Clinical Applications of Radioimmunoscintigraphy With Prostate-Specific Antibodies for Prostate Cancer

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Radiolabeled monoclonal antibodies may provide more precise localization of prostate cancer.

Background: The presence of metastasis is the most important prognostic indicator in patients with prostate carcinoma and is the predominant determinant of therapeutic choices. Current tools for detection of recurrence or metastasis are less than optimal. Recent clinical trials with radiolabeled monoclonal antibodies appear to provide more precise localization of prostate cancer in these clinical circumstances.

Methods: Multicenter national trials of patients at relatively high risk for metastasis at diagnosis and patients with biochemical evidence of recurrence after prostatectomy underwent radioimmunoscintigraphy with capromab pendetide.

Results: Tissue confirmation of scan results demonstrated a 15-fold and 4-fold increase in sensitivity over computed tomography and magnetic resonance imaging, respectively, for newly diagnosed patients. Preliminary data have shown a 3- to 4-fold increase in durable complete response to radiation therapy in patients with biochemical failure following radical prostatectomy.

Conclusions: Patients at relatively high risk for metastasis at diagnosis and those with biochemical evidence of recurrence after prostatectomy may benefit from radioimmunoscintigraphy.

Introduction

Once a patient is diagnosed with prostate cancer, he and his family are faced with an often bewildering range of therapeutic options. One of the most crucial issues in the selection of the most appropriate option for that patient is an assessment of the disease extent. Despite a current perception that fewer patients with prostate cancer present with metastatic disease, the 1996 national data from the National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER) reported that between 1986 and 1992, approximately 30% of prostate cancer patients presented with regional or distant disease. It is now clear that combinations of biopsy histopathologic characteristics and serum levels of prostate-specific antigen (PSA) may be useful to predict disease extent. These combinations are most predictive when these values are in their extremes, but they are less correlative when patients present with these parameters in an intermediate range. Clinical algorithms also are not designed to take into consideration characteristics that are associated with a higher likelihood of extraprostatic disease, such as perineural invasion. Because most patients currently fall into an intermediate category at initial presentation, further information about disease extent is desirable before a decision about treatment options is reached.

The impetus for retropubic access for radical prostatectomy that began over a decade ago provided simultaneous pathologic assessment of the most likely pelvic lymphatic sites for soft-tissue metastasis. However, the comfort provided by direct sampling of potential major metastatic pathways has been diminished by the pathologic analyses of surgical specimens in several series that demonstrated less than 50% of these patients actually had disease confined to the prostate. When one recognizes the resurgence of perineal surgical approaches and the introduction of somewhat less invasive techniques for definitive therapy, such as brachytherapy and cryotherapy, it is clear that there will be a decrease in simultaneous performance of regional lymphadenectomy with treatment. This shift in practice trends further strengthens the argument for more accurate pretreatment evaluation and emphasizes the need to have more relevant information about both local and distant disease extent.

A diagnostic dilemma also confronts the physician for the patient suspected to harbor recurrent prostate cancer after therapy. Although it has become apparent that PSA elevation precedes radiographic or physical detection of recurrence by at least several months, if not longer, PSA does not distinguish between local recurrence and more widespread disease. Neither digital rectal examination nor transrectal ultrasound, useful in the initial diagnosis of prostate cancer, are reliable for detection of recurrence.

The various standard modalities for noninvasive imaging have been used to evaluate patients with prostate cancer, but the clinical utility of current imaging studies is limited because a relatively large volume of disease generally is required for detection. Conventional cross-sectional radiographic imaging has substantial limitations for identification of locally recurrent, regional, or distant disease. Despite advances in imaging technology, current imaging modalities rarely furnish evidence of local tumor extension and cannot detect microscopic metastases. Tumor volume can be correlated to capsular invasion, seminal vesicle invasion, and metastasis, but the actual tumor volume is difficult to assess by current imaging technology, including transrectal ultrasound. The limitations of current radiographic evaluation are particularly troublesome when one encounters a patient with a relatively high risk of local or regional neoplastic spread.

In the constant search for new approaches to improve diagnostic capabilities, radioimmunoscintigraphy has long captured the imagination of researchers and clinicians alike. Recent advances in monoclonal antibody (MAB) technology have improved the recognition of tumor-associated antigens and have regenerated interest in their use for tumor imaging. One of the most useful MABS is chelated to 111Indium and recognizes a transmembrane prostatic glycoprotein (PSMA) that is expressed to a greater degree in prostate adenocarcinoma than in normal prostate tissue. Preclinical testing demonstrated little or no cross-reactivity with other tissue while maintaining a 9:1 ratio of antibody in tumor compared with serum levels. Preliminary data also indicated increased concentration of the radioimmunoconjugate in metastatic deposits and no difference or up-regulation of PSMA expression in patients on exogenous hormonal ablative therapy.

Radioimmunoscintigraphy with this chelated antibody has been studied for use in both newly diagnosed prostate cancer patients who are at relatively high risk for disease extent. The presence of metastasis is the most important prognostic indicator in patients with prostate carcinoma and is the predominant determinant of therapeutic choices. Current tools for detection of recurrence or metastasis are less than optimal. Recent clinical trials with radiolabeled monoclonal antibodies appear to provide more precise localization of prostate cancer in these clinical circumstances.

Background: The presence of metastasis is the most important prognostic indicator in patients with prostate carcinoma and is the predominant determinant of therapeutic choices. Current tools for detection of recurrence or metastasis are less than optimal. Recent clinical trials with radiolabeled monoclonal antibodies appear to provide more precise localization of prostate cancer in these clinical circumstances.
Radiographic Detection of Regional and Distant Metastasis

Soft-Tissue Metastasis

The presence of lymph node metastases from prostate carcinoma is a significant risk factor for development of distant metastases and death. Because treatment options differ for patients with regional or distant disease, it is especially important to identify lymphatic involvement in patients with clinically localized disease. Though recent reports have documented a decrease in the incidence of lymph node metastasis to 5% to 7% in the tissue sampled at the time of surgery for suspected localized prostate cancer, up to 17% of patients have been reported to have a solitary metastasis in the iliac lymphatic chains outside of the conventional area for dissection. In addition, the presacral or presciatic area has been the site of solitary metastases in 7% to 14% of patients with extended pelvic lymphadenectomy. Algorithms evaluating serum PSA, histopathologic characteristics of the tumor biopsy, and nuclear grade allow some prediction of patients at higher risk for regional metastasis. It must be remembered, however, that the predictive value of such algorithms should be tempered by a consideration of all patient characteristics before therapeutic options are decided. Any further information would be useful in those cases where relatively younger patients present with higher risk for metastatic disease.

Conventional Cross-Sectional Imaging

There are recognized limitations for both computed tomography (CT) and magnetic resonance imaging (MRI) to detect lymph node metastasis. Earlier studies concluded that CT was unreliable to detect lymphadenopathy of less than 2 cm. CT resolution has improved with technological advances, but the threshold for CT detection of lymph node involvement remains between 1.0 cm and 1.5 cm. This improved resolution is generally of little clinical value in prostate cancer because most patients currently with lymphadenopathy present with small volume of metastatic disease. Common factors leading to failure to detect lymph node metastases by CT include node size that is less than the size threshold for detection, presence of microscopic tumor foci without enlargement, or technical performance of the scan and interobserver variability in interpretation. When adenopathy is detected, CT does not distinguish between inflammatory and neoplastic involvement, and fine needle aspiration has been advocated for confirmation of suspected metastasis. Consequently, CT is now usually reserved by most urologists for selected patients at high risk for metastasis.

Although MRI may be useful in cases where suspicion of local disease extension is high, MRI has not proven to be significantly better than CT for evaluation of nodal involvement. Pooled data from four series with more than 50 patients demonstrate an overall sensitivity of 42% and specificity of 98%. Size has been the only useful criterion for detection of malignant lymphadenopathy, and microscopic disease is clearly missed. Uniformity of the size criterion may vary with the anatomic location of lymphatic channels, however, because the 95th percentile value for normal lymph node size has been suggested to be 7 mm for internal iliac, 8 mm for obturator, 9 mm for external iliac, 10 mm for common iliac, 11 mm for paraaortic, and 12 mm for subdiaphragmatic areas.
for common iliac, and 10 mm for external iliac lymph nodes. Enhancement of MRI images is being sought through use of agents such as superparamagnetic iron oxide, which has differentiated between large reactive and neoplastic lymph nodes in animal models, though no agent yet has proven clinically useful.

Radioimmunoscintigraphy

The recent introduction of MAb-derived radioimmunoscintigraphy based on PSMA recognition has stimulated interest because of the possibility for enhanced diagnosis of regional and distant prostatic metastasis. The radioimmunoconjugate capromab pendetide (ProstaScint) is the first of several described MAbs to undergo clinical trials. This compound has been under evaluation for use in two clinical settings: (1) newly diagnosed prostate cancer patients with a relatively high risk for metastasis and (2) postradical prostatectomy patients with a rising PSA. Patients who undergo radioimmunoscintigraphy receive an intravenous injection containing 5.0 mCi. In-Mab followed by planar and cross-sectional single photon emission computed tomography (SPECT) images. Repeat studies are performed 72 to 120 hours after injection to allow for clearance from the vascular and intestinal structures. Clinical studies have shown that asymmetrical vessels or bone marrow distribution can create false interpretation of the scan without both initial and delayed images. It also has been recognized that, on occasion, focal areas of inflammation can present with nonspecific localization (Table 1). Expertise is required for proper interpretation of these scans, making it imperative that the nuclear medicine physician undergo training to become adept at interpretation and to understand the need for proper image acquisition.

<table>
<thead>
<tr>
<th>Table 1. – Sources for Misinterpretation of Radiolabeled Monoclonal Antibody Scan**</th>
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<tr>
<td>Asymmetrical pelvic vasculature</td>
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<tr>
<td>Radionuclide excretion in gastrointestinal tract or bladder</td>
</tr>
<tr>
<td>Asymmetry in normal bone marrow</td>
</tr>
<tr>
<td>Non-specific localization in scar or inflammation</td>
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Repeat studies 72 to 120 hours after injection are necessary for comparison to avoid these pitfalls.

In the pivotal clinical trial, investigators scanned radical prostatectomy candidates before surgery who were considered to be at relatively high risk for lymph node metastasis. Relatively high risk for this study was defined as a Gleason score of 7 or higher with a PSA of at least 20, a Gleason score of 8 or higher regardless of PSA, clinical T3 disease with a Gleason score of at least 6, or an elevated PSA and equivocal CT or MRI evidence of lymph node metastasis. Patients were excluded from entry if they had abnormal serology, previous exposure to MAb products, or previous therapy for prostate cancer. Of the 152 evaluable patients in the 24 participating sites, 64 patients had surgically confirmed pelvic lymph node metastases in whom 40 scans were interpreted as positive. Thirty-eight (95%) of the 40 scans were positive on the side with pathologic confirmation of disease. The sensitivity of 63% in this group was far superior compared with the sensitivity of CT (4%) or MRI (15%) in the same group.

Sixty-three of the 88 patients with no pelvic lymph node malignancy had negative scans. The specificity of 72% is misleading when compared with the CT and MRI results. Since only two patients each had a positive scan with CT and MRI (which correctly identified disease), the specificity for CT and MRI was inflated at 100%. The results from this newly diagnosed high-risk group provided a positive predictive value of 62% for the presurgical study and a negative predictive value of 72%.

The most striking conclusion from the data came through statistical analysis with logistic regression, a strong predictor of the significance of a single variable. Logistic regression analysis of these data demonstrated that the most powerful single predictor of metastatic disease when compared with any other variable, including PSA or Gleason score, was ProstaScint scan. However, when taken together with PSA and Gleason score, this scan provides a greater than 90% positive predictive value for patients with PSA less than 40 ng/mL and Gleason score of less than 7. For patients with PSA equal to or greater than 40 ng/mL and Gleason score of 7 or greater, the positive predictive value of radioimmunoscintigraphy is greater than 80% (Table 2). The data suggest that MAb imaging of prostate cancer may represent a significant advance in the detection of soft-tissue metastases. The acknowledged limitations of CT and MRI to detect metastatic lymphadenopathy, confirmed in this study, suggest that radioimmunoscintigraphy with ProstaScint may provide the best opportunity to detect disease spread in those soft-tissue areas.

Table 2. – Logistic Regression Analysis Using Scan Results, Serum PSA, and Gleason Histopathologic Grading System in Patients at Relatively High Risk for Metastasis (152 Patients)

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>PSA &gt;40 ng/mL</th>
<th>% Sensitivity</th>
<th>% Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7</td>
<td>&lt;40</td>
<td>80</td>
<td>79</td>
<td>57</td>
<td>92</td>
</tr>
<tr>
<td>&gt;7</td>
<td>&gt;80</td>
<td>77</td>
<td>77</td>
<td>81</td>
<td>67</td>
</tr>
</tbody>
</table>

PPV (positive predictive value) = the proportion of those patients with a positive test who actually have the disease

NPV (negative predictive value) = the proportion of patients with a negative test who are actually free of the disease

The potential for repeated use of this nuclear scan increases its clinical utility. The safety profile for the radioimmunoconjugate is excellent, with the radiation dose well within the accepted limits of safety. Transient discomfort at the injection site is the most common side effect experienced in the approximately 4% reported incidence of adverse events. It is also important to note that capromab pendetide is an unusual murine antibody because it has an exceptionally low human anti-mouse antibody (HAMA) titer after infusion. The elevated HAMA titer in 8% of patients was transient and not correlated with any adverse event. Repeat infusions resulted in a 19% elevated HAMA titer that also was transient. This suggests that serial monitoring of many patients can be performed with this modality.

Osseous Metastasis

The propensity for prostate cancer to metastasize to bone tissue forces one to consider that possibility during evaluation in the newly diagnosed patient. However, the vast amount of clinical data with PSA correlation has refined the indications for previously routine bone scintigraphy. Bone scan findings suggestive of metastasis are reported to be extremely low in patients with PSA less than 20 ng/mL. Most urologists currently are much more judicious with the use of bone scintigraphy and reserve its use for patients who present with PSA values greater than 10 ng/mL, high Gleason scores (8 to 10), or elevated serum alkaline phosphatase.

On occasion, other imaging modalities may be of use to determine presence of osseous metastasis for an individual patient. MRI can detect neoplastic involvement of...
Occult Recurrent Disease

Few tools are available to evaluate a patient in whom recurrent prostate cancer is suspected. Digital rectal examination, the most readily available test, has proven to be an unreliable early indicator of recurrent local disease after either radical prostatectomy or radiation therapy.27 In several studies, biopsies that demonstrated recurrent malignancy were preceded by an unremarkable digital rectal examination in a significant number of cases.19 It is clear that in most patients, PSA elevation is detected several months to several years before physical evidence of recurrence manifests.

Standard imaging modalities rarely provide useful information about local recurrence. Transrectal ultrasound appears to be of limited value because of low sensitivity and specificity. Mature scar is rich in collagen and is hypocellular, thereby giving an acoustical signal similar to that ascribed to recurrent malignancy. Even the purportedly classical hypoechoic acoustic signal of recurrent prostate cancer is called into question by the findings of one study that demonstrated a 57% isoechoic pattern in proven recurrent disease.28

CT and MRI have not proven to be useful for determination of local recurrence in most studies. Both have been used most often to evaluate the possibility of regional or distant disease with the same limitations noted as those seen in patients with newly diagnosed prostate cancer. On occasion, MRI can reveal an increased signal on T2-weighted images (T2WI) suggestive of recurrent disease. Caution during interpretation must be exercised after primary radiation therapy, however, because of the diffuse decreased signal seen in the prostate and seminal vesicles on T2WI.21

Preliminary indications are that radioimmunoscintigraphy with ProstaScint may provide information about local recurrence. The capromab pendetide radioimmunoconjugate was used to evaluate 181 patients with rising PSA after radical prostatectomy for suspected localized disease. Patients enrolled in the occult disease study had undetectable PSA values after surgery with a subsequent rise in PSA to 0.8 ng/mL and a negative bone scan. No evidence of signal was seen in 73 men, while 108 patients had positive scans. The location of detectable signal varied with 32 patients demonstrating activity in the surgical site only, 30 patients registering signal in both the surgical site and in extraprostatic sites, and 46 patients with signal only in area outside of the prostate.29

Transrectal ultrasound-guided biopsy of the surgical anastomotic site was performed after scans were completed. Needle biopsies detected malignancy in 59 patients in which 29 were localized by ProstaScint.30 An additional 29 patients had a positive scan in the prostatic area without tissue confirmation of disease. However, biopsy appears to be a poor standard by which to judge recurrence rates as evidenced by reports that only approximately 50% of men with postsurgical detectable PSA levels have a positive biopsy and that 25% of those men with proven recurrence require two or more biopsies to identify the local recurrence.31 Continued follow-up of these biopsy-negative, scan-positive patients may provide a more accurate assessment of recurrent cancer in time.

An intriguing finding in this study was the pattern of distribution observed in extra-prostatic sites of radioimmunoscintigraphic signal (Table 3). This is of great interest because of the known lengthy interval between PSA elevation and identifiable local recurrence or distant disease.32 Tissue confirmation is difficult in many cases because of the location of suspected metastases. Yet these observations are consistent with the incidence and location of lymph node metastases in previous large series of autopsy reports of prostate cancer patients.33,34 Coincident with these findings are preliminary reports of results from external beam radiation therapy for suspected local recurrence that suggest a greater than threefold difference in response rates between patients with and without detectable signal outside of the prostatic fossa.35,36 Furthermore, more than 70% of a cohort of these patients with radioimmunoscientigraphic findings suggestive of abdominal and retroperitoneal disease have gone on to biochemical failure within 18 months (G. Hinkle, personal communication, 1998). Both of these findings suggest that radioimmunoscintigraphy is more sensitive for localization of disease recurrence and spread. Longer-term evaluation is required to determine the durability of these intriguing results.

Table 3. Sites of Radioimmunoscintigraphic Activity Outside of the Prostate in Patients With Suspected Recurrence

<table>
<thead>
<tr>
<th>Site</th>
<th>%</th>
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<tbody>
<tr>
<td>Pelvis</td>
<td>43</td>
</tr>
<tr>
<td>Pari-aortic; mesenteric</td>
<td>45</td>
</tr>
<tr>
<td>Mediastinal</td>
<td>1</td>
</tr>
<tr>
<td>Supraclavicular</td>
<td>3</td>
</tr>
<tr>
<td>Bone</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
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* 110 extraprostatic sites in 76 patients.

Conclusions

The prognosis of a patient with newly diagnosed prostate cancer is closely tied to the status of local disease extension and presence of regional or distant metastasis. Decision algorithms for treatment options are also dependent on an accurate assessment of disease extent. While some measure of probability for local disease extension and regional or distant involvement is afforded by combinations of PSA and histopathologic characteristics, the current tools available for staging prostate cancer lack the degree of accuracy desired by most patients and physicians in many cases. Advances in imaging technology are necessary to enhance the capabilities of the physician to counsel patients on the most appropriate therapy for their individual circumstances. Radioimmunoscintigraphy may provide such an opportunity for the patient with newly diagnosed malignancy at relatively high risk for metastasis. Although preliminary, the data suggest that this modality also may be useful in the selection of patients most likely to benefit from salvage radiotherapy after failed radical prostatectomy.

References
2. Partin AW, Yoo J, Carter HB, et al. The use of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage in men with localized


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