Influence of Radioimmunoscintigraphy on Postprostatectomy Radiotherapy Treatment Decision Making

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The aim of this study was to evaluate the role of radioimmunoscintigraphy (RIS) directed against prostate-specific membrane antigen (PSMA) in influencing postradical retropubic prostatectomy (RRP) radiotherapy (RT) decision making. **Methods:** The records of consecutive patients who underwent RRP, who were referred for consideration of RT, and for whom an RIS scan was obtained were reviewed. The RT decisions, with regard to (a) the decision to offer RT and (b) the general volume to be treated [prostate fossa (PF) only versus PF + pelvis (P)] before knowledge of the RIS findings were charted. The RIS findings, with regard to uptake in the PF, uptake in the P, or extrapelvic (EP) uptake were tabulated. Then, the RT treatment decisions based on the RIS knowledge were evaluated and compared with the pre-RIS RT treatment decisions. **Results:** Of the 54 patients originally referred for post-RRP RT, the initial decision was to recommend RT to the PF only in 52 cases and to PF+P in 2 cases. The RIS findings were as follows: PF only, 43 patients; PF+P, 8 patients; PF+EP, 2 patients; PF+P+EP, 1 patient. After knowledge of these RIS results, the decision to offer RT was withdrawn in 4 of 54 patients (7.4%; $P = 0.046$). Furthermore, RIS changed the general treatment volume (PF only to PF+P) in 6 of 54 patients (11.1%; $P = 0.015$). In total, RIS altered the RT decision in 10 of 54 patients (18.5%; $P = 0.0067$). Three-year biochemical failure-free survival (with failure defined as 2 consecutive prostate-specific antigen [PSA] rises above 0.2 ng/mL after PSA nadir) was 78%; no patient, disease, or treatment factor reached statistical significance on univariate or multivariate analysis. **Conclusion:** RIS was found to influence post-RRP RT decision making for the identification of patients not likely to benefit from RT and for guiding general target volume definition.

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 worldwide and, in many Western countries, prostate cancer is the most common noncutaneous malignancy (*1,2*). The results of widespread screening efforts, which have typically involved digital rectal examination (DRE) and serum prostate-specific antigen (PSA), have enabled prostate cancer to be diagnosed at an earlier stage than previously possible (*3*). This earlier diagnosis has in turn allowed a myriad of treatment options to be available for the patient with localized prostate cancer (*4*).

The 2 principal curative treatment modalities for prostate cancer are surgery and radiotherapy (RT) (*4–6*). The radical retropubic prostatectomy (RRP), the most commonly performed surgical procedure for prostate cancer, allows sampling of lymph nodes for those patients for whom preoperative factors warrant ruling out lymph node–positive disease before proceeding with removal of the prostate (*5*). Evaluation of the pathologic specimen provided at the time of RRP can result in upstaging of the cancer and can facilitate the decision of whether to administer adjuvant RT.

A large proportion of the recurrences after radical prostatectomy, even in those patients with negative margins at the time of surgery, are local. Some recurrences are detected clinically (i.e., on DRE) but, more often, the postprostatectomy PSA trend can assist in determining whether the recurrence is local only. For those patients who are believed to have high-risk disease that is predictive of a local recurrence, or for those who likely have a local-only recurrence either by PSA (i.e., the PSA nadired to an undetectable level postoperatively and then becomes detectable at a later date) or by clinical examination or radiologic findings, postoperative RT can be considered. Although a consensus does not yet exist in the RT community on the definition of high-risk disease or on the precise group of patients who should have

immediate or late adjuvant RT, external-beam radiation has been used with success in the postoperative setting (*7–10*).

Radioimmunoscintigraphy (RIS) was performed in this study by targeting the prostate-specific membrane antigen (PSMA) (ProstaScint; Cytogen Corp.). RIS has been carefully studied in the diagnostic setting for prostate cancer (*11–16*). RIS can assist in the staging work-up, particularly in helping to determine whether pelvic or abdominal lymphadenopathy exists, and can complement conventional studies such as the bone scan or CT scan. A recent multicenter study documented the incidence of prostate fossa (PF), pelvic node, and extrapelvic (EP) uptake among different clinical settings (*15*). From this investigation and others (*11*,*16*,*17*), the approximate values for diagnostic parameters in the postsurgery setting (the primary scenario under current study) are sensitivity = 75% (extraprostatic) and 92% (PF), specificity = 86%, positive predictive value = 81%, and negative predictive value = 67%.

In this context of the current investigation, RIS can assist in identifying the patient population most likely to benefit (or not to benefit) from RT and, in theory, this would lead to improved locoregional control of persistent or recurrent prostate cancer and improve the ultimate outcome of prostatectomy patients. Studies have demonstrated the upstaging of prostate cancer with RIS in the postprostatectomy setting (*14*,*15*). However, the use of RIS to determine the population most likely to benefit from adjuvant RT and the manner in which to integrate the RIS information into postprostatectomy RT treatment planning has not yet been studied systematically. This may be due in part to the current lack of a consensus on the clinical utility of RIS: The correlation of RIS findings with clinical outcome has been documented but remains controversial, with both positive (*18*) and negative (*19*) studies having been documented. Indeed, although other RT investigators have used RIS to guide, for example, radioactive seed placement (*20*,*21*), to our knowledge, no report has yet documented the incorporation of RIS findings to guide postprostatectomy external-beam RT.

It is the goal of this work to evaluate the role of RIS in influencing the decision to recommend RT and in determining the general RT treatment volume for prostate cancer patients having biochemical recurrence (or having high risk of recurrence) after RRP.

MATERIALS AND METHODS

The patient population under study for this investigation was the group of post-RRP prostate cancer patients appearing for consultation in our hospital consortium between 1998 and 2002. These years were selected because, although post-RRP RT has been done within our consortium for many years, RIS first became available and was first clinically implemented in our consortium in the post-RRP setting in 1998. The charts of 54 consecutive patients having prostate cancer who (a) underwent RRP, (b) were referred to our hospital consortium for consideration of external-beam RT for biochemical failure post-RRP or for high-risk of failure post-RRP, and (c) had an RIS scan ordered for aiding RT decision making were reviewed. The database used for this investigation was approved by the Institution Review Boards of all of the hospitals whose patient data were used for this investigation. Because this investigation was retrospective, a formal waiver of informed consent was requested and approved before conducting the study.

The general demographics and pre-RT treatment and follow-up history were reviewed. The characteristics of these patients are shown in Table 1, which displays the patient age, RRP pathologic findings (stage, grade, margin status, seminal vesicle invasion status, extracapsular extension, and lymph node status), postprostatectomy course leading to RT consultation (post-RRP PSA nadir, post-RRP PSA follow-up course, interval from RRP to RT consultation, and administration of hormones), and post-RT follow-up information. In a very few patients, due to the long interval between surgery and RT consultation, the original prostatectomy pathology report was unavailable for tabulation of the pathologic findings; these are recorded as "uncharted" in Table 1. As displayed, there are several patients with very low pre-RT PSAs that may not have expected to impact the study greatly. Although one might at first consider excluding these patients, thus allowing analysis of patients expected to have a higher yield of RIS-based decision changes, it was important to include these patients to preserve the consecutive nature of the study.

The RT recommendations before knowledge of the RIS findings were reviewed with regard to (a) the decision to recommend RT and with regard to (b) the general target volume to be treated (i.e., whether to deliver RT only to the PF or whether to deliver RT to the PF and the pelvis [PF+P] [defined as treatment to a pelvic volume larger than the PF, including unilateral or bilateral pelvic lymph nodes]). This review was feasible because the RIS scan was ordered by the radiotherapist or referring urologist at or near the time of the RT consultation. In the majority of cases, the RIS scan was ordered by the radiation oncologist at the time of initial consultation, so the initial plan was recorded before knowledge of the RIS information. In other cases in which the RIS scan was ordered by the referring urologist before the RT consultation, the official RIS reading was often unavailable at the time of consultation. In a few instances, the result of the RIS scan was available before the RT consultation, and even in these cases it was possible to infer from the consultation dictation or record what the RT plan would have been without the RIS information. Thus, it was possible in all cases to chart the RT plan before the knowledge of the RIS findings.

Of note, the most commonly used radiologic scans—the bone scan and CT scan of the abdomen or pelvis—were ordered in 20 and 15 patients, respectively, immediately before or at the time of RT consultation, and in all cases these tests were negative. The intent in all cases at the time of radiation referral was to offer RT with curative intent, as the metastatic work-up (when performed) and the pace of PSA rise was, before obtaining the RIS scans, believed to be consistent with disease localized to the pelvis. Although no uniform guidelines are yet established or adhered to (in the RT community in general or in our particular institution consortium), in general, PF radiation was thought to be indicated for patients with low-grade pathology, low PSA nadir, and long interval between nadir and failure; these criteria applied to the vast majority of patients in the current study. PF+P was recommended primarily because of aggressive pathology (Gleason score, >8 with seminal vesicle invasion) and corresponding increased lymph node risk. The absolute PSA (pre-RRP or the highest value pre-

TABLE 1
Patient Characteristics

Characteristic	Finding
No. of patients	54
Age (y)	Mean, 64; range, 47–82
Prostatectomy findings	
Pathologic T-stage	pT1/T2, 18; pT3, 32; pT4, 2; pTx, 2
Grade	GS 5, 3; GS 6, 14; GS 7, 23; GS 8, 6; GS 9, 5; uncharted, 3
Margins	Positive, 23; negative, 29; uncharted, 2
Seminal vesicle invasion	Positive, 14; negative, 38; uncharted, 2
Extracapsular extension	Yes, 31; no, 21; uncharted, 2
Pelvic lymph node involvement	Yes, 0; no, 52; unsampled, 2
Postprostatectomy and postradiation course	
Postprostatectomy PSA nadir (ng/mL)	
PSA ≤ 0.1	25
0.1 < PSA ≤ 0.2	8
0.2 < PSA ≤ 0.3	12
0.3 < PSA ≤ 0.5	3
0.5 < PSA ≤ 1.0	4
1.0 < PSA	1
Uncharted	1
Highest postprostatectomy PSA before RT consultation (ng/mL)	
PSA ≤ 0.1	4
0.1 < PSA ≤ 0.2	5
0.2 < PSA ≤ 0.3	5
0.3 < PSA ≤ 0.5	8
0.5 < PSA ≤ 1.0	13
1.0 < PSA ≤ 2.0	11
2.0 < PSA	8
Time from prostatectomy to RT consultation (mo)	Range, 1.0–136.0; mean, 29.8
Hormone therapy (*n*)	Yes, 20; no, 34
Follow-up post-RT (mo)	Mean, 19.6; median, 14.2; maximum, 69.3

Uncharted = original prostatectomy pathology report was unavailable for tabulation of pathologic findings (due to long interval between surgery and RT consultation).

RT) was generally not a significant factor in determining the RT to the pelvis in our hospital consortium; this may be subtly different from practices at other institutions. Review of the initial (pre-RIS) RT recommendations revealed that, of the 54 total patients, the RT decision was to treat the PF only in 52 patients and to treat the PF+P in 2 patients.

The RIS reports were then reviewed on each of these patients and summarized. 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. Planar and volume SPECT datasets were obtained using a dual-head SPECT Prism 200 Picker camera (Philips). This dual-energy procedure for acquisition of data and interpretation is described in considerable detail elsewhere (*16*) 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, a CT/SPECT system was not used. For each patient, the RIS findings, with regard to uptake in the PF, uptake in the P (i.e., uptake within the pelvis in a region outside of the PF), or EP uptake were reviewed.

Finally, the RT treatment decisions based on the RIS findings were reviewed for each patient. Any change in the recommendation to offer RT and any change in the general target volume to be treated were noted. Thus, there were 3 categories of final RT decisions: (a) no RT, (b) RT to PF only, and (c) RT to PF+P. The decision to abort RT was generally based on the RIS scan showing uptake in EP regions or the pattern of pelvic uptake (intensity and level of pelvic involvement [i.e., solitary vs. matted or multiple sites within the pelvis], as the risk for occult EP disease may rise). The decision to offer RT to the PF+P (changed from the decision to offer RT to the PF alone), was usually undertaken if the RIS scan showed uptake in the pelvis but not strong enough uptake to warrant consideration of occult EP disease. In each case, the provider reviewed the RIS findings in the clinical context of the patient's pathology, PSA nadir, disease-free interval, pace of PSA rise, CT or bone scan findings [if available], pre-RIS decision, and the known sensitivity or specificity rates of RIS to determine whether RIS would override the established pre-RIS decision. Because the study was retrospective, spanning several hospitals, each with several providing physicians, and because no specific published guidelines existed (or exist to date) in the literature on how to incorporate RIS into RT decision making, stylistic variations were expected to exist among the 8 different practitioners represented in this study and among the individual patients in their level of desire for aggressive management of the prostate cancer weighed against the potential side effects of RT. Within this

framework, however, each individual provider was usually consistent in the approach.

Although the treatment technique and dose delivered are not critical to the analysis of the decision making in this investigation, they do bear brief description: In category (b) of the final RT decision, the PF dose typically used at our institution was 66.0 Gy (in 2.0-Gy, once-daily fractions), and in category (c), the regional pelvic lymph nodes were treated to an initial dose of 50.4 Gy (in 1.8-Gy, once-daily fractions) or 50.0 Gy (in 2.0-Gy, once-daily fractions) followed by a PF boost to 16 Gy (in 2.0-Gy, once-daily fractions) to achieve a final dose of 66.0–66.4 Gy. The final dose used was based on the American Society for Therapeutic and Radiation Oncology consensus conference (*22*), which recommended a minimum dose of 64.0 Gy. When the pelvic lymph nodes were treated, a 4-field technique was typically used. The prostate bed was treated with 6-field conformal therapy between 1998 and 2000 and was treated with intensity-modulated RT from 2000 onward.

A Kaplan–Meier curve (*23*) was generated for biochemical failure-free survival, based on available post-RT follow-up PSA information. The definition of failure used was the presence of 2 consecutive PSA rises above the level of 0.2 ng/mL after reaching a nadir; patients were also declared to fail after 2 rises if no nadir was reached. This definition of failure combines features of definitions relying on successive rises and definitions relying on an absolute PSA threshold (*7–10*). In addition, univariate and multivariate analyses of patient, disease, and treatment factors were performed using the log rank test and Cox proportional hazards regression, respectively (*23*).

RESULTS

Table 2 shows the results of these analyses. Displayed for each patient are the individual RT provider, the RT decision before knowledge of the RIS findings, the RIS findings, and the RT decision after the knowledge of the RIS findings. Of the 54 patients originally referred for prostate RT, the initial decision was to recommend RT in all 54. In 2 cases (patients 24 and 36), the initial plan was to treat the PF+P; for the remaining 52 patients, the initial decision was to deliver RT to the PF only.

As shown in Table 2, the RIS findings were as follows: PF only in 43 patients, PF+P in 8 patients (patients 17, 20, 21, 25, 30, 37, 45, and 53), PF+EP in 2 patients (patients 11 and 22), and PF+P+EP uptake in 1 patient (patient 54).

As shown by the listing of post-RIS decisions in Table 2, after knowledge of the RIS results, the decision to withdraw the RT recommendation was made in 4 patients (patients 22, 30, 45, and 54). This decision was made due to pelvic uptake in 2 patients (patients 30 and 45), EP uptake in 1 patient (patient 22), and both pelvic and EP uptake in 1 patient (patient 45). Of the 54 patients for whom RT was initially recommended, RIS changed the general treatment volume in 6 patients (patients 17, 20, 21, 25, 37, and 53). This decision was due to pelvic uptake outside of the prostate bed in all 6 patients, causing the radiotherapist to design a more generous volume that encompassed the regional lymphadenopathy seen on RIS or, in most cases, a more generous volume to include the whole pelvis.

TABLE 2
RIS Decision Summary

Patient no.	RT provider	Pre-RIS decision (PF/P)	RIS findings (PF, P, EP)	Post-RIS decision*	
				RT	PF/P
1	1	PF	PF	Yes	PF
2	2	PF	PF	Yes	PF
3	1	PF	PF	Yes	PF
4	1	PF	PF	Yes	PF
5	1	PF	PF	Yes	PF
6	1	PF	PF	Yes	PF
7	1	PF	PF	Yes	PF
8	1	PF	PF	Yes	PF
9	3	PF	PF	Yes	PF
10	4	PF	PF	Yes	PF
11	4	PF	PF+EP	Yes	PF†
12	1	PF	PF	Yes	PF
13	1	PF	PF	Yes	PF
14	3	PF	PF	Yes	PF
15	5	PF	PF	Yes	PF
16	5	PF	PF	Yes	PF
17	1	PF	PF+P	Yes	PF+P
18	1	PF	PF	Yes	PF
19	3	PF	PF	Yes	PF
20	1	PF	PF+P	Yes	PF+P
21	6	PF	PF+P	Yes	PF+P
22	**3**	**PF**	**PF+EP**	**No**	**n/a**
23	3	PF	PF	Yes	PF
24	1	PF+P	PF	Yes	PF+P†
25	1	PF	PF+P	Yes	PF+P
26	1	PF	PF	Yes	PF
27	1	PF	PF	Yes	PF
28	7	PF	PF	Yes	PF
29	3	PF	PF	Yes	PF
30	**3**	**PF**	**PF+P**	**No**	**n/a**
31	1	PF	PF	Yes	PF
32	3	PF	PF	Yes	PF
33	6	PF	PF	Yes	PF
34	1	PF	PF	Yes	PF
35	1	PF	PF	Yes	PF
36	3	PF+P	PF	Yes	PF+P†
37	3	PF	PF+P	Yes	PF+P
38	6	PF	PF	Yes	PF
39	3	PF	PF	Yes	PF
40	1	PF	PF	Yes	PF
41	1	PF	PF	Yes	PF
42	3	PF	PF	Yes	PF
43	3	PF	PF	Yes	PF
44	3	PF	PF	Yes	PF
45	**3**	**PF**	**PF+P**	**No**	**n/a**
46	1	PF	PF	Yes	PF
47	1	PF	PF	Yes	PF
48	8	PF	PF	Yes	PF
49	5	PF	PF	Yes	PF
50	5	PF	PF	Yes	PF
51	3	PF	PF	Yes	PF
52	3	PF	PF	Yes	PF
53	3	PF	PF+P	Yes	PF+P
54	**3**	**PF**	**PF+P+EP**	**No**	**n/a**

*Bold type and line indicate patients had major RT decision change (RT to no RT); dotted line indicates patients had RT field change (PF to PF+P).
†RIS findings were not incorporated into final decision.
n/a = not applicable.

The influence of the RIS findings and a systematic comparison of the pre-RIS and post-RIS RT decisions are summarized in Table 3:

The top part of Table 3 displays the results of the analysis of the influence of RIS on the decision to offer RT. After knowledge of the RIS results, the decision to withdraw the RT recommendation was made in 4 of the 54 patients (7.4%). Although the χ^2 statistic is used when comparing proportions in 2 populations and was computed, the simple χ^2 statistical test is not entirely appropriate for evaluation of the significance level, as the 2 populations being compared are not independent. Thus, the significance level was evaluated using the McNemar test (*24*), which is a standard statistical test used for comparing the proportions of 2 dependent populations. As displayed in this part of Table 3, the χ^2 statistic is 4.0 (with 1 degree of freedom), and this reached statistical significance ($P = 0.045$).

The middle part of Table 3 displays the results of the analysis of the influence of RIS on the specific RT treatment field recommendations. In 6 of the 54 patients (11.1%), the knowledge of the RIS findings resulted in changing the treatment volume from PF to PF+P. These findings were analyzed in a manner similar to that of the top part of Table 3, again using the McNemar test. As displayed, the χ^2 statistic was 6.0 (with 1 degree of freedom), and this also reached statistical significance ($P = 0.015$).

Finally, the bottom part of Table 3 displays the results of the overall influence of RIS on the RT recommendations. As discussed earlier, knowledge of the RIS findings altered the RT decision a total of 10 times (a treatment volume change in 6 cases and the decision to withdraw RT altogether in 4 cases), in 54 patients (10/54 = 18.5%). This part of Table 3 displays the overall decisions pre- and post-RIS. Again, as for the top and middle parts of Table 3, although the χ^2 statistic was computed, it was not appropriate to test the significance level using the simple χ^2 test. Furthermore, because in this case there are 3 possible outcomes (RT to PF, RT to PF+P, and no RT), the McNemar test was also not entirely appropriate. Assuming that all 3 decisions are equally weighted, the statistical test of choice was the Stuart–Maxwell test (*25*,*26*), which is a standard test used to compare nondichotomous decisions in 2 dependent populations. (The Stuart–Maxell test actually reduces to the McNemar test used for the top and middle parts of Table 3 when the decision is dichotomous.) As displayed, the χ^2 statistic was 10.0 (with 2 degrees of freedom), and this also reached statistical significance ($P = 0.0067$).

Figure 1 displays the Kaplan–Meier curve for the entire cohort; as shown, the 3-y biochemical failure-free survival was approximately 78%. Table 4 shows the results of the univariate and multivariate analyses, which were performed using the listed patient, disease, and treatment factors as covariates. As displayed in Table 4, no factors demonstrated statistical significance. Only pathologic T-stage, highest pre-RT PSA, and hormone therapy demonstrated trends on the univariate analysis; on further multivariate analysis, even these parameters did not display statistical trends.

TABLE 3
Statistical Analyses of Influence of RIS on RT Decision Making

Influence of RIS on decision to recommend RT

	No RIS		
RIS	Offer RT	No RT	Total
Offer RT	50	0	50
No RT	4	0	4
Total	54	0	54

χ^2 statistic = 4.0 (1 degree of freedom), $P = 0.045$ (McNemar test)

Influence of RIS on specific RT treatment field recommendations

	No RIS		
RIS	RT to PF	RT to PF+P	Total
RT to PF	42	0	42
RT to PF+P	6	2	8
Total	48	2	50

χ^2 statistic = 6.0 (1 degree of freedom), $P = 0.015$ (McNemar test)

Overall influence of RIS on RT recommendations

	No RIS			
RIS	RT to PF	RT to PF+P	No RT	Total
RT to PF	42	0	0	42
RT to PF+P	6	2	0	8
No RT	4	0	0	4
Total	52	2	0	54

χ^2 statistic = 10.0 (2 degrees of freedom), $P = 0.0067$ (Stuart–Maxwell test)

DISCUSSION

RIS directed against PSMA was found in this investigation to influence postprostatectomy RT decision making for the identification of patients with disease not likely to benefit from RT and for guiding general RT treatment volume definition. This study demonstrated that in the select group of patients who have a rising PSA post-RRP or are at high risk of failure post-RRP, and in many cases having negative bone scan or abdomen or pelvis CT scan, the RIS scan provides additional information that is useful in guiding the RT decision making. This was demonstrated in 2 ways: (a) altering the decision to offer RT and (b) altering the decision to offer RT to a different target volume than initially intended. These results might be expected, because RIS has a different mechanism of identification of the disease and the information it provides would be expected to be somewhat complementary to the current tools currently available to guide RT decision making. However, to our knowledge,

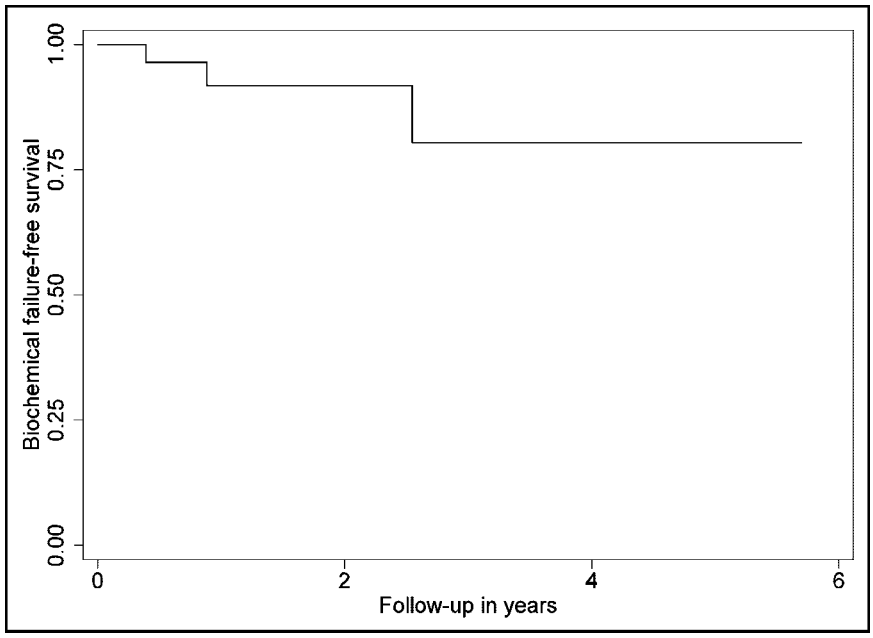

FIGURE 1. Kaplan–Meier biochemical failure-free survival curve.

this investigation is the first report to demonstrate a statistically significant change in RT decision making based on RIS findings.

The number of changes in the RT decision making is a strong function of the yield of the RIS findings in the patient population under study. In this context, the expected rates of uptake in different anatomic regions at the time of RIS are relevant. The key multiinstitutional study (*15*) sheds light on this matter, and the rates of RIS uptake in the setting of post-RRP in that study were as follows: PF, – 65%; PF+P, –25%; PF+P+EP, – 20%; EP, – 10%. Our investigation showed a higher percentage of PF-only uptake (42/54 = 78%) and a corresponding lower percentage of P and EP uptake, due in part to the fact that bone scans and CT scans may have excluded some individuals who also would have had RIS uptake in the P and EP regions. Thus, it is probable that if the RIS scans were done on a de novo population to guide RT (i.e., a population in which no prior bone scan or CT scans were obtained), the percentage uptake on the RIS scans would be higher than that of the current investigation. Consequently, the RT decisions would likely have been altered more frequently, and the conclusions of the current investigation would likely be further strengthened.

TABLE 4
Univariate and Multivariate Analyses

Covariate	Univariate analysis *P**	Multivariate analysis *P*†
Age	0.73	
Pathologic T-stage	0.14	0.58
Grade	0.71	
Margin status	0.85	
Seminal vesicle invasion	0.36	
Extracapsular involvement	0.95	
PSA nadir	0.98	
RRP to RT interval	0.90	
Highest pre-RT PSA	0.11	0.63
Hormone therapy	0.06	0.99
RIS findings	0.78	
RT provider	0.66	

*Using log rank test.
†Using Cox proportional hazards regression.

The effect of the referral pattern on interpretation of the results warrants discussion. In particular, there is expected to be a strong referral bias, as the current investigation only evaluates those patients who were referred by urologists for consideration of curative RT. Patients who had positive bone scans, positive CT scans, or even positive RIS scans before the RT referral were excluded from this study and therefore cannot be addressed by the current analysis. However, although the results of our study may not be relevant to the general group of post-RRP patients, the results are relevant to the practicing radiotherapist, as the patient population in our study is similar to that seen in most RT clinics, and our study addresses the use of RIS in assisting decision making in this specific setting.

Although the RIS information was useful in the vast majority of patients in this study, there were instances in which the RIS findings were not fully incorporated into the final decision, resulting in several seeming inconsistencies that bear discussion. Specifically, in 2 patients (Table 2, patients 24 and 36), the original plan was to deliver RT to the prostate and regional lymph nodes. This plan was carried through, despite the RIS scan showing uptake in the PF only. Thus, the RIS scans in these cases were believed to represent false-negative findings in the pelvis in both cases, and the RT clinician opted to make the decision, based on

the rise in PSA and post-RRP findings, to continue with the original plan. In these cases, RIS was, however, useful as an additional tool (similar to the bone scan and the CT scan of the abdomen or pelvis) to rule out EP disease. Conversely, although EP uptake was demonstrated in patient 11, this was not thought to be consistent with the patient's clinical picture (the EP uptake was in the supraclavicular fossa, a site amenable to physical examination), and the RIS reading was viewed as a false-positive finding; in other instances of EP uptake (patients 22 and 54), the location of the EP uptake was intraabdominal, and the RIS findings were read as true-positives. Finally, there are seeming inconsistencies in the use of the RIS scan showing PF+P uptake; in some cases (patients 17, 20, 21, 25, 37, and 53), RIS uptake in the PF+P led to a decision to treat the PF+P, whereas in other cases (patients 30 and 45), uptake in the PF+P caused a decision to abort RT altogether. These seeming inconsistencies are due in part to the pattern of uptake in the PF+P (and relative concern for occult EP disease) and in part to provider bias. In summary, although RIS did influence the RT decision making significantly in this investigation, there were instances in which clinical judgment did override the RIS findings. Many of the seeming inconsistencies can be explained by false-positive and false-negative findings, the pattern of RIS uptake, and variations in clinical judgment. Although there are expected variations between different providers, each provider was usually consistent in the decision making. Because no institutional policy existed or has been reported in the published literature on the incorporation of RIS for RT decision making, our results are likely a representative cross section of those expected in the general RT community. Of important note, the RT provider did not reach significance on univariate analysis (Table 4), suggesting that, within the limitations of the power of the study (as there were numerous radiation oncologists participating in the study), provider bias does not confound interpretation of the biochemical control outcome reported in this investigation.

Even with knowledge of the variations among providers, it is nonetheless important to quantify the findings to determine the general influence of RIS in this study population, which is what Table 3 sought to answer. Table 3 and the corresponding statistical tests account for the cases in which the RIS scan was ignored as well as when it did influence the decision: The off-diagonal elements represent a positive influence, whereas ignoring the test causes greater weighting of the diagonal elements and weakens the role of the RIS scan. The statistical test used in the top part of Table 3 assumes equal weighting of the decision to withdraw RT and the decision to offer RT, the statistical test used in the middle part of Table 3 assumes equal weighting of the decision to offer RT to the PF only and to offer RT to the PF+P, and the statistical test used in the bottom of Table 3 assumes equal weighting of the decision to withdraw RT and the decision to offer RT to a different volume than originally intended. Although modeling these weightings poses its own set of challenges, if the decision not to offer RT (a fundamentally major change in treatment course) or to offer RT to the PF+P is weighted higher than the decision to offer RT to PF, the off-diagonal elements in Table 3 would be weighted greater and the current study would reach even higher statistical significance than that currently reported.

Independent of these observations about statistical tests used to determine the influence of RIS on decision making, a key contribution of this investigation for the practicing clinician is the biochemical control analysis. The biochemical failure-free survival rate in the current investigation is, with available follow-up, similar to or higher than most reported postprostatectomy RT series (*7–10*). As shown in Table 4, no patient, disease, or treatment factor reached statistical significance. It is noteworthy that, in the current investigation, the interval between prostatectomy and RT (a surrogate for immediate RT vs. salvage RT) and hormone therapy did not reach significance, suggesting that these factors did not impact RIS uptake and the resulting treatment decisions strongly enough to influence the survival outcome. It is also noteworthy that the RIS findings themselves did not affect the survival. Correlating RIS findings with survival outcome has been undertaken by other investigators, with both positive (*18*) and negative (*19*) studies having been reported. It is important to understand that our investigation was not designed to answer this particular question, and the lack of significance of the RIS findings on univariate analysis should not be interpreted as a negative finding for the influence of RIS on survival, as in our study the survival detriment in having RIS uptake outside the PF was likely negated by the survival advantage in designing, in most cases, larger RT portals to encompass these areas of uptake.

The results of this study can form the basis for undertaking similar studies examining the role of RIS in the setting of pre-RRP decision making, in the setting of guiding decisions related to seed placement when performing a brachytherapy implant, and for decision making regarding selection of therapy in the setting of recurrent disease after radical RT.

In addition, the results of our study can be expanded to further analyze the role of RIS even within the current study population. First, the true survival advantage of using RIS to assist in decision making would require the study of a matched-pair cohort not undergoing RIS, as the patients in the current study can serve as their own controls for the decision-making process but not for the treatment outcome analysis. Second, the potential to use the exact regions of uptake on the RIS scan to guide the definition of the PF target bed, as an extrapolation of the work done in registering the RIS scan to the planning CT scan (*27*), has been studied (*28*).

The biases and limitations inherent in a retrospective review are understood by the investigators. Within these limitations, however, the current investigation sheds light

on the role of RIS in the setting of post-RRP RT decision making as a tool to aid in selecting the patients most likely to benefit from RT and to aid in designing the general radiation field arrangement. It is hoped that the results of this investigation can guide prospective investigations in this area.

CONCLUSION

RIS was found in this investigation to influence post-RRP RT decision making for the identification of patients not likely to benefit from RT and for guiding general target volume definition. Our study can serve as a framework with which to design prospective trials in this area of investigation.

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REFERENCES

1. Gronberg H. Prostate cancer epidemiology. *Lancet.* 2003;361:859–864.
2. Potosky AL, Feuer EJ, Levin DL. Impact of screening on incidence and mortality of prostate cancer in the United States. *Epidemiol Rev.* 2001;23:181–186.
3. Neal DE, Donovan JL. Prostate cancer: to screen or not to screen? *Lancet Oncol.* 2000;1:17–24.
4. Jani AB, Hellman S. Early prostate cancer: clinical decision-making. *Lancet.* 2003;361:1045–1053.
5. Sokoloff MH, Brendler CB. Indications and contraindications for nerve-sparing radical prostatectomy. *Urol Clin North Am.* 2001;28:535–543.
6. Hanlon AL, Hanks GE. Failure patterns and hazard rates for failure suggest the cure of prostate cancer by external beam radiation. *Urology.* 2000;55:725–729.
7. Anscher MS, Clough R, Dodge R. Radiotherapy for a rising prostate-specific antigen after radical prostatectomy: the first 10 years. *Int J Radiat Oncol Biol Phys.* 2000;48:369–375.
8. Schild SE, Buskirk SJ, Wong WW, et al. The use of radiotherapy for patients with isolated elevation of serum prostate specific antigen following radical prostatectomy. *J Urol.* 1996;156:1725–1729.
9. Petrovich Z, Lieskovsky G, Langholz B, Jozsef G, Streeter OE Jr, Skinner DG. Postoperative radiotherapy in 423 patients with pT3N0 prostate cancer. *Int J Radiat Oncol Biol Phys.* 2002;53:600–609.
10. Kalapurakal JA, Huang CF, Neriamparampil MM, et al. Biochemical disease-free survival following adjuvant and salvage irradiation after radical prostatectomy. *Int J Radiat Oncol Biol Phys.* 2002;54:1047–1054.
11. Manyak MJ, Hinkle GH, Olsen JO, et al. Immunoscintigraphy with indium-111-capromab pendetide: evaluation before definitive therapy in patients with prostate cancer. *Urology.* 1999;54:1058–1063.
12. Quintana JC, Blend MJ. The dual-isotope ProstaScint imaging procedure: clinical experience and staging results in 145 patients. *Clin Nucl Med.* 2000;25:33–40.
13. Hinkle GH, Burgers JK, Neal CE, et al. Multicenter radioimmunoscintigraphic evaluation of patients with prostate carcinoma using indium-111 capromab pendetide. *Cancer.* 1998;83:739–747.
14. Murphy GP, Elgamal AA, Troychak MJ, Kenny GM. Follow-up ProstaScint scans verify detection of occult soft-tissue recurrence after failure of primary prostate cancer therapy. *Prostate.* 2000;42:315–317.
15. Sodee DB, Malguria N, Faulhaber P, Resnick MI, Albert J, Bakale G. Multicenter ProstaScint imaging findings in 2154 patients with prostate cancer: the ProstaScint Imaging Centers. *Urology.* 2000;56:988–993.
16. Blend MJ, Sodee DB. ProstaScint: an update. In: Freeman LM, ed. *Nuclear Medicine Annual 2001.* Philadelphia, PA: Lippincott Williams and Wilkins; 2001:109–142.
17. Polascik TJ, Manyak MJ, Haseman MK, et al. Comparison of clinical staging algorithms and 111indium-capromab pendetide immunoscintigraphy in the prediction of lymph node involvement in high risk prostate carcinoma patients. *Cancer.* 1999;85:1586–1592.
18. Kahn D, Williams RD, Haseman MK, et al. Radioimmunoscintigraphy with In-111-labeled capromab pendetide predicts prostate cancer response to salvage radiotherapy after failed radical prostatectomy. *J Clin Oncol.* 1998;16:284–289.
19. Thomas CT, Bradshaw PT, Pollock BH, et al. Indium-111-capromab pendetide radioimmunoscintigraphy and prognosis for durable biochemical response to salvage radiation therapy in men after failed prostatectomy. *J Clin Oncol.* 2003;21:1715–1721.
20. Ellis RJ, Sodee DB, Spirnak JP, et al. Feasibility and acute toxicities of radioimmunoguided prostate brachytherapy. *Int J Radiat Oncol Biol Phys.* 2000;48:683–687.
21. Ellis RJ, Kim EY, Conant R, et al. Radioimmunoguided imaging of prostate cancer foci with histopathological correlation. *Int J Radiat Oncol Biol Phys.* 2001;49:1281–1286.
22. Cox JD, Gallagher MJ, Hammond EH, Kaplan RS, Schellhammer PF. Consensus statements on radiation therapy of prostate cancer: guidelines for prostate rebiopsy after radiation and for radiation therapy with rising prostate-specific antigen levels after radical prostatectomy. *J Clin Oncol.* 1999;17:1155.
23. Fleming TR, Lin DY. Survival analysis in clinical trials: past developments and future directions. *Biometrics.* 2000;56:971–983.
24. Bowker AH. A test for symmetry in contingency tables. *J Am Stat Assoc.* 1948;43:572–574.
25. Stuart A. A test for homogeneity of the marginal distributions in a two way classification. *Biometrika.* 1955;42;412–416.
26. Maxwell AE. Comparing the classification of subjects by two independent judges. *Br J Psychiat.* 1970;116:651–655.
27. Hamilton RJ, Blend MJ, Pelizzari CA, Milliken BD, Vijayakumar S. Using vascular structure for CT-SPECT registration in the pelvis. *J Nucl Med.* 1999; 40:347–351.
28. Jani AB, Spelbring D, Hamilton R, et al. Impact of radioimmunoscintigraphy on definition of clinical target volume for radiotherapy after prostatectomy. *J Nucl Med.* 2004;45:238–246.