Stereotactic body radiation therapy with simultaneous integrated boost for prostate cancer: does MRI-targeted biopsy alter the boost field?

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Introduction: *We aim to investigate if the addition of MRI-US fusion biopsy (FB) can aid in radiation planning and alter the boost field in cases of stereotactic body radiation therapy (SBRT) for prostate cancer with a simultaneous integrated boost (SIB) to a magnetic resonance imaging (MRI)-defined intraprostatic lesion.*
Materials and methods: *Patients undergoing SBRT with SIB for biopsy-proven prostatic adenocarcinoma and a pre-radiation MRI were retrospectively reviewed. 36.25 Gy in 5 fractions was delivered to entire prostate along with SIB of 40 Gy to an MRI-defined intraprostatic lesion. Demographic, radiation planning details, and post-procedural outcomes were compared between patients undergoing systematic transrectal ultrasound (TRUS) biopsy followed by MRI to those undergoing an MRI followed by a FB prior to radiation planning.*
Results: *Forty-three patients underwent systematic TRUS biopsy followed by MRI and 46 patients underwent FB prior to radiation planning. Patients undergoing systematic TRUS biopsy had a smaller prostate volume when compared to the FB cohort (37.58 ± 13.78 versus 50.28 ± 26.76 cc, p = 0.007). No differences in prostate planning target volume (PTVprostate) and boost volume (PTVboost) were noted, but those undergoing TRUS biopsy prior to MRI had a higher integrated boost volume density (IBVD = PTVboost/total prostate volume) (0.16 ± 0.09 versus 0.13 ± 0.06, p = 0.045). No differences were observed in genitourinary or gastrointestinal toxicity rates.*
Conclusions: *Compared to systematic TRUS biopsy, implementation of prebiopsy prostate MRI and FB allows for safe and feasible SBRT in patients with significantly larger prostate volumes without increasing SIB cancer-directed treatment volumes, oncologic outcomes, quality of life measures, or treatment-related toxicities.*

Key Words: prostate cancer, MRI fusion biopsy, transrectal ultrasound

Introduction

External beam radiation therapy (EBRT) has long been a treatment option with curative intent for clinically-localized prostate cancer.[1] In order to increase the efficacy of EBRT for higher grade prostate cancer and reduce the risk of relapse and post-treatment side effects, dose escalation and hypofractionation are continually being explored as further modifications. Multiple studies have demonstrated that while dose escalation reduces relapse rates, it also raises the risk of high-grade toxicity.[2-4] Alternatively, selectively increasing the dose of radiation to an area of interest is also being examined. The slow proliferation rate, α/β ratio, of prostate cancer has been found to be at least equivalent or lower than that of its surrounding

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tissues.[5] To take advantage of the α/β ratio, stereotactic body radiotherapy (SBRT) approach utilizes extremely hypofractionated regimens to deliver image-guided radiation doses to areas of suspected malignancy. Focal escalation of radiation has the potential to achieve similar oncologic benefit as whole gland dose escalation, but with a lessened toxicity risk.[6]

Over the last several years, magnetic resonance imaging (MRI) has had an increasing role in the diagnosis and work up of prostate cancer due to its ability to detect clinically-significant cancers.[7-9] Capitalizing on the advantages of MRI, several studies have demonstrated that a simultaneous integrated boost (SIB) to an MRI-defined area of interest during prostate SBRT is a safe and feasible approach.[6,10-12] Furthermore, the addition of MRI-transrectal ultrasound (TRUS) fusion-targeted biopsy (FB) protocols have also further aided in the work up of prostate cancer by increasing the detection of higher-grade foci of prostate cancer, while decreasing the detection of low-grade cases.[13] Several studies have also demonstrated that FB led to upstaging of men with prostate cancer to higher risk groups that ultimately led them to pursue more aggressive radiation treatment plans.[14-16]

Therefore, we aim to assess the addition of FB to our clinical experience with whole prostate SBRT with a focal SIB. We hypothesize that patients undergoing FB will have smaller relative SIB volumes compared to the total prostate volume due to biopsy confirmation of imaging regions of interest compared to patients who underwent only systematic TRUS biopsy and post biopsy MRI only for radiation planning.

Materials and methods

After approval from our institutional review board, a retrospective review of all patients who underwent SBRT for pathologically proven prostate adenocarcinoma at our institution was performed. All patients at our institution who undergo SBRT for treatment of primary prostate cancer standardly have an MRI-derived SIB performed concurrently if eligible to undergo MRI. All patients had a pelvic MRI performed within 6 months prior to the start of radiation therapy. Exclusion criteria included a history of inflammatory bowel disease, previous transurethral procedures, current antiplatelet therapy besides 81 mg aspirin daily, immunosuppressant use, and tumor involvement > 50% of the prostate volume as determined on MRI.

Patients either underwent a TRUS-guided systematic extended sextant 12-core biopsy followed by an MRI or an MRI followed by a FB prior to radiation treatment planning. The MRIs were examined at a multidisciplinary prostate imaging conference consisting of fellowship-trained urologic oncologists and radiologists.[17] Eligible patients were offered SBRT and their informed consent obtained. The prostate planning target volume ($PTV_{prostate}$) and boost planning target volume (PTV_{boost}) were determined in a multidisciplinary fashion between the urologic oncologist and radiation oncologist managing the case. The PTV_{boost} was defined as a 5-mm margin around the dominant lesion(s) seen on MRI (specifically noted as a hypointense region on T2-weighted MRI corresponding to extended sextant location with systematic biopsy sampling proof of cancer for the patients in the systematic biopsy cohort or the alternatively entire MRI lesion targeted for cases of FB); however, a 3 mm margin was used posteriorly. Additionally, PTV_{boost} was limited to less than 50% of the prostate volume. The $PTV_{prostate}$ was defined as the remaining prostate treatment volume with the same expansion margins and was edited so as not to overlap PTV_{boost}. Prostate volumes were calculated based on MRI using the 3-dimensional gland segmentation tool on the DynaCad post-image processing software (Philips/InVivo Corp, Gainesville, FL, USA). Once there was consensus on the prostate gland segmentation and the intraprostatic regions of interest for the SIB, the patients proceeded to SBRT simulation and treatment.

Three gold fiducial markers were implanted into the prostate under TRUS guidance by the urologic oncologist. A computed tomography (CT) scan was performed with a patient in a supine position. The patient's bladder was full and rectum emptied prior to simulation imaging. The MRI images were then fused with the CT. The radiation oncologist and urologic oncologist then determined intraprostatic lesion of interest, the prostatic volume, prostatic anatomy, and at-risk organs. Radiation planning goals were set as previously described.[7,15] 36.25 Gy was delivered to the $PTV_{prostate}$ and 40 Gy to the PTV_{boost} simultaneously in 5 fractions on nonconsecutive days with the entire treatment course being completed within 17 days. Orthogonal kilovoltage X-rays and a cone-beam CT scan were used to align the patient using on-board imaging technology. Gantry angle triggered kilovoltage radiographs were also used to confirm positioning with imaging of the internal fiducial markers. Both the radiation oncologist and urologist were present during these treatments to confirm patient positioning and allow for real-time alignment based on the real-time cone-beam CT with the fused pretreatment simulation CT.[6,18]

The primary aim of the study was to determine if the use of FB prior to radiation treatment planning led to a difference in the radiation delivered to the target area versus post systematic biopsy MRI planning alone. To determine this primary aim, the integrated boost volume density (IBVD) was determined by dividing the PTV_{boost} by the total prostate volume ($IBVD = \frac{PTV_{boost}}{PTV_{boost}-PTV_{prostate}}$). Secondary endpoints included acute toxicity events that occurred during the follow up period that were graded using the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0), post-radiation PSA, post-radiation AUA symptom score (AUASS), and post-radiation Sexual Health Inventory for Men (SHIM) score. The clinical dataset was maintained and analyzed using Microsoft Excel (Edmond, WA, USA) and IBM SPSS Statistics (Armonk, NY, USA). T-test and chi-square was used to analyze the cohorts with a preset threshold of statistical significance of p value < 0.05.

Results

Ninety-six patients were registered to have undergone prostate SBRT at our institution for pathologically proven prostate adenocarcinoma. However, retrospective chart review led to the exclusion of 7 patents as 6 patients did not receive the SIB and 1 patient did not have an MRI prior to radiation planning. Of the 89 remaining patients who were evaluable for this study, 43 patients underwent standard TRUS biopsy followed by an MRI prior to radiation treatment planning. The other 46 patients underwent an MRI followed by FB prior to radiation treatment planning.

No differences were observed between the two cohorts in terms of age, race, smoking status, and BMI. Furthermore, there were no differences in pre-radiation AUASS, pre-radiation SHIM score, and pre-radiation prostate specific antigen (PSA) values. No significant difference was found in the grade group or clinical

TABLE 1. **Demographic data**

	Standard TRUS biopsy (n = 43)	**Fusion biopsy (n = 46)**	**p value**
Age (years)	65.26 ± 7.12 (50-85)	64.59 ± 7.97 (39-79)	0.678
Race			0.195
White	21 (50.0%)	21 (56.8%)	
African American	21 (50.0%)	16 (43.2%)	
Smoker			0.405
No	18 (41.8%)	24 (52.2%)	
Former	20 (46.5%)	15 (32.6%)	
Current	5 (4.7%)	7 (15.2%)	
BMI (kg/m^2)	29.51 ± 4.66 (19.3-44.35)	30.85 ± 5.92 (22.35-53.17)	0.243
Pre-radiation AUASS	8.28 ± 7.04 (0-29)	10.95 ± 6.97 (0-25)	0.108
Pre-radiation SHIM	15.67 ± 8.10 (5-25)	14.71 ± 7.96 (5-25)	0.619
Pre-radiation PSA (ng/mL)	8.93 ± 9.63 (1.1-62.8)	7.11 ± 3.02 (2.4-16.1)	0.251
Grade group			0.906
1	10 (23.3%)	11 (23.9%)	
2	26 (60.5%)	26 (56.5%)	
3	7 (16.3%)	9 (19.6%)	
Clinical stage			0.382
cT1	35 (81.4%)	40 (87.0%)	
cT2	8 (18.6%)	5 (10.9%)	
cT3	0 (0%)	1 (0.02%)	
ADT			0.67
No	35 (81.4%)	39 (84.8%)	
Yes	8 (18.6%)	7 (15.2%)	

TRUS = transrectal ultrasound; BMI = body mass index; AUASS = AUA symptom score; SHIM = Sexual Health Inventory for Men; PSA = prostate-specific antigen; ADT = androgen deprivation therapy

TABLE 2. **Radiation planning parameters**

	Standard TRUS biopsy (n = 43)	Fusion biopsy (n = 46)	p value
Prostate TRUS volume (cc)	35.41 ± 13.33 (18-71.5)	48.21 ± 24.26 (14.9-110)	0.005
Prostate MRI volume (cc)	37.58 ± 13.78 (13.7-65.13)	50.28 ± 26.76 (13.7-140.9)	0.007
$PTV_{prostate}$ (cc)	82.60 ± 26.29 (42.6-146.6)	92.70 ± 32.29 (51.8-195.7)	0.111
PTV_{boost} (cc)	13.45 ± 7.58 (3.9-31.3)	13.45 ± 6.86 (2.4-34.5)	0.308
IBVD	0.16 ± 0.09 (0.047-0.41)	0.13 ± 0.06 (0.02-0.27)	0.045

TRUS = transrectal ultrasound; MRI = magnetic resonance imaging; PTV = prostate target volume; IBVD = integrated boost volume density

stage between the standard TRUS biopsy cohort and the FB with a similar number in each receiving pre-procedural and concurrent androgen deprivation therapy (ADT), as demonstrated in Table 1.

Patients undergoing the standard TRUS biopsy had a significantly smaller prostate volume than the FB cohort when measured by TRUS and MRI (35.41 ± 13.33 versus 48.21 ± 24.26 cc, p = 0.005; 37.58 ± 13.78 versus 50.28 ± 26.76 cc, p = 0.007, respectively). Furthermore, there was no difference in $PTV_{prostate}$ and PTV_{boost} between standard TRUS biopsy and FB cohorts. However, the standard TRUS biopsy cohort had a larger IBVD than the FB cohort (0.16 ± 0.09 versus 0.13 ± 0.06, p = 0.045), Table 2.

Regarding post-radiation evaluation and follow up, Table 3, there was no significant difference between the standard TRUS biopsy cohort and the FB cohort in post-radiation AUASS, post-radiation SHIM, or post-radiation PSA. Furthermore, genitourinary toxicity rates including dysuria, frequency, hesitancy, hematuria were similar between the two cohorts. Gastrointestinal toxicity including diarrhea, hematochezia, pain with bowel movements, and fecal urgency were also found to be similar. The mean duration of last recorded follow up in the standard TRUS biopsy cohort was shorter than FB cohort (418.29 ± 309.41 days versus 643.29 ± 424.84 days, p = 0.006).

Discussion

In this study, we successfully incorporated FB into our radiation planning for SBRT with a SIB to an MRI-defined intraprostatic lesion. While the $PTV_{prostate}$ and PTV_{boost} did not differ between patients undergoing FB compared to systematic TRUS biopsy followed by MRI, the IBVD was lower in patients undergoing FB ($p < 0.05$). Interestingly, patients undergoing FB also had significantly larger prostate volumes on TRUS and MRI measurements ($p < 0.05$).

The addition of MRI and FB to the work up of prostate cancer has improved the diagnostic capacity to more optimally identify clinically-significant prostate cancer, while decreasing the detection of low-risk malignancies.[8,12,19] The PRECISION study group (Prostate Evaluation for Clinically Important Disease: Sample Using Image Guidance or Not?) randomized 500 biopsy-naïve patients between FB and standard TRUS biopsy. They found that FB was noninferior in diagnosing clinically significant prostate cancer when compared to standard biopsy methodology alone (p = 0.005).[7] Large prostates, greater than 40 cc, have proven to be more difficult to diagnose prostate cancer, as the sensitivity and specificity of standard systematic TRUS-guided biopsy decreases with increasing prostate volumes due to decreased relative sampling.[20] However, the inclusion of FB has led to improved prostate cancer detection in large prostates when compared to TRUS biopsy, normalizing in part the cancer detection due to the suspicion targeting afforded with the use of MRI guidance.[21] Furthermore, due to its ability to detect high-risk lesions, MRI has been included in active surveillance protocols with a meta-analysis of 43 studies determining MRI sensitivity of 0.81 and negative predictive value of 0.78 in upgrading in this select population already harboring a prostate cancer diagnosis.[22]

These advances in imaging technology and diagnosis of prostate cancer are reflected in our findings. Of the patients undergoing FB, only 5 (11.1%) were biopsy naïve, while the remainder of the cohort consisted of 11 (24.4%) patients with a history of negative biopsy and 29 (64.4%) patients on active surveillance. Furthermore, patients undergoing FB had larger prostates than those that underwent systematic TRUS biopsy alone. Therefore, the lower IBVD seen in the FB cohort is likely a reflection of the management team's confidence in identifying a biopsy-

TABLE 3. Post-radiation outcomes and toxicity

	Standard TRUS biopsy (n = 43)	**Fusion biopsy (n = 46)**	**p value**
Post-radiation AUASS	8.33 ± 6.18 (0-25)	9.24 ±6.69 (1-29)	0.56
Post-radiation SHIM	12.64 ± 8.90 (5-25)	14.89 ± 7.90 (5-25)	0.303
Post-radiation PSA	1.24 ± 1.41 (0.01-6.62)	1.12 ± 1.78 (0.01-8.82)	0.723
Dysuria			0.391
0	35 (85.4%)	33 (73.3%)	
1	3 (7.3%)	6 (13.3%)	
2	3 (7.3%)	6 (13.3%)	
Frequency			0.78
0	22 (53.7%)	29 (64.4%)	
1	9 (22.0%)	7 (15.6%)	
2	9 (22.0%)	8 (17.8%)	
3	1 (2.4%)	1 (2.2%)	
Hesitancy			0.756
0	31 (77.5%)	35 (77.8%)	
1	3 (7.5%)	4 (8.9%)	
2	6 (15.0%)	5 (11.1%)	
3	0	1 (2.2%)	
Hematuria			0.192
0	37 (88.1%)	44 (97.8%)	
1	4 (9.5%)	1 (2.2%)	
2	0	0	
3	1 (2.2%)	0	
Diarrhea			0.074
0	39 (95.1%)	34 (75.6%)	
1	1 (2.4%)	8 (17.8%)	
2	1 (2.4%)	2 (4.4%)	
3	0	1 (2.2%)	
Hematochezia			0.6
0	37 (90.2%)	39 (86.7%)	
1	2 (4.9%)	4 (8.9%)	
2	1 (2.4%)	2 (4.4%)	
3	1 (2.4%)	0	
Pain			0.52
0	39 (95.1%)	42 (93.3%)	
1	2 (4.9%)	1 (2.2%)	
2	0	1 (2.2%)	
3	0	1 (2.2%)	
Fecal urgency			0.549
0	40 (97.6%)	42 (93.3%)	
1	1 (2.4%)	2 (4.4%)	
2	0	1 (2.2%)	
Follow up post radiation (days)	418.29 ± 309.41 (10-1168)	643.29 ± 424.843 (32-1730)	0.006

TRUS = transrectal ultrasound; AUASS = AUA symptom score
SHIM = Sexual Health Inventory for Men; PSA = prostate-specific antigen

proven lesion on MRI in the setting of a larger overall prostate gland volumes. By maintaining a comparable PTV_{boost} in the setting of a larger prostate, the addition of FB to SBRT may potentially reduce patient toxicity. The incorporation of a urologist in delineating the prostatic lesions, prostate gland boundaries, prostate apex margins, bladder neck margins, neurovascular bundles, and urethra during the radiation planning and delivery, allows for a multidisciplinary consensus to be made. Therefore, more precise radiation fractions can be delivered with potentially less toxicity. Further studies investigating the benefits of multidisciplinary efforts on SBRT planning and delivery are needed.

Dose escalation by hypofractionation and SIB to the tumor are currently being investigated in hopes of improving disease control, decreasing toxicity profiles, and reducing the number of radiation treatment visits. The addition of MRI has allowed more accurate delineation of intraprostatic tumors for focal boosting.[23] Current ASTRO-ASCO-AUA guidelines recommend offering SBRT to low-risk or intermediate-risk prostate cancer patients, as an alternative to conventional EBRT, as part of a clinical trial. The efficacy and safety of SIB to an intraprostatic tumor in the setting of EBRT was first demonstrated by the phase III, multicenter FLAME trial (NCT01168479). Seventy-seven Gy was delivered to the entire prostate gland in 35 fractions with a SIB of 95 Gy to the MRI-defined lesion. Gastrointestinal and genitourinary toxicity at 2 years post-treatment demonstrated no significant difference between the SIB and standard treatment group.[11,24]

Integration of SIB into hypofractionated treatment regimens are currently being investigated. Our institution reported our initial experience with this technique in 26 patients. 36.25 Gy was successfully delivered to the whole prostate along with a 40 Gy focal boost to an MRI-defined intraprostatic lesion in 5 fractions without any high-grade complications.[6] Other phase I trials have further demonstrated the feasibility of SIB in a hypofractionated schedule.[25,26] Herrera et al was able to deliver 36.25 Gy with a dose escalation of the boost up to 45 Gy, 47.5 Gy, and 50 Gy in 5 fractions.[27] Patients in the phase II hypo-FLAME trial were given an extreme hypofractionated dose of 35 Gy with a SIB to an MRI-defined lesion of 50 Gy in 5 fractions. No high-grade toxicity was reported.[28] While there are currently no published phase III clinical trials comparing hypofractionated SBRT with SIB to standard fractionated radiation treatment options, hypofractionated radiation regimens offer similar gastrointestinal and genitourinary toxicity as conventional regimens. The PACE-B phase III trial randomized 874 men between conventional fractionation or moderately hypofractionated radiotherapy (78 Gy in 39 fractions over 7-8 weeks or 62 Gy in 20 fractions over 4 weeks, respectively) in one arm to SBRT (36.25 Gy in five fractions over 1-2 weeks) in the other. Similar gastrointestinal and genitourinary toxicity rates were found between the two arms.[29] Our study further adds to the feasibility and safety of a SIB to a hypofractionated regimen. Of the 89 patients undergoing SBRT and a SIB, 4 (4.5%) and 3 (3.4%) patients reported a high-grade genitourinary and gastrointestinal toxicity (CTCAE, grade ≥ 3), respectively.

Our study has multiple limitations. The first being the inherent selection bias in the decision for a patient to undergo FB prior to radiation planning. As mentioned previously, this likely stems from a two-part effect. First, most patients undergoing FB do so as part of an active surveillance protocol or due to a history of a negative biopsy. Second, patients undergoing FB in our study had a larger prostate that likely initially contributed to under-sampling and negative biopsies that would lead a patient toward an active surveillance or repeat biopsy route. However, this strong bias towards FB in patients with large prostates, history of negative biopsy, and those in active surveillance protocols, strengthen the potential benefit that FB has on radiation planning in this subset of patients. Additionally, fellowship-trained urologic oncologists and radiation oncologists with extensive experience in MRI and FB contributed to the multidisciplinary approach to radiation planning, which limits the generalizability of adding FB to certain practices without those resources readily available. Lastly, we recognize that the follow up and toxicity data is heterogenous, with an overall median follow up of only 432 days, and that it lacks standardization for meaningful comparison. As such, case-controlled cohorts or randomized trials with adequate follow-up will be needed to identify if the addition of FB, in a prostate volume-controlled manner, affects the radiation density and toxicity of patients undergoing SBRT with SIB.

Conclusions

SBRT with SIB to an MRI-defined intraprostatic lesion is a rapidly advancing area of interest. Integration of FB to radiation planning is safe and feasible with potential advantage in patients with larger prostate gland volumes.

Disclosures

Soroush Rais-Bahrami serves as a consultant for Philips Corp, Genomic Health Inc, Blue Earth Diagnostics,

Intuitive Surgical, and Bayer Healthcare. Jeffrey W. Nix serves as a consultant for Philips Corp and Intuitive Surgical. Rex A. Cardan and Andrew M. McDonald serve as consultants for Varian Medical Systems. All authors report no other potential conflicts of interest or financial disclosures that were pertinent to the following study.

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