary toxicity was 19% and 1%, respectively. Late Grade 2 and 3 rectal bleeding rates were 1% and 0%, respectively. No difference in biochemical control was observed with preimplant short course androgen deprivation or between Gleason score 3 + 4 vs. 4 + 3 patients. No dosimetric parameter was predictive of biochemical failure. Patients with FR had a significantly decreased risk of failure (hazard ratio = 0.26; 95% confidence interval = 0.09−0.78; $p = 0.02$) compared with those with IR. Patients with a prostate-specific antigen nadir >0.4 ng/mL had an increased risk of failure (hazard ratio = 1.37; 95% confidence interval = 1.27−1.47; $p < 0.0001$).

CONCLUSIONS: Our initial biochemical and clinical outcomes using real-time IO-PSI persisted with extended followup and support our original hypothesis for use of a reduced number of sources, needles, and total activity, suggesting that with IO, less is more.

Keywords: Prostate cancer; Brachytherapy; Intraoperative; Biochemical control

Introduction

Prostate seed implant (PSI) brachytherapy developed into an accepted modality for treating localized favorable-risk (FR) and selected intermediate-risk (IR) prostate cancer during the early prostate-specific antigen (PSA) screening era, despite historical techniques derived from nomograms that lacked consistent qualitative dosimetric evaluation. Unfortunately, the utilization of this modality has been declining, especially in the community setting where the vast majority of patients receive treatment. This decline has been observed despite 15-year biochemical control rates of >85% in the early PSA screening era (1) and its relatively low cost as compared with intensity-modulated radiation therapy (IMRT)

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* Corresponding author. Department of Radiation Oncology, Helen F Graham Cancer Center, 4701 Ogletown-Stanton Road, Newark, DE 19713. Tel.: +1-302-623-4857; fax: +1-302-623-4850.

E-mail address: araben@christianacare.org (A. Raben).

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techniques (2) or proton therapy. Market and financial reimbursement incentives may be partly responsible for this trend, particularly in the United States. With the shifting health care reimbursement models on the horizon, efficient resource utilization may become more important than ever in the coming years.

In the modern PSA screening era, long-term (7–10 years of followup) biochemical control rates as high as 97% have been reported by high-PSI-utilization academic centers (3–5). Modern brachytherapists use sophisticated preoperative computer algorithms and techniques with either loose or stranded sources and either iodine-125 (^{125}I) or palladium-103 (^{103}Pd). Recently, long-term outcomes with intraoperative planned brachytherapy have been reported with 10 years of minimum followup time and biochemical nonevidence of disease (BNED) rates of 94% and 98% for IR and FR patients, respectively. These reports used a hybrid technique of peripheral loading, followed by a second optimization of the inner seed arrangement to achieve desired dosimetry (6). We were the first to report favorable dosimetric (7) and early clinical outcomes for biochemical control and toxicity (8) with a real-time inverse optimization PSI (IO-PSI) technique. Our IO-PSI methodology was derived from the concept of inverse planning IMRT, which showed improved conformality, the ability to deliver a differential dose distribution (dose painting), and reduced toxicity (9) but with the added opportunity to make real-time intraoperative adjustments in planning through computer dosimetric feedback. This ability to use preplan-based intraoperative optimization has been shown to confer dosimetric advantages in other institutions as well (10).

Although community programs have long been at the forefront of PSI brachytherapy, few community programs have reported long-term biochemical and clinical results with real-time IO-PSI. In some cases, academic institutions have earlier access to novel techniques and the infrastructure to test and implement such advances; community practices may thus lag behind the adoption of these approaches. Our initial dosimetric results were favorable, and our early clinical experience demonstrated promising actuarial biochemical control rates approaching 97% at 4 years, with low toxicity. We observed that using real-time inverse optimization (IO) allowed us to reduce the number of needles, number of seeds, and total activity required to achieve a high-quality implant, which we confirmed on postimplant dosimetric evaluation, thus resulting in less trauma and a reduction in sustained side effects and complications. We sought to confirm their persistence over longer followup, which is the purpose of the present report. We propose that our results may provide an example of a successful PSI program in the community setting, a tool that may become ever more important as the landscape of health care delivery continues to evolve.

Methods and materials

Patients (N = 491) with primarily either low-risk (FR) or low IR prostate cancer, as defined by the National Comprehensive Cancer Network guidelines, underwent PSI alone by a single brachytherapist using real-time IO with ultrasound guidance with either loose uncoated or coated ^{125}I or ^{103}Pd sources. A minority of selected patients with intermediate (Gleason score 3 + 4 ± >5/12 positive biopsy cores) or high intermediate (Gleason score 4 + 3 ± >5 positive biopsy cores, PSA >10) or favorable high risk (Gleason scores 8 and 9) were also implanted without supplemental IMRT. Details of our IO technique, dosimetry, and dosimetric objectives are described previously (7), as are our clinical techniques (8). Postimplant CT-based dosimetric analysis was performed on every patient, generally between 4 and 5 weeks after the implant. For the purpose of this study, only patients with a minimum of 2 years of followup time were included (N = 357). Biochemical failure was defined using the Radiation Therapy Oncology Group (RTOG)-Phoenix definition of PSA nadir of 2 ng/mL. Late toxicity was scored using the RTOG scoring assessment tool.

As previously reported, total implanted activity in megabecquerels, number of needles, number of seeds implanted, and seed strength were recorded. Dosimetry for the optimized intraoperative plan (day of prostate implant [D0] and postimplant CT [D30]) was recorded. Baseline gastrointestinal (GI), genitourinary (GU), and sexual symptoms were recorded before implant using International Prostate Symptom Score (IPSS; range, 0–35) and Sexual Health Inventory for Men (SHIM; range, 0–25) surveys, which incorporated questions about GI symptoms and side effects. GU and GI toxicity were prospectively recorded and updated at each followup visit or through mailed IPSS and SHIM surveys. Preimplant and postimplant IPSS scores were recorded and compared to objectively evaluate the effect of implant on lower urinary obstructive symptoms, with higher scores indicating increased symptoms. Postimplant IPSS scores were obtained at each followup visit, with the reported scores from the most recent appointment. SHIM >20 was considered normal or near-normal sexual function.

Patient characteristics, dosimetric parameters, and measures of toxicity were described using medians, interquartile ranges, frequencies, and percentages. Biochemical failure–free survival (BFFS) was estimated using Kaplan–Meier methodology with comparisons accomplished using log-rank statistics. To assess the individual impact of various patient characteristics and dosimetric parameters on survival time in this patient population, univariate Cox proportional hazards models were examined. Because of the limited number of biochemical events, multivariable modeling was not possible. Overall uncertainty of variables examined was lower than 3%. Statistical significance was taken at the 0.05 level and did not account for multiplicity.