The Role of Indium-111 Radioimmunoscintigraphy in Post-Radical Retropubic Prostatectomy Management of Prostate Cancer Patients

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Indium-111 radioimmunoscintigraphy (RIS) has an increasing role in the treatment of prostate cancer and is most commonly performed at this disease site using labeled monoclonal antibody against prostate-specific membrane antigen. There are many limitations of RIS, including low spatial resolution, low diagnostic yield and limited availability. Despite these limitations, the efficacy of RIS has been demonstrated in many clinical studies, including multi-institutional investigations. The highest sensitivity and specificity of RIS appears to be in the post-radical retropubic prostatectomy (post-RRP) setting. RIS has recently been explored for its role in clinical radiotherapy decision-making, and was found to have a significant impact in selecting patients for radiotherapy and for the general radiotherapy treatment volume definition. RIS has also recently been explored for its role in radiotherapy planning and was found to impact clinical target volume design. However, manual editing of the RIS volume is still necessary when projected into the radiotherapy-planning scan, as there is often overlap in the RIS-defined uptake regions with normal structures (rectum, bladder and symphysis bone marrow). The impact of RIS on biochemical control has been explored, with studies in this area yielding conflicting results. It appears that the maximum impact of RIS is possible when areas of labeled antibody uptake regions are co-registered with the radiotherapy-planning computed tomography scan. The larger RIS-guided target volumes do not appear to be prohibitive in increasing radiotherapy-related toxicity. Future directions of the use of RIS for post-RRP prostate cancer are discussed.

Keywords: Prostate cancer; Radioimmunoscintigraphy; Radiotherapy

Prostate cancer is among the most commonly detected malignancies in men due in part to the widespread use of serum prostate specific antigen (PSA) and digital-rectal examination-based screening.¹ The two main curative options for localized prostate cancer are surgery and radiotherapy.² Radical retropubic prostatectomy (RRP), although successful for many early stage patients with favorable prognostic factors, can be inadequate to achieve long-term biochemical control.^{2,3} Several clinical situations comprising high-risk disease found at the time of surgery or on pathological review, or rising PSA or clinical failure after surgery, warrant the use of post-RRP radiotherapy.⁴⁻¹⁴

The precise population that should undergo immediate/adjuvant radiotherapy based on high-risk pathological features is controversial with seminal vesicle invasion, high grade

(Gleason score >7), extracapsular extension and/or positive margins often used in making this decision, in addition to the preoperative stage, grade and PSA. Recently, a disease-free survival advantage with the use of adjuvant radiotherapy has been demonstrated in randomized trials.^{11,12} Similarly, the decision to administer salvage radiotherapy (often defined as radiotherapy administered 1 year or later from the time of surgery) is complex. The pre-surgical disease factors, the findings at the time of surgery, disease-free interval after surgery and PSA nadir/velocity after surgery are all factors used in making the decision to offer salvage treatment. Salvage radiotherapy has demonstrated excellent results for selected patients.¹³ Both radiotherapy approaches (adjuvant or salvage) require patients to be properly selected for radiotherapy and require that the radiotherapy be planned in a manner that will maximize the chance of tumor and biochemical control while minimizing treatment complications.¹⁴

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Received: August 16, 2006
Revised: December 28, 2006
Accepted: January 18, 2007

Grant Support: NCMHD grant
5P60 MD000525

doi:10.3121/cmr.2007.740

In addition to patient disease and follow-up characteristics, imaging studies are increasingly used to select patients for post-RRP radiotherapy. When rising PSA values are detected after prostatectomy, it is important to attempt to determine the source of the PSA. In addition to a careful digital rectal examination, a transrectal ultrasound can also be used to evaluate the prostate bed,¹⁵ with biopsies usually performed if there is suspicion for a mass in the prostate fossa. A magnetic resonance imaging (MRI) scan can be obtained, typically while using an endorectal coil, to evaluate soft tissue detail.¹⁶ A computed tomography (CT) scan of the abdomen/pelvis is often used in evaluating the prostate bed and can also assist in determining if there is involvement of the pelvic/peri-aortic lymph nodes.^{17,18} A bone scan is often used to rule out skeletal metastases as the source of PSA.¹⁹ While the CT scan, ultrasound and bone scan can be useful for evaluating the source of PSA, all these studies often have relatively low yield in the setting of post-RRP disease, particularly if the PSA is rising but still low (<1.0 ng/ml). Because the chance of distant metastases is usually low in patients selected for prostatectomy, imaging studies that have a higher yield in evaluating loco-regional recurrence are becoming increasingly important in patient selection for radiotherapy.

The limitations of many of the above imaging modalities have motivated the development of radioimmunoscintigraphy (RIS) for prostate cancer.²⁰⁻³¹ The most common type of RIS employs capromab pendetide (Prostascint, Cytogen Corporation, Princeton, NJ), a site-specific murine monoclonal antibody labeled with indium-111 that is reactive with prostate specific membrane antigen, a glycoprotein expressed by prostate tissue. It is strongly reactive with both primary and metastatic prostate carcinoma in addition to normal prostate tissue.³² Indium-111 RIS will be the only method of RIS discussed herein, as it is the only approach for which any substantial clinical correlation has been reported. RIS can assist in the staging workup, particularly in helping to determine whether pelvic or abdominal lymphadenopathy exists and can complement conventional imaging studies. When correlated with biopsy results, RIS yielded an overall accuracy of 80% (sensitivity=79%, specificity=80%, positive predictive value=68%, negative predictive value=88%).³³ Although the role of RIS in the setting of the intact prostate has been explored, particularly for guiding external beam radiotherapy³⁴ and brachytherapy^{35,36} treatment planning, the major reported experience for use of RIS is in the post-RRP setting, and the discussion of RIS herein will be limited to this scenario. Several studies have been done documenting the efficacy of RIS in evaluating post-RRP disease, including multi-institutional analyses.^{23,25} The approximate values for diagnostic parameters of RIS in the post-surgery setting are: sensitivity 75% (extraprostatic), 92% (prostate fossa); specificity 86%; positive predictive value 81%; negative predictive value 67%.^{21,23,25,26} These parameters for RIS, particularly the sensitivity figures, are higher than the corresponding values for CT, ultrasound or digital rectal examination.

The role of RIS in the management of prostate cancer remains an area of intense controversy, as there are both positive²⁹ and negative^{30,31} studies. The goal of the current report is not to resolve this controversy but rather to explore some of the potential roles of RIS in the context of the mixed results in the current literature.

In this review, we describe some of the recent clinical developments related to RIS in the post-RRP setting and discuss (1) applications of RIS to the patient selection for radiotherapy, (2) the influence of RIS on the radiotherapy target volume design, and (3) the impact of RIS on the radiotherapy toxicity and biochemical control outcomes.

Patient Selection

The selection of post-RRP patients for RT is a complex process. The decision to offer immediate/adjuvant radiotherapy is, as described above, often driven by the preoperative disease factors and by the presence of adverse pathological features such as positive margins, seminal vesicle invasion and/or high-grade disease. Adjuvant radiotherapy has been shown in randomized controlled trials to improve biochemical control and disease-free survival without risk of severe morbidity.^{11,12} In the adjuvant radiotherapy setting, the preoperative imaging workup is often recent enough so that repeating a preoperative CT or bone scan has too low a diagnostic yield. Similarly, additional radiological studies, including RIS, often have too low a yield in this setting. Thus, the major role of RIS in patient selection is for salvage radiotherapy.

The process of selecting patients for salvage radiotherapy has been studied in considerable detail recently. The largest study of its type examining outcomes of salvage radiotherapy employed recursive partitioning algorithms to stratify the factors influencing post-radiotherapy biochemical control.¹³ The major prognostic factors were Gleason score (<7 vs ≥7), post-RRP PSA prior to radiotherapy (<1.0 ng/ml), seminal vesicle invasion, margin status (with positive margins paradoxically being prognostic for success with radiotherapy due to the higher likelihood of local-only recurrence in these patients) and PSA doubling time (with 10 months being the breakpoint). Although these parameters were successful in stratifying patients likely to benefit from salvage radiotherapy, there is still considerable heterogeneity in biochemical control rates within each recursive partitioning bin due perhaps to small patient numbers in some of the bins, and due perhaps to regional or extra-pelvic sources of PSA not identified in some patients. Although bone scan and/or CT scans were done in many patients in this trial, there is still a need for improvement of the confidence intervals within each partition with the use of additional tools to stratify patients likely to benefit from salvage radiotherapy.

In this context, the role of RIS in the post-RRP radiotherapy decision-making process has been examined.³⁷ In this study, the records of 54 patients who had undergone prostatectomy,

Figure 1. Flow diagram of image data demonstrating how the planning CT was registered with simultaneously-acquired dual-isotope Tc-99m-labeled RBC SPECT and indium-111-MoAb RIS scans, enabling the projection of CTV_{RIS} into the planning CT scan for assistance in modifying CTV_{pre} to define CTV_{post} (reprinted with permission from Su et al, Clin Nucl Med 2006;31:139-144. Copyright 2006 Lippincott Williams & Wilkins. All rights reserved).

were referred for post-surgical radiotherapy and had an RIS scan performed, were reviewed. Prior to the RIS scans, 20 of these patients had bone scans and 15 patients had CT scans; all bone and CT scans were negative. The RIS findings with regard to prostate fossa, pelvic and/or extra-pelvic uptake were recorded. The radiotherapy treatment decisions with respect to (1) the decision to administer or not administer radiotherapy, (2) the decision to treat the prostate fossa only, and (3) the decision to treat the prostate fossa plus regional lymph nodes were examined. After incorporation of the RIS findings, decision changes were made for 4 patients that resulted in not offering radiotherapy ($P=0.046$) due to either extra-pelvic uptake or strong pelvic uptake on the RIS scan. Furthermore, decision changes were made in 6 patients that resulted in incorporating the pelvic nodes additionally to the prostate fossa in the treatment field ($P=0.015$) due in each case to pelvic uptake on the RIS scan. Within the limitations of this study, including its retrospective nature, varied treatment decision-making philosophies among different radiotherapy providers (for instance, strong pelvic uptake was viewed as a marker for distant disease by some providers and as loco-regional disease by others) and the occasional false positives (due to uptake in the supraclavicular region in one case and to uptake in the bowel in another), RIS does appear to be one additional advantageous tool in the salvage radiotherapy decision-making process. However, it is important to consider that the extra-pelvic sensitivity (75%) and negative predictive value (67%) preclude the use of RIS as the sole criterion for decision-making;^{23,25} the RIS results must be used in the context of other available clinical information when making the decision to administer post-RRP radiotherapy.

Radiotherapy Target Design

Following the decision to administer post-RRP radiotherapy, the next challenge is to design the radiotherapy target volume. This target definition process has undergone significant changes over the past few decades. Prior to the development of modern CT-based radiotherapy treatment planning, a retrograde urethrogram was often used to estimate the location of the urogenital diaphragm, and hence, the inferior aspect of the prostatic fossa. The size of the prostate and seminal vesicles, and hence the radiotherapy portals, were then estimated either using standard nomograms or using the prostatectomy specimen.^{15,16} The use of CT for radiotherapy planning later permitted improved precision both in target definition and in design of conformal radiotherapy (using beam arrangements and beam blocking that maintained target dose coverage with reduction of rectum and bladder dose).³⁸ Additionally, a preoperative CT scan, when available, could be used to guide the post-RRP target design. As the yield of CT scan in visualizing post-RRP disease is low, other imaging modalities warrant consideration. MRI allows visualization of gross disease to a greater extent than CT but still has a low diagnostic yield if the PSA is low.¹⁶ The role of RIS is better examined in this setting with multi-institutional studies^{23,25} demonstrating an overall accuracy of approximately 80%.

Although the radiotherapy planning and delivery processes have become increasingly precise, particularly with the development of intensity-modulated radiotherapy,^{39,40} there has still been considerable variation and subjectivity in the design of the post-RRP target volume. RIS has been explored for this specific task of post-RRP prostate bed target design.⁴¹⁻⁴⁴ Figure 1 demonstrates how the planning CT scan

Figure 2. CTV_{RIS} (red contours) drawn on 5-day post-injection transaxial RIS images at level of prostatic fossa.

and the RIS scan were used in these prior investigations to define the prostate bed clinical target volume (CTV). On the planning CT scan, the blood vessels were outlined, as well as the CTV that would have been treated without the RIS knowledge (CTV_{pre}). The design of CTV_{pre} incorporated information provided by the planning CT, the prostatectomy findings and the PSA record, but did not incorporate information provided by the RIS scan. The bladder, rectum, pubic symphysis and penile bulb were also contoured. The major arterial vessels (abdominal aorta, bifurcation into the common iliac arteries, subsequent bifurcation to the internal and external iliac arteries) were outlined on the Tc-99m-labeled red blood cell (RBC) single photon emission computed tomography (SPECT) scan. These same vessels were outlined on the planning CT scan, and the two scans (CT scan and RBC SPECT scan) were then registered. Next, the areas of uptake, as shown on the RIS scan, were entered by the nuclear medicine physician. An example of this process is shown in figure 2. As shown, the area of uptake in the prostate fossa (at the level of the femoral heads) was delineated.²⁶ This volume was denoted CTV_{RIS}. Of note, a vessel subtraction technique was often used to prevent shadowing of the volume of interest by the vessel uptake, in order to facilitate accurate delineation of CTV_{RIS}. Then, because the RIS scan was acquired simultaneously with (and hence, automatically registered) to the RBC SPECT scan, the CTV_{RIS} could be projected into the planning CT scan. A fundamental problem in projecting the CTV_{RIS} into the planning CT scan is that of registration. There are many ways to perform this process, and using bony landmarks does not in most cases align the soft tissue properly. Thus at our institution we used the vessel-registration approach described above, which enabled registration of the soft tissue. Although this process minimized the registration

error to the range of approximately 3 mm, it does not overcome the low resolution of RIS and potential overlap with surrounding normal rectum/bladder. Thus, this projection of CTV_{RIS} in the planning CT was used in conjunction with the CTV_{pre} described above in order to assist in defining the final CTV (CTV_{post}). A formal statistical comparison of CTV_{pre} and CTV_{post} on 25 patients found a significant difference in volume (24.4 cm³ vs 35.0 cm³, $P=0.032$),⁴¹ suggesting a significant impact of the use of RIS in changing a 'standard' post-RRP prostate fossa target volume.

A follow-up study which compared CTV_{post} versus CTV_{RIS} demonstrated, however, that caution is warranted in simply using the regions of RIS uptake to define the post-RRP target volume.⁴⁴ Figure 3 shows an example of a planning CT scan with four axial slices at different levels, from superior to inferior, with normal structures displayed: bladder (blue), rectum (green), pubic symphysis (pink) and penile bulb (yellow). On each of these four axial slices, the CTV volumes are shown in red: CTV_{pre} (left), CTV_{RIS} (center) and CTV_{post} (right). This study demonstrated that throughout the patient population, CTV_{RIS} overlapped significantly more than CTV_{pre} did in the bladder ($P=0.04$), rectum ($P=0.04$) and symphysis ($P=0.02$), but not in the penile bulb ($P=0.25$). Similar results were found when comparing CTV_{RIS} to CTV_{post}. These findings suggested that the RIS volumes do overlap with many normal structures when projected into the planning CT scan and points to the need for manual supervision/editing of RIS volumes, even with an accurate vessel-based registration process.

Cancer Control and Toxicity Outcomes

As described above, several investigations, including multi-center studies, demonstrated high sensitivity and specificity for the use of RIS in correlating with sites of disease. However, the more important clinical question is whether such areas of positive uptake correlate with ultimate cancer 'cure.' The role of RIS in influencing post-RRP biochemical control remains highly controversial.

One early study²⁹ showed that positive RIS findings correlated with biochemical failure. Men with negative RIS scans were more likely to have a durable response with salvage radiotherapy. Consistent with other studies,^{45,46} 70% were biochemically controlled if there was no uptake seen outside the prostatic fossa compared to 22% of patients controlled when there was uptake outside the prostatic fossa and pelvis ($P=0.0225$). However, many of these studies had relatively short follow-up, and standard prognostic factors were in many cases not balanced between those with negative and positive RIS scans, limiting the ability to determine how much of the difference in outcome was due to RIS findings and how much was due to differences in prognostic factors. In another recent study of men without extra-prostatic uptake on RIS prior to salvage radiotherapy,⁴⁷ 62% had a response to radiotherapy and 40% had undetectable PSA levels at last follow-up with a median follow-up of 3 years. These results

Figure 3. Axial images of planning CT and 4 different levels from superior to inferior. Normal structures are displayed: bladder (blue), rectum (green), pubic symphysis (pink) and penile bulb (yellow). On each of the 4 axial cuts, the CTV volumes are shown in red: CTV_{pre} (left), CTV_{RIS} (center) and CTV_{post} (right) (reprinted with permission from Su et al, Clin Nucl Med 2006;31:139-144. Copyright 2006 Lippincott Williams & Wilkins. All rights reserved).

may not suggest an improved biochemical control advantage of RIS compared with historical controls. However, the biochemical survival curves did not continue to drop to the same degree as often seen with other salvage radiotherapy studies. Further follow-up is required to see if this durability of response is maintained.

Other recent studies do not confirm differences in outcome based on RIS uptake. One study reported the results of 30 men who were radiographically negative for metastatic disease and who received salvage radiotherapy for rising PSA post-prostatectomy.³⁰ The results of the RIS scan were analyzed for correlation with PSA control. No differences in 2-year biochemical control were found between those with positive RIS scans versus negative RIS scans (38% vs 31%). Furthermore, a retrospective review of 42 patients with post-RRP PSA failure was recently performed.⁴⁸ Sixteen of these

patients underwent salvage radiotherapy, 15 had RIS uptake only in the prostate bed, and only 7 (47%) of these 15 had durable PSA response. The authors concluded that rate of PSA rise was as good or better of predictor of biochemical control than the results of the RIS scan.

While the argument on the role of RIS as a diagnostic test is ongoing, the separate question of the role of RIS in improvement of biochemical control for those patients having RIS integrated into the treatment planning process has been studied recently.⁴⁹ In this retrospective study, the charts of 107 patients receiving post-RRP salvage radiotherapy were reviewed. No RIS scan was obtained in 54 patients (group A), and an RIS scan was obtained in 53 patients (group B). Of these 53 patients, 40 (subgroup B1) underwent a vessel-based registration that allowed projecting the region of uptake on the RIS scan into the radiotherapy-planning CT scan, whereas 13 (subgroup B2) did not undergo such a

registration. Three-year biochemical control was higher for group B versus group A (81% vs 76%), but on multivariate analysis, use of RIS, in and of itself, was not a significant factor predicting PSA control ($P=0.92$). However, 3-year biochemical control was higher for subgroup B1 versus B2 (84.5% vs 71.6%), and on multivariate analysis, use of the RIS-CT scan correlation was the only factor prognostic for improvement in biochemical control ($P=0.042$). The findings of this study may explain some of the negative results using RIS, either (1) RIS may not have been used adequately for patient selection, or (2) the true potential of RIS, which may require projection of the regions of uptake on the RIS scan into the radiotherapy-planning CT, was not realized in some of the above negative studies.

Toxicity results with the use of RIS for post-RRP radiotherapy planning have also been reported,⁴⁹ and documents a minor increase in acute toxicity but no difference in late toxicity between those patients having RIS scan versus those that did not, suggesting that radiotherapy using the often-larger RIS-guided target volumes is generally tolerable. This study was well-powered ($n=107$), and also, the median follow-up of 2 years in this study was adequate to analyze acute toxicity results (minor increase in grade 1 rectal toxicity observed in the RIS arm, but no differences in grade 2-5 rectal toxicity or grade 1-5 bladder toxicity observed) and late toxicity results (no differences in toxicity along any axis were observed between the RIS and no-RIS arms). The mean RIS dose in this study (65.0 Gy) was similar to that recommended by a consensus conference on post-RRP radiotherapy (64.0 Gy).⁵⁰ Thus, the approximate 5% benefit in biochemical failure-free survival afforded by the use of RIS in the context of small differences in toxicity supports a benefit to using RIS to assist in post-RRP radiotherapy planning.

Discussion/Future Directions

Prostate cancer management has advanced significantly over the past decade, most notably with improved methods of risk stratification, which allow for more appropriate treatment selection for individual patients based on their individual prognostic factors. Some of these improvements have come in the area of imaging (including RIS) and, foremost, in combining of modalities with new image fusion techniques. As prostate cancer is one of the most common diagnoses and requires considerable healthcare resources, it is important for clinicians to select treatments in a manner that maximizes patient outcomes. The balance between cancer control and toxicity must be tempered with the individual clinical scenario and begins both with patient selection and with treatment optimization. The role of imaging, initially with CT, ultrasound and bone scans, and now with more sophisticated imaging such as RIS, lies in both of these areas.

Importantly, although successful at many cancer disease sites, positron emission tomography (PET) using 18-F-fluorodeoxyglucose (FDG) does not adequately detect local recurrence after RRP due to the low metabolic activity of prostate cancer and interference with normal urinary

activity in the bladder.⁵¹ Thus, PET currently only has a role in evaluating aggressive advanced prostate cancer patients. However, recent efforts suggest a promising role for PET imaging in prostate cancer patients with recurrent disease at PSA relapse using 11-C-acetate,⁵² and more recently, 11-C-choline.⁵³ A principal advantage of PET over indium-111 RIS is the higher spatial resolution. The impact of other novel technologies, such as nanoparticles, which have demonstrated potential in the intact prostate setting,⁵⁴ remain to be seen for the process of patient selection in the post-RRP setting. Magnetic resonance spectroscopy, which has a demonstrated role as a functional imaging technique to identify areas of prostate cancer in the setting of the intact prostate⁵⁵ remains to be explored for post-RRP disease.

RIS has demonstrated its role in both patient selection and in guiding therapy. As described above, RIS has a promising role in (1) selection of patients not likely to benefit from radiotherapy and in the decision-making regarding general treatment volumes to use with radiotherapy, (2) guiding the post-RRP target volume definition within the limitations posed by overlap of RIS-uptake regions with normal structures, and (3) in influencing biochemical control outcomes with radiotherapy, particularly if the RIS regions are registered with the radiotherapy planning CT scan.

Although RIS has a number of demonstrated uses for the post-RRP radiotherapy process, many areas are currently under investigation. Future directions for RIS involve continued improvement of inter-observer variability by improving the technical features. Recent advances in image acquisition protocols and computer processing techniques (i.e., iterative reconstructive processing) have refined and improved the quality of RIS images.⁵⁶⁻⁵⁸ Perhaps the most significant advance in RIS imaging in prostate cancer patients has been the introduction of fusion or co-registration of RIS and SPECT datasets with CT or MRI volume data sets to render functional images for interpretation. This technology was initially developed to aid nuclear medicine physicians in scan interpretation. Early results from a multi-institutional study⁵⁹ indicate that fusion techniques can significantly enhance the detection of nodal disease, eliminate some of the false positive results from bowel activity, and accurately map the prostate gland for tumor distribution. Because of these results, it is now recommended that all RIS studies be performed with either CT or MRI fusion.⁶⁰⁻⁶³ Increasingly, nuclear medicine departments are looking to purchase SPECT/CT gamma cameras or post-hoc fusion software to enhance their RIS studies.

The impact of RIS on cancer control outcomes is controversial. This is an area where a meta-analysis⁶⁴ or number-needed-to-treat analyses⁶⁵ could be undertaken, although such analyses may be limited due to the retrospective nature of many studies and inability to model the harms of treatment due to the scarcity of reports of complications in this setting. Perhaps the most important future direction in RIS and

in post-RRP imaging in general is the conduction of prospective randomized trials evaluating the impact of RIS on post-RRP biochemical control. These studies would best be done in a consortium or multi-institutional setting.

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