Radioimmunoscintigraphy for Postprostatectomy Radiotherapy: Analysis of Toxicity and Biochemical Control

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Our goal was to evaluate the role of radioimmunoscintigraphy (RIS) directed against prostate-specific membrane antigen (PSMA) in influencing postprostatectomy radiotherapy (RT) toxicity and biochemical control. **Methods**: The records of 107 postprostatectomy RT patients were reviewed. The group for whom no RIS scan was obtained (group A, $n = 54$) was identified as was the group for whom a RIS scan was obtained (group B, $n = 53$). Group B was further subdivided into those who had a RIS and CT-scan correlation to aid in treatment planning (subgroup B1, $n = 40$) versus those who did not (subgroup B2, $n = 13$). Gastrointestinal (GI) and genitourinary (GU) toxicities were reviewed for each of these groups and subgroups and compared. Biochemical failures (defined as 2 successive PSA rises after a nadir of ≥0.2 ng/mL) were identified to generate biochemical failure-free survival (BFFS) curves for each of the groups and subgroups. **Results:** No significant differences in late toxicity were observed between any group or subgroup. However, acute GI toxicity was higher in group B versus group A ($P = 0.026$), and acute GU toxicity was higher in subgroup B2 versus subgroup B1 ($P = 0.050$). Overall, most toxicity was grade 1 or 2; only one case of grade 3 toxicity and no cases of grade 4 or 5 toxicity were observed. Three-year BFFS was higher for group B versus group A (80.7% vs. 75.5%) and for subgroup B1 versus subgroup B2 (84.5% vs. 71.6%). On multivariate analysis of pretreatment (age, race), surgical/staging (stage, grade, margin status, extracapsular extension, lymph node status, seminal vesicle invasion, post–radical retropubic prostatectomy [RRP] prostate-specific antigen [PSA] nadir, maximum post-RRP PSA, and RRP-to-RT interval), and treatment (hormone therapy, RT dose, RT technique, RIS scan, and RIS/CT correlation) factors on BFFS, the only covariate reaching significance was RIS/CT correlation ($P = 0.042$). **Conclusion:** A small BFFS advantage was observed in patients for whom RIS was used to guide RT decision making and treatment planning; however, this advantage only reached significance in this study for those for whom the RIS/CT correlation was used to guide target definition. The improved PSA control using RIS was achieved with a small increase in acute toxicity but with no observed change in late toxicity. These findings can serve as the basis for prospective studies in this area of investigation.

Key Words: prostate cancer; prostatectomy; radiotherapy; radioimmunoscintigraphy

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Prostate cancer is among the most common malignancies for which health care intervention is sought (*1–3*), and it is treated most commonly with radical retropubic prostatectomy (RRP) (*4*) or radical radiation therapy (RT) (*5–6*). For those patients who are assessed after RRP to have high-risk disease that is predictive of a local recurrence by pathologic findings or for those patients who likely have a local-only recurrence by prostate-specific antigen (PSA) record, clinical examination, or radiologic findings, post-RRP RT can be considered and has been used with success (*7–16*).

Radioimmunoscintigraphy (RIS), performed in the current study by targeting the prostate-specific membrane antigen (PSMA) (ProstaScint; Cytogen Corp.), has been studied in the diagnostic setting for prostate cancer (*17–24*). The sensitivity and specificity have been examined in a recent multiinstitutional trial (*21*) that documented the incidence of prostate fossa, pelvic nodes, and extrapelvic uptake among different clinical settings; the approximate values for diagnostic parameters in the postsurgery setting (the primary scenario in this study) are as follows: sensitivity, 75% (extraprostatic) and 92% (prostate fossa); specificity, 86%; positive predictive value, 81%; and negative predictive value, 67%.

RIS is useful in determining whether pelvic or extrapelvic lymphadenopathy exists before undertaking local or locoregional therapy. Recent efforts have evaluated the role of RIS

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in the setting of postprostatectomy RT decision making, and RIS was found to aid, by providing information complementary to that provided on the bone scan or abdominopelvic CT scan, in (a) guiding the decision to offer RT and (b) guiding the decision of the general treatment volume (prostate bed only vs. prostate bed and regional pelvic lymph nodes) (*25*). At our institution consortium in Chicago, we have integrated further RIS into the treatment planning process; we have developed and reported a technique to register the RIS scan with the RT treatment-planning CT scan using vessel registration (*26–28*), and we reported on how this technique was used to guide and to modify the definition of the prostate bed portion of the postprostatectomy clinical target volume (CTV) for external beam RT (*29*). Although there appears to be consensus on the diagnostic and technical aspects of RIS, the impact of RIS on clinical outcome is currently a matter of controversy. The survival advantage using RIS as a diagnostic study has been formally examined by several groups, with both positive (*30*) and negative studies (*31*) having been reported thus far.

The specific goals of the current study were (a) to determine the effects of RIS and the RIS/CT correlation on post-RRP RT acute and late gastrointestinal (GI) and genitourinary (GU) toxicity and (b) to determine the influence of RIS (particularly the RIS/CT image correlation specific to our institution) on the biochemical outcome of post-RRP RT patients.

MATERIALS AND METHODS

The patient population we studied consisted of 107 consecutive post-RRP prostate cancer patients who were treated in our hospital consortium between 1988 and 2002 and for whom treatment and follow-up information were available. The patient database was approved by the Institution Review Boards of all of the hospitals (University of Chicago, University of Illinois, and LaGrange Memorial Hospital) whose patient data were used for this investigation. Furthermore, because the current study is retrospective, a formal waiver of informed consent was requested and approved before conducting this study.

From the original cohort of 107 patients, a group consisting of 54 patients (group A) was identified, which comprised patients who had not had a RIS scan. The remaining 53 patients (group B) had a RIS scan; this group was further subdivided into the 40 patients who had the RIS/planning-CT correlation conducted (subgroup B1) versus those 13 patients who did not have such a correlation performed (subgroup B2). In subgroup B2, it should be noted that although the RIS/CT correlation was not performed, RIS was used as a diagnostic test to guide the RT decision and general treatment fields.

The patient and disease characteristics of these groups are shown in Table 1. This table displays the patient demographics (age, race), RRP pathologic findings (stage, grade, margin status, seminal vesicle invasion status, extracapsular extension, and lymph node status), and postprostatectomy course leading to RT consultation (post-RRP PSA nadir, post-RRP PSA follow-up course, hormone therapy, and interval from RRP to RT consultation). As demonstrated in Table 1, margin status and T stage were somewhat different among the groups; for this reason, these pa-

TABLE 1
Patient and Disease Characteristics Summary

	Group A	Group B	Group B1	Group B2
No. of patients	54	53	40	13
Demographics				
Age (y [mean])	63.3	57.8	50.0	60.3
Race				
White	24	33	26	7
African American	29	16	11	5
Hispanic	1	3	2	1
Other	0	1	1	0
Prostatectomy findings				
T stage				
pT1/T2	10	16	10	6
pT3	42	32	26	6
pT4	2	3	2	1
pTx	0	2	2	0
Gleason score (GS)				
GS 5	4	3	2	1
GS 6	15	12	7	5
GS 7	20	27	21	6
GS 8	4	5	5	0
GS 9	5	4	3	1
Not recorded	6	2	3	0
Margins				
Positive	40	28	19	9
Negative	12	23	19	4
Not recorded	2	2	2	0
Seminal vesicle inv.				
Positive	15	15	13	2
Negative	37	36	25	11
Not recorded	2	2	2	0
Extracaps. extension				
Yes	33	32	26	6
No	20	19	12	7
Not recorded	1	2	2	0
Lymph nodes inv.				
No	42	47	37	10
Yes	4	0	0	0
Not sampled	8	6	3	3
Post-RRP PSA nadir				
PSA $\leq$ 0.1	22	28	19	9
0.1 $<$ PSA $\leq$ 0.2	10	6	5	1
0.2 $<$ PSA $\leq$ 0.3	3	11	10	1
0.3 $<$ PSA $\leq$ 0.5	6	1	1	0
0.5 $<$ PSA $\leq$ 1.0	5	5	4	1
1.0 $<$ PSA	7	2	1	1
Not recorded	1	1	1	0
Highest PSA post-RRP				
PSA $\leq$ 0.1	13	7	3	4
0.1 $<$ PSA $\leq$ 0.2	8	7	5	2
0.2 $<$ PSA $\leq$ 0.3	4	5	5	0
0.3 $<$ PSA $\leq$ 0.5	6	6	5	1
0.5 $<$ PSA $\leq$ 1.0	9	12	9	3
1.0 $<$ PSA $\leq$ 2.0	7	11	10	1
2.0 $<$ PSA	6	5	3	2
Not recorded	1	0	0	0
RRP-to-RT interval (d)				
Mean	352	564	544	573

T = tumor; inv. = invasion; Extracaps. = extracapsular.

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TABLE 2
Treatment Characteristics Summary

	Group A	Group B	Group B1	Group B2
No. of patients	54	53	40	13
Volume				
Whole pelvis initially	9	6	4	2
Prostate bed only	45	47	36	11
Technique				
4-Field	41	21	16	5
6-Field	8	21	13	8
IMRT	5	11	11	0
Final dose				
<60	23	2	0	2
60–64	8	5	5	0
64–66	17	29	22	27
>66	9	17	13	4
Mean	6,430.5	6,644.4	6,780.0	6,677.5
Follow-up post-RT (d)				
Mean	814	648	661	673
Median	696	480	433	532
Maximum	3,561	2,080	2,268	1,536
Hormone therapy				
Yes	6	29	22	6
No	46	24	18	7
Not recorded	1	0	0	0

rameters were later analyzed using multivariate analysis (as were all pathologic features).

For each patient, a planning pelvic CT scan was obtained at the time of simulation using 5-mm spacing. Rectal and bladder contrasts were used to visualize these critical and avoidance structures. RIS scans, when conducted, were obtained in the nuclear medicine department, typically during the same week as the planning CT scan. The RIS scan had 2 components: a ^{99m}Tc-labeled red blood cell (RBC) SPECT scan and a simultaneously acquired ^{111}In-labeled monoclonal antibody (mAb) capromab pendetide (7E11.C5) RIS scan (*26–29*). For those patients having the RIS and CT registration performed, intravenous contrast was used during the planning CT scan to enable the vessel registration (*26–29*).

If the whole pelvis was treated, a 4-field technique was used for this portion; however, different techniques were used for the prostate bed RT: 4-field or 6-field conformal therapy or intensity-modulated radiotherapy (IMRT) (*32*). The treatment characteristics for these groups are shown in Table 2. As this table displays, a higher percentage of group A patients were treated with the older 4-field technique. In addition, a higher percentage of patients received hormone therapy in group B versus group A. Although this difference in percentages is a potential source of bias, hormone therapy and treatment technique were entered (as were all treatment characteristics) as covariates in the multivariate analysis, as described. In addition, hormone therapy, when administered, was short-term neoadjuvant or adjuvant therapy that affected the PSA time course only transiently and would not be expected to prohibit later biochemical failure analysis (*33–34*). The other treatment factors—radiation dose and general treatment volume—were similar between groups A and B and between subgroups B1 and B2. The radiation dose was selected according to a consensus conference examining this issue (*35*), which recommended approximately 64 Gy.

For group B patients, the RIS reports were reviewed and tabulated. The RIS scans were read by one board-certified nuclear medicine physician who was involved in the initial development of the procedure as well as in several RIS clinical trials. Because only one physician read the RIS scans, interobserver variability in interpretation of the scans is not a confounding variable in this particular investigation. Although the authors recognize that having multiple observers reading would reduce potential errors of one reader, the experience of the reader and the later correlation with the clinical outcome make retroactive multiple readings inappropriate, as the toxicity and biochemical control analyses were analyzed as a function of administered therapy, which was guided by the single observer. Planar and volume SPECT datasets were obtained using a dual-head SPECT Prism 2000 Picker/Philips camera. This dual-energy procedure for acquisition of data and interpretation is described in considerable detail in a separate communication (*22*) and thus is not repeated here. The scans were read with knowledge of the patient's clinical history but not with the aid of CT or MRI information; in addition, CT and SPECT systems were not used. Of important note, the RIS/CT correlation described earlier was not a diagnostic test: The RIS scan was performed and read separately from the CT study, often several weeks before the planning CT scan. Thus, the RIS/CT correlation was not intended to be a novel diagnostic entity but rather a tool to assist the treatment-planning target design. This use of the RIS/CT correlation as a treatment-planning tool, which did involve several observers, is described in considerable detail in a prior article (*29*). For each patient, the RIS findings, with regard to uptake in the prostate fossa (PF), pelvis (P) (i.e., uptake within the pelvis in a region outside of the prostate fossa), or extrapelvic (EP) uptake, were reviewed. The summary of these findings, for group B1 versus group B2, is shown in Table 3. The influence of the RIS findings on RT decision making at our institution has been previously reported (*25*). Except for one patient for whom EP uptake was viewed to be a false-positive, the presence of EP uptake usually caused the clinician to abort the decision to offer RT, and no treatment or follow-up information would be expected on these patients. In this manner, group B represents a selected patient population over that of group A, because the group B patients had the RIS scan done in addition to standard testing, including CT scan and bone scan when available. It is in this setting in which most previous RT studies analyzing RIS outcome analyses have been done (*30,31*) (i.e., to determine the impact of RIS as a diagnostic test). One additional role that RIS had was in guiding the clinician in some cases to offer RT to the PF + P group as opposed to the PF-only group (*25*).

TABLE 3
RIS Results Summary

Variable	Group B	Group B1	Group B2
No. of patients	53	40	13
Result			
PF only	40	32	9
P only	0	0	0
EP only	1	0	1
PF + P	10	7	3
PF + EP	1	1	0
PF + P + EP	0	0	0

PF = prostate fossa; P = pelvic node uptake; EP = extrapelvic uptake.

TABLE 4
Acute Toxicity Analysis

Variable	Rectum				Bladder			
	Group A	Group B	Subgroup B1	Subgroup B2	Group A	Group B	Subgroup B1	Subgroup B2
Grade 0	21/54 = 39%	15/52 = 29%	12/39 = 31%	3/13 = 23%	18/54 = 33%	16/52 = 31%	13/39 = 33%	3/13 = 23%
Grade 1	**11/54 = 20%**	**19/52 = 37%**	13/39 = 33%	4/13 = 31%	25/54 = 46%	25/52 = 48%	21/39 = 54%	4/13 = 31%
Grade 2	21/54 = 39%	18/52 = 35%	14/39 = 36%	6/13 = 46%	11/54 = 20%	11/52 = 21%	**5/39 = 13%**	**6/13 = 46%**
Grade 3	1/54 = 2%	0/52 = 0%	0/39 = 0%	0/13 = 0%	0/54 = 0%	0/52 = 0%	0/39 = 0%	0/13 = 0%
Grade 4	0/54 = 0%	0/52 = 0%	0/39 = 0%	0/13 = 0%	0/54 = 0%	0/52 = 0%	0/39 = 0%	0/13 = 0%
Grade 5	0/54 = 0%	0/52 = 0%	0/39 = 0%	0/13 = 0%	0/54 = 0%	0/52 = 0%	0/39 = 0%	0/13 = 0%
P	0.026 (B > A)		0.720 (B1 − B2)		0.923 (A − B)		0.050 (B2 > B1)	

The acute and late toxicities were reviewed and tabulated for group A, group B, subgroup B1, and subgroup B2 according to the Radiation Therapy Oncology Group (RTOG) toxicity grading criteria (*36–38*) for all patients. Then, we made group and subgroup comparisons by using the χ^2 test (*39*) to determine the influence of RIS and the influence of the RIS/CT correlation, respectively, on the toxicity outcomes.

In addition, we analyzed biochemical failure-free survival (BFFS). Using the definition of biochemical failure as 2 consecutive rises from PSA nadir to an absolute level greater than or equal to 0.2 ng/mL (with time of failure being declared midway between the nadir and the first PSA rise), we constructed Kaplan–Meier BFFS curves (*40*). Under this failure definition, those PSA levels that continually rise without a nadir are also counted as failures (effectively, the first follow-up after RT was taken to be the nadir in these cases). This definition combines features of definitions that rely on an absolute threshold and those that rely on successive rises (*6–16*). Survival curves were generated for the different groups and subgroups for qualitative comparison. Furthermore, a multivariate analysis, using the Cox proportional hazards model (*40*), was performed to quantitatively determine the influence of all pretreatment factors (age, race), surgical and staging factors (stage, grade, margin status, extracapsular extension, lymph node status, seminal vesicle invasion, post-RRP PSA nadir, maximum post-RRP PSA, and RRP to RT interval), and treatment factors (hormone therapy, RT dose, RT technique, RIS scan, RIS findings, and RIS/CT correlation) on BFFS.

RESULTS

Tables 4 and 5 show the analyses for acute toxicity and late toxicity, respectively. As Table 4 demonstrates, there was a higher rate of acute GI toxicity in group A versus group B ($P = 0.026$, χ^2); this was principally because of higher grade 1 toxicity (37% vs. 20%), shown in boldface in Table 4. In addition, there was a higher rate of GU toxicity in group B1 versus group B2 ($P = 0.050$, χ^2); this was predominantly because of the higher grade 2 toxicity (46% vs. 13%), again shown in boldface. As demonstrated, we observed no difference in acute GU toxicity between groups A and B and no difference in acute GI toxicity between subgroups B1 and B2. Table 5 demonstrates no difference in late GI or GU toxicity in any of the group or subgroup comparisons. As shown in the Tables 4 and 5, most of the observed toxicity was grade 1 or grade 2, the absolute incidence of grade 3 toxicity was low (only one case of acute GI toxicity was seen [in group A]), and we did not observe any grade 4 or grade 5 toxicity.

Figure 1 shows the BFFS curves for the various group and subgroup comparisons: Figure 1A displays the BFFS curves for group B versus group A; this comparison demonstrates the overall influence of RIS on biochemical control. As shown, 3-y BFFS for group B versus group A was 80.7% versus 75.5%. Figure 1B displays the BFFS curves for subgroup B1 versus subgroup B2; this comparison demonstrates the influence, within the group that underwent the RIS scan, of the RIS/CT correlation on biochemical control. As shown, 3-y BFFS for subgroup B1 versus subgroup B2 was 84.5% versus 71.6%. Figure 1C displays the BFFS curves for subgroup B1 versus group A; this comparison

TABLE 5
Late Toxicity Analysis

Variable	Rectum				Bladder			
	Group A	Group B	Group B1	Group B2	Group A	Group B	Group B1	Group B2
Grade 0	29/52 = 56%	30/46 = 65%	22/33 = 67%	8/13 = 62%	24/52 = 46%	26/46 = 57%	18/33 = 55%	7/13 = 54%
Grade 1	18/52 = 35%	13/46 = 28%	7/33 = 21%	5/13 = 38%	17/52 = 33%	12/46 = 26%	10/33 = 30%	3/13 = 23%
Grade 2	5/52 = 10%	3/46 = 7%	4/33 = 12%	0/13 = 0%	9/52 = 17%	8/46 = 17%	5/33 = 15%	3/13 = 23%
Grade 3	0/52 = 0%	0/46 = 0%	0/33 = 0%	0/13 = 0%	2/52 = 4%	0/46 = 0%	0/33 = 0%	0/13 = 0%
Grade 4	0/52 = 0%	0/46 = 0%	0/33 = 0%	0/13 = 0%	0/52 = 0%	0/46 = 0%	0/33 = 0%	0/13 = 0%
Grade 5	0/52 = 0%	0/46 = 0%	0/33 = 0%	0/13 = 0%	0/52 = 0%	0/46 = 0%	0/33 = 0%	0/13 = 0%
P	0.375 (A = B)		0.178 (B1 = B2)		0.327 (A = B)		0.722 (B1 = B2)	

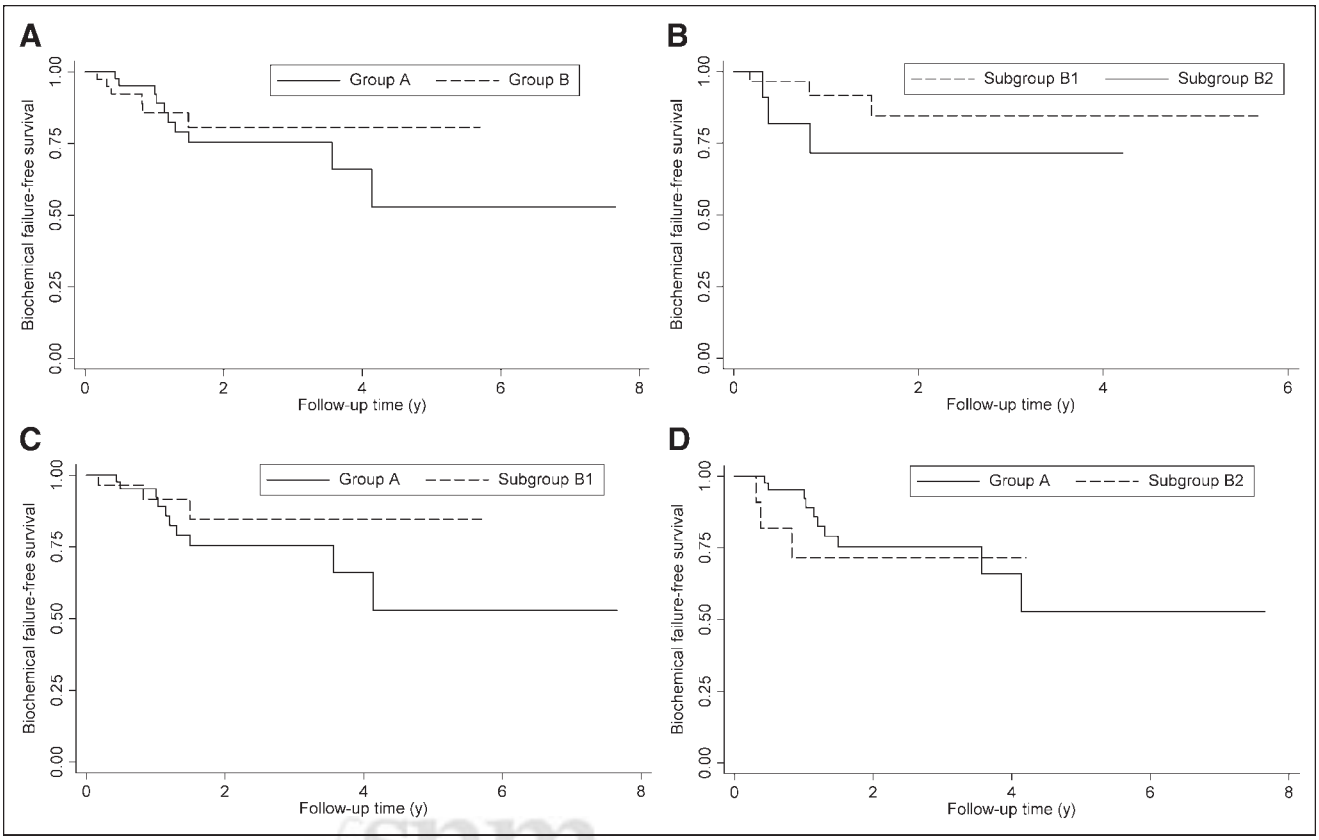

FIGURE 1. Kaplan–Meier BFFS curves: group A vs. group B (A); subgroup B1 vs. subgroup B2 (B); group A vs. subgroup B1 (C); group A vs. subgroup B2 (D).

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displays biochemical control in the group undergoing the RIS/CT correlation against the comparison group not undergoing RIS. As shown, 3-y BFFS for subgroup B1 versus group A was 84.5% versus 75.5%. Last, Figure 1D displays the BFFS curves for subgroup B2 versus group A; this comparison demonstrates the biochemical control in the subgroup undergoing RIS (but not undergoing the RIS/CT correlation) against the comparison group not undergoing RIS. As shown, 3-y BFFS for subgroup A versus subgroup B2 was 75.5% versus 71.6%. It should be emphasized that although the overall cohort was well-powered (with >100 patients), this statistical power was diminished when the groups were broken into groups and subgroups. For this reason, meaningful pairwise statistical comparisons among the different groups and subgroups would not be adequately interpretable, and the pairwise results described above are intended to be for qualitative purposes only.

The qualitative results of the group and subgroup comparisons in Figure 1 were extended quantitatively by performing a multivariate analysis of pretreatment factors, surgical and staging factors, and treatment factors on biochemical outcome. The results of this multivariate analysis are shown in Table 6. It is noteworthy that although RIS scan is a covariate (representing the group A versus group B comparison), as is the RIS/CT correlation (representing the subgroup B1 vs. group A + subgroup B2 comparison), RIS findings cannot be an independent covariate because it is colinear with RIS scan when performing a multivariate analysis. Additionally, the results for lymph node status, which was included as a covariate in the multivariate analysis, are not displayed because of the degeneracy in the

TABLE 6
Multivariate Analyses of Factors Influencing BFFS

Factor	Multivariate analysis: Hazard ratio [95% confidence interval]	*P*
Age	1.031 [0.881, 1.207]	0.701
Race	0.449 [0.074, 2.715]	0.383
T stage	0.178 [0.005, 6.126]	0.339
Grade (Gleason score)	2.771 [0.794, 9.663]	0.110
Margins	0.181 [0.003, 10.732]	0.412
Seminal vesicle inv.	0.405 [0.406, 4.034]	0.441
ECE	0.930 [0.057, 14.951]	0.959
Post-RRP PSA nadir	1.289 [0.485, 3.421]	0.611
Highest post-RRP PSA	0.911 [0.359, 2.310]	0.845
RRP-to-RT interval	1.004 [0.999, 1.008]	0.096
Treatment technique	1.762 [0.250, 12.393]	0.569
Final RT dose	0.998 [0.994, 1.001]	0.194
Hormone therapy	8.836 [0.023, 3,268.082]	0.470
RIS scan	1.209 [0.030, 48.349]	0.920
RIS/CT correlation	0.010 [0.0001, 0.848]	0.042

inv. = invasion.

absence of event rates in the small number of patients having node-positive disease. As displayed in Table 6, the only covariate reaching significance among all the pretreatment factors (age, race), surgical and staging factors (stage, grade, margin status, extracapsular extension, seminal vesicle invasion, post-RRP PSA nadir, maximum post-RRP PSA, and RRP to RT interval), and treatment factors (hormone therapy, RT dose, RT technique, RIS scan, and RIS/CT correlation) displayed was the RIS/CT correlation ($P = 0.042$).

DISCUSSION

Previous reports of the role of RIS in RT document the role of RIS as a diagnostic test (*17–24,30–31*). At our institution, we have tried to better understand the role of RIS as it relates to post-RRP RT by (a) describing the influence of RIS on RT decision making (*25*) and (b) analyzing the role of a RIS/CT correlation in designing the RT target (*29*). The current work extends these investigations by providing toxicity and biochemical control data of the population who underwent RIS and a comparison group who did not undergo RIS. The current efforts also add to the growing body of data examining the outcome after using RIS to guide prostate RT in different settings, such as brachytherapy (*41*).

Several observations about the toxicity analysis deserve mention. First, it appears as though the group who underwent RIS displayed higher grade 1 GI toxicity than those who did not undergo RIS. Also, the subgroup who underwent the RIS/CT correlation displayed higher grade 2 GU toxicity than the subgroup who did not undergo the correlation. The reason for the higher toxicity in these cases may be related to the larger volume of prostate bed receiving a higher dose. A previous investigation found that the larger volumes would be expected to impact on the bladder dose–volume histograms (DVHs), but impact on the rectal DVHs in this investigation was higher than that predicted (*29*). In any case, the incidence of toxicity was low in absolute terms (as described, only one case of grade 3 toxicity was observed and no grade 4 or 5 toxicity was observed) and should not prohibit prospective investigation of RIS or RIS/CT correlation. Another fundamental issue is whether the increase in acute toxicity is acceptable in the face of the small BFFS advantage. That the late toxicity was not found to be significantly different between any group or subgroup is suggestive that the long-term outcome benefit/harm ratio is acceptable. However, this question, both for the acute as well as for the late toxicity, can only be quantitatively explored in the prospective setting, with tools such as quality-adjusted time without symptoms and toxicity (Q-TWiST) (*42*).

Several qualitative observations about the biochemical control analysis also bear mention. As Figure 1A describes, there was a small BFFS advantage to the overall use of RIS. On closer examination, Figure 1B shows that within the group receiving RIS, the subgroup undergoing the RIS/CT correlation had higher biochemical control than those who did not. Figure 1C, in addition, shows the higher survival curve of the subgroup undergoing RIS/CT correlation compared with the comparison group who did not undergo RIS. The biologic implications of this finding are that performing the RIS/CT correlation potentially allowed for better encompassing of the regions at risk. It should be emphasized, though, that as described in the Results section, the pairwise survival curve comparisons shown in Figure 1 were intended to be only qualitative comparisons, and as such, a statistically significant BFFS advantage cannot be shown in the subgroups.

Also bearing mention is the results of Figure 1D, which display similar curves between those RIS patients not undergoing RIS/CT correlation and the comparison group not undergoing RIS. These curves look very similar, implying that RIS did not assist in improving the survival rate in and of itself (i.e., without the correlation). This may be because, in this study, the RIS findings were acted on (i.e., uptake to PF + P often involved increasing the RT fields to encompass this disease). This agrees with some previous reports documenting the absence of difference of RIS in assisting biochemical control when used as a diagnostic test (*30*) but does not agree with other studies that demonstrated such a difference (*31*). Caution is warranted in interpreting the conclusions in this subgroup versus the comparison group, because the study was underpowered to answer this question and, more important, not designed to answer this question formally. Indeed, for this reason, as well as the colinearity with RIS scan as described in the Methods section, RIS findings were not analyzed as an independent covariate.

In our investigation, the vast majority of patients undergoing RIS underwent the RIS/CT correlation specific to our institution. Over the past several years, several radiation treatment-planning software packages have been introduced that can perform multimodality registration; although in this study we used our institution-developed software, similar clinical results could be expected with any of several commercially available registration techniques. Of particular note, all pretreatment and treatment factors were not significant on multivariate analysis other than RIS/CT correlation. Even factors such as Gleason score and RT dose (which were fairly balanced between the different arms) and hormone therapy (which was given more commonly in group B than group A) did not reach significance, suggesting that these factors did not (within limitations of statistical power of this particular study) influence survival.

Because using RIS in the post-RRP RT setting is a relatively recent development, the follow-up for group B is predictably shorter than for group A. Although the current analysis does compare group B with the entire available length of follow-up in group A, because prostate cancer has a long natural history, longer follow-up is needed to see if the results described herein are maintained. However, it should be noted that the median follow-up of the study,

particularly that of group A, is similar to that of many investigations examining post-RRP RT.

The definition of biochemical failure used in this investigation was, as described, a hybrid between those definitions relying on an absolute PSA threshold and those relying on successive PSA rises. Both of these general approaches have been used, and no consensus has been reached on the standard definition of failure in the post-RRP population. Within the successive rises approach, investigators have reported results using 3 successive rises or 2 successive rises. Within the absolute threshold approach, the threshold has varied among various reports from 0.2 to 1.0 (*6–16*). Although absolute failure rate is, of course, dependent on the definition of failure, the results of the current study are less sensitive to this issue, as the same definition was applied to all groups, so the relative difference in failures would not be expected to change significantly as a function of the definition of failure.

We understand the biases and limitations inherent to the retrospective nature of the analyses reported here, but within these limitations the current investigation sheds light on the role of RIS in the post-RRP setting. The conclusion for the clinician is that the RIS appears to be of use to assist the post-RRP RT process but, if used, should be correlated with the planning-CT scan to maximize its benefit. We hope that the current study can provide a preliminary framework on which to design a prospective investigations in this area.

CONCLUSION

A small BFFS advantage was observed in patients in whom RIS was used to guide RT decision making and treatment planning; however, this advantage only reached significance in this study for those for whom RIS/CT correlation was used to guide target definition. The improved PSA control using RIS was achieved with a small increase in acute toxicity but with no observed change in late toxicity. These findings can serve as the basis for prospective studies in this area of investigation.

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