Isolated pulmonary metastasis of prostate adenocarcinoma detected by ProstaScint scan

Brendan Patrick Boyer
The University of Toledo
2008
Dedication

To my parents, for their support and guidance throughout my education.
Acknowledgements

Many thanks to my father, Dr. Marty Boyer, for providing me with this unique case and for lending his knowledge and expertise. Also, thank you to my major advisor Jolene Miller, MLS, for her editing and proofreading, and classmate and friend Michelle Sovern, PA-S, for her input.
Case report

A 65-year-old male was originally diagnosed with prostate cancer in 1995 when prostate biopsies revealed adenocarcinoma. Upon radical retropubic prostatectomy, disease was determined to be confined to the prostate; pelvic lymph nodes were negative for disease. The patient’s serum PSA was subsequently undetectable, and he was lost to follow up for several years. In 2002, his PSA was detected at 0.2 ng/ml. The PSA rose to 0.3 ng/ml the following year and was detected at 1.9 ng/ml in 2005. In July of 2006, screening showed a PSA of 9.4 ng/ml and the following month his PSA had climbed to 10.56 ng/ml. The patient remained asymptomatic apart from erectile dysfunction, a common side effect of prostatectomy. He had no new areas of bone pain and no new respiratory, gastrointestinal, genitourinary, or neurological complaints.

CT with contrast of the pelvis and abdomen showed no obvious evidence of metastatic disease. Whole body bone scan displayed some osteoarthritic changes, but no definite evidence for bony metastatic disease. A ProstaScint whole body image was ordered (Figure 1). Results showed a low level of reactivity in the prostate fossa, but less intense than normally seen with recurrence. Further, no reactive adenopathy or evidence of bony metastatic disease was apparent. However, focal ProstaScint reactivity appeared within the upper lobe of the left lung (Figure 2). CT of the chest was ordered for comparison and a spiculated lesion measuring 2.8 cm in diameter was identified. The nodular density resembled a primary lung carcinoma, but the lesion seemingly correlated with the area of ProstaScint reactivity. Upon biopsy, the tumor was determined to be a prostate metastasis. The margins of the excision were negative for disease but vascular channel invasion by carcinoma existed. The patient soon began continuous hormonal management with Lupron injections as treatment for systemic prostate metastasis.
In November 2006, a month after biopsy, the patient’s PSA dropped to 2.06 ng/ml. In March 2007, his serum PSA was 0.07 ng/ml and in June 2007, 0.16 ng/ml. At this point the patient chose to proceed with pulse hormonal therapy. As of September 2007, his PSA had risen to 2.19 ng/ml. He continued to experience erectile dysfunction and noted hot flashes attributable to the hormonal treatment. Otherwise he had no symptoms of metastatic prostate cancer. To our knowledge, this is the only case report of an isolated pulmonary metastasis of prostate adenocarcinoma discovered by ProstaScint.
Introduction

Prostate cancer is the most prevalent cancer in males with a predicted incidence of 186,320 in 2008. An estimated 28,660 will die in 2008 as a result of prostate cancer, second among cancers only to lung malignancies. The lifetime risk of developing prostate cancer is over 16% (American Cancer Society [ACS], 2008). Because most men who present with prostate cancer will be asymptomatic (Miller, Hafez, Stewart, Montie, & Wei, 2003), the American Cancer Society (ACS) recommends screening the general population at age fifty with a yearly digital rectal exam (DRE) and serum prostate specific antigen (PSA) test (2007). Although relatively effective when used together, each technique has its limitations. DRE allows palpation of only the posterior aspect of the prostate gland; as such, some nodules can go undetected. Additionally, 50% of palpable nodules are benign (Jewett, Bridge, Gray, & Shelley, 1968). An elevated PSA raises the suspicion of prostate cancer, but may be secondary to other processes like benign prostatic hyperplasia (BPH) or prostatitis (ACS, 2007). While either DRE or PSA screenings can be used to estimate a high or low risk for prostate cancer, neither test can definitively diagnose or stage it. Accurate staging of the cancer is important in guiding selection of treatment options as well as determining prognosis.

Radical prostatectomy, which involves removal of the gland and nearby lymph nodes, has become the most common treatment for localized cancer, with 60,000 procedures being performed yearly (Bill-Axelson et al., 2005). The surgery is intended to be curative, and in theory, the PSA should drop and remain at undetectable levels. Unfortunately, 27-53% of patients will show measurable PSA levels in the blood, known as biochemical recurrence, within ten years of surgery (Ohori et al., 1994; Trapasso, deKernion, Smith, & Dorey, 1994). Further, 15% of patients undergoing radical prostatectomy develop clinical evidence of distant metastasis.
within ten years (Bill-Axelson et al.). A rise in the PSA may be due to local recurrence in the prostate fossa and/or distant metastases (Lattouf & Saad, 2003). Therefore, identifying the presence and location of cancerous tissue is essential in determining a localized or systemic treatment regimen. Disease most often spreads to bone and pelvic lymph nodes (Nakamachi et al., 2002). As such, CT of the pelvis/abdomen and radionuclide bone scan are commonly used to find metastases, but with limited effectiveness (Kane et al., 2003). Activity seen on bone scans is not specific to prostate cancer, and CT can only detect lymph nodes enlarged to greater than 1 cm in diameter.

While metastases most often present in bone and local lymph nodes, they can occur in any tissue and therefore may not appear in the above scans. Specifically, studies suggest evidence of metastasis to the lung is found in 46-63% of autopsies on men with prostate cancer (Bubendorf et al., 2000; Nakamachi et al., 2002); however, symptomatic presentation of pulmonary metastasis is quite uncommon (Fabozzi, Schellhammer, & el-Mahdi, 1995; Nakamachi et al.). Lung metastasis with no known bone or lymph node involvement is even less likely; a number of such instances have been reported as case studies. Tracking the source of the rising PSA can be a difficult task. Without respiratory symptoms, it would be hard to warrant imaging of the lungs over any other area of the body.

Capromab pendetide, trade name ProstaScint, is a murine monoclonal antibody attached to an Indium-111 radio-tracer approved by the FDA in 1996. It reacts with a specific protein, prostate-specific membrane antigen (PSMA), which is expressed by both normal and cancerous prostate epithelial cells. ProstaScint is indicated “as a diagnosing imaging agent in newly diagnosed patients with biopsy-proven prostate cancer, thought to be clinically localized after standard diagnostic evaluation, who are at high risk for pelvic lymph node metastases, and in
post prostatectomy patients with a rising PSA and a negative or equivocal standard metastatic evaluation in whom there is a high clinical suspicion of occult metastatic disease” (Food and Drug Administration, Center for Drug Evaluation & Research, 2001). ProstaScint should not replace bone scans for the evaluation of skeletal metastasis as bone scans are more sensitive for such lesions. Nor is ProstaScint indicated for screening the general population (Cytogen, 1997).

In theory, the monoclonal antibody should only react with cells within the prostate gland or prostate cancer metastases throughout the body. However, laboratory studies indicate that other human cells produce PSMA, suggesting a decreased specificity. Likewise, clinical studies have varied in their reports of the sensitivity, specificity, and accuracy of the ProstaScint scan. This review summarizes original research and retrospective studies assessing the effectiveness of the ProstaScint scan in detecting local recurrence or distant metastasis. Reviewed works have been limited to published studies in which patients had been previously treated with curative intent, but upon follow-up had reason to suspect treatment failure. Further, only studies providing statistical analysis and comparing ProstaScint to histologic confirmation are discussed, as biopsy or surgical dissection is regarded as the gold standard for cancer confirmation. A number of these studies also described ProstaScint relative to conventional methods of imaging, such as CT or MRI. This information is discussed where appropriate; however, as ProstaScint hopes to be an improved alternative to these tests, studies using conventional imaging as the standard for comparison were not included. Another subset of studies on prostate cancer recurrence and metastasis express the effectiveness of ProstaScint scans with respect to patients’ reactions to salvage therapy. These works are mentioned, but are not the primary focus of this review. Searches were performed in MEDLINE, PubMed, and Science Citation Index, searching keywords: prostatic neoplasm, prostate cancer, prostate carcinoma, pulmonary metastasis, lung
metastasis, ProstaScint, and capromab pendetide. References from reviewed articles were traced using the same databases. Websites of relevant organizations, such as the Food and Drug Administration and the American Cancer Society, were also consulted.
FDA trials

Clinical trials for FDA approval of ProstaScint assessed the performance of the scan on two populations in two separate studies. The first population consisted of newly diagnosed patients with tissue confirmation of prostate cancer considered to be at high risk for metastases to lymph nodes. These patients underwent ProstaScint immunoscintigraphy prior to staging via pelvic lymphadenectomy. The scan demonstrated a 62% sensitivity, 72% specificity, 62% positive predictive value (PPV), 72% negative predictive value (NPV), and a 68% overall accuracy relative to histological results (Cytogen, 1997). Of greater interest to this review is the second population: patients with high clinical suspicion of occult recurrent or residual disease following radical prostatectomy. Admission criteria included a PSA >1.0 ng/ml, a negative bone scan within eight weeks before the study, and a prostatic fossa biopsy scheduled within eight weeks following administration of the monoclonal antibody. The study included patients with a PSA ≤1.0 ng/ml only if they had a history of increasing PSA and a DRE suggesting recurrent disease. Patients who had received hormonal therapy, chemotherapy, or radiation therapy after radical prostatectomy were excluded (Kahn, Williams, Manyak et al., 1998). Of the 181 patients with interpretable ProstaScint scans, 158 underwent biopsy. Using tissue confirmation from the prostatic fossa as the standard for comparison in the 158 patients, ProstaScint yielded a 49% sensitivity, 71% specificity, 50% PPV, 70% NPV, and 63% overall accuracy (Cytogen; Kahn, Williams, Manyak et al.).

The authors admit that the lack of an accurate standard was a crucial limitation in their study. A single biopsy of the prostatic fossa served as the standard for comparison. They are confident that increased biopsies would have decreased the sampling error and thus revealed a significantly higher sensitivity of the scan. Regarding the specificity, researchers point to the
radioactivity of the pubic bone marrow and rectum as incorrectly interpreted prostate fossa uptake. They insist that urine within the bladder did not contribute to false positives, as patients were catheterized through the duration of the imaging sessions (Kahn, Williams, Manyak et al., 1998). On another note, this clinical trial did not specifically examine the ability of the scan to identify distant metastases. Of the 181 interpretable scans, 76 showed evidence of disease beyond the prostatic fossa. Conventional imaging in the form of CT or MRI was performed on 48 of the 76 patients. This imaging, though, was not part of the study protocol and is not representative of the entire population. MRI or CT confirmed 6 extra fossa abnormalities. However, only one site outside the prostate bed was biopsied. This limits the ability to compare ProstaScint to conventional imaging, as one can not determine if ProstaScint yielded false positives or if conventional imaging lacks sensitivity. The researchers do not indicate whether patients had achieved PSA remission following prostatectomy, further limiting clinical application. Lastly, the ProstaScint scans seem to have been interpreted by a number of nuclear medicine physicians at multiple sites. As such, the study has introduced an additional confounding variable, in that ProstaScint scans can be difficult to interpret and certain physicians may have less skill in doing so (Howell & Hailey, 1999).
Efficacy on patients after prostatectomy as primary treatment

This section includes two studies (Burgers et al. and Kahn et al.) that assessed the use of the ProstaScint scan on patients with suspicion of occult recurrent or residual disease after prostatectomy. The population is similar to that in FDA trial, however the inclusion criteria vary with each series.

Burgers and colleagues (1995) describe a group of men who underwent prostatectomy and later presented with suspected residual or recurrent prostate cancer based on increasing PSA levels. Patients who had treatment in addition to prostatectomy were excluded from the study. Similar to the FDA trial, a PSA >1.0 ng/mL with a life expectancy of more than six months or a PSA ≤1.0 ng/mL with a trend of increasing values with a DRE suggestive of residual or recurrent disease was necessary for inclusion. This group consisted of 35 patients, 33 of whom showed evidence of occult prostate cancer on ProstaScint scan. Prostatic fossa uptake alone was seen in 11 men, distant metastasis alone was seen in 9 men, and fossa and distant uptake were seen in 12 men. Notably, the sum of these numbers is 32, not 33. The authors do not offer an explanation for this discrepancy. All 35 men in this study underwent biopsy of the prostate bed. The authors describe a scan sensitivity of 94%, specificity of 65%, and an overall accuracy of 80% compared to the histological results. Further, 20 of the patients also underwent conventional radiological imaging in the form of MRI and PET to detect fossa recurrence. Relative to biopsy, these methods showed a sensitivity, specificity, and accuracy of 27, 67, and 45% respectively (Burgers et al.; Kahn et al., 1994).

Burgers et al. do not provide information regarding the ages or presenting PSA levels of the subjects. Furthermore, the authors do not indicate if patients achieved biochemical remission following initial treatment. These inadequacies limit the clinical application of the results. Of 6
false positive ProstaScint scans, Burgers et al feel that biopsy missed the tumor in 3 cases, based on positive PET scans and PSA falling in response to radiotherapy. While the study offers comparison of MRI and PET to ProstaScint in the prostatic fossa, not all of the participants underwent such conventional imaging. This study is also limited by the lack of histological confirmation of distant metastasis; only 2 biopsies were attempted in 21 patients with extraprostatic fossa antibody uptake. Without histological confirmation, one can not determine if ProstaScint yields false positives, or if conventional imaging lacks sensitivity. All patients with uptake beyond the fossa received serial CT follow up and at the time of publication, 12 patients showed radiological confirmation. This may suggest ProstaScint can detect metastatic lesions before they are detectable by more conventional imaging.

The second study, performed by Kahn et al. (1994), enrolled 27 men with a PSA of $\geq 0.8$ ng/ml with increasing values on two consecutive evaluations following prostatectomy. Patients included were otherwise negative for disease, including negative DRE, bone scan, and transrectal ultrasound. Not all patients underwent histological confirmation; a total of 13 men had a single TRUS guided biopsy of the prostate fossa performed. Of these 13 men, 11 had shown ProstaScint uptake in the fossa, while 2 had negative scans. Each of the 2 negative scans correlated with histologically negative specimens. Biopsy confirmed 8 of the 11 positive scans. The study also compared PSA values in patients with positive scans versus those with negative scans, but found no significant difference (11.8 ng/ml and 4.4 ng/ml, $p>.05$).

The biggest limitation in this study is the small sample size, with only 13 subjects undergoing histological confirmation. Additionally, single biopsy is used for comparison, allowing for sampling error. Given the lack of a perfect standard and the small sample size, the authors could not determine sensitivity and specificity values. For the sake of comparison,
sensitivity and specificity were calculated and are included in Table 1. Further, the authors state that 18 subjects showed distant uptake of ProstaScint, however, none of these sites were biopsied. The authors are specific in stating the images were interpreted by one of two nuclear medicine physicians, reducing but not eliminating interreader variability.
Efficacy on patients after radiation therapy as primary treatment

One study (Fang et al) discusses a population of patients initially treated with radiation therapy. Subjects were being considered for salvage brachytherapy as a result of biochemical failure, defined as three consecutive elevations in their PSA.

A study by Fang and colleagues (2000) looked at 24 men who had previously received radiation therapy as primary treatment. Scans in 21 of the 24 men showed activity in the prostate. Biopsy at the prostate guided by ultrasound was performed on 17 of the 24 patients. Several patients had multiple prostatic biopsies; if any sample was positive, the biopsy result was considered positive. A single pathologist determined 12 biopsies positive. Comparing the results, the authors report an overall accuracy of 50%. They calculate a false positive rate of 24% and a false negative rate of 67%. In calculating their data, the authors seem to have made assumptions regarding scans of 7 patients who did not undergo biopsy. The validity of such data is questionable. Likely due to the small sample size, the authors do not report a sensitivity or specificity, further limiting one’s ability to compare these results to other studies. The authors note that in comparison to studies on postprostatectomy patients, their population more frequently showed activity confined to the prostate. They speculate that some false positives may have been a result of uptake by normal prostate cells. They additionally state that false positives likely resulted from sampling error, as most patients had only one biopsy. Further, the lack of control over the number of biopsies compromises the validity of the results. Based on the data, the authors feel further treatment plans should not be based on ProstaScint results alone, and that rebiopsy of the prostate should continue to be the gold standard for assessment after radiation therapy. They suggest that the more useful aspect of the scan may be in identifying extraprostatic disease.
Efficacy on patients after varying forms of primary treatment

The three studies (Elgamal et al, Bermejo et al, and Haseman et al) assess ProstaScint scan usage in patients who have undergone treatment with curative intent, but later had reason to suspect recurrence or residual disease. That is, the populations in each study are not limited to one form of treatment for prostate cancer recurrence.

Elgamal, Tryochak, and Murphy (1998) analyzed 136 scans of 100 patients. All patients had been histologically diagnosed with prostate cancer and treated with curative intent with radical prostatectomy, radiation, and/or hormonal therapy. Most patients had been referred following PSA failure. However, 3 patients were included “with poor pathologic prognostic features.” The authors do not define these features or indicate why these 3 patients were included without PSA failure. ProstaScint uptake was evident in 124 of the scans. A total of 7 lymph nodes and 26 prostate/prostatic fossa biopsies served as a standard for comparison. Comparing these findings gave a sensitivity of 89%, a specificity of 67%, PPV of 89%, and an accuracy of 89%. Each of 20 positive prostatic biopsies showed corresponding reactivity on the ProstaScint scan. There were 6 negative prostatic biopsies; 2 of these patients had shown ProstaScint uptake at the prostate/prostatic fossa. All 7 lymph node biopsies were positive; 4 correlated with ProstaScint uptake while 3 did not. Due to the small number of negative biopsies, the authors could not calculate the negative predictive value. Having only 2 false positive immunoscintigraphy results perhaps speaks to the accuracy of the biopsies performed. ProstaScint detected 57% of bone lesions visible on bone scan. While bone scan is not specific, the difference suggests a limited role of ProstaScint in detecting bony metastasis of prostate cancer. Further, the data again indicate a greater percentage of “local recurrence only” in patients with an intact prostate compared to those presenting postprostatectomy.
While the study included 100 patients, only 33 were biopsied, leaving a relatively small sample size. Additionally, the authors do not specifically define treatment failure in the inclusion criteria. Another limitation exists as 34 patients had repeat scans. While it is not clear if any of these patients were biopsied, the duplication potentially influences the statistical analysis. Furthermore, the statistical analysis combines data from distant and local biopsy sites. However, the effectiveness of the scan may vary by site. In addition, 3 lymph node biopsies were performed on patients with a negative ProstaScint scan. It is not clear what prompted these lymph node biopsies or how the sites for biopsy were determined on such patients. The study protocol did not call for other soft tissue imaging (only 7 patients underwent CT or MRI), limiting comparison to ProstaScint scans and conventional detection methods. On another note, the authors indicate that patients with positive ProstaScint scans had a significantly higher mean serum PSA than those with negative ProstaScint scans (61.3 ng/ml and 0.9 ng/ml, p <0.01). Similarly, patients with extrapelvic involvement on ProstaScint scan tended to have higher serum PSA than those with pelvic uptake only (104.6 ng/ml and 36.3 ng/ml, p=0.03). However, the range of serum PSA spans 0.0-2185 ng/ml, with a mean of 55.9 ng/ml and a median of 4.5 ng/ml. The authors fail to comment on what seems to be at least one outlier and how this affects the correlation.

A study by Bermejo and colleagues (2003) included patients who had undergone a ProstaScint scan and surgical exploration/biopsy confirmation of metastatic or recurrent disease following definitive treatment. A mail survey to 60 urologic oncologists collected information on 31 patients with 43 sites of investigation. Some sites were within the prostate fossa while others were distant metastases. According to the authors, analyzing the data by site of biopsy yield a sensitivity of 94%, specificity of 42%, PPV of 53%, NPV of 92%, and overall accuracy of 65%.
The authors also performed statistical analysis with regards to each patient, finding a sensitivity, specificity, PPV, NPV, and overall accuracy of 100, 33, 62, 100, and 68% respectively. Only analyses by site of biopsy are included in Table 1.

The design of the study limits the reliability of the results given the inherent bias and lack of control in a mail survey. Further, the type of treatment received by each patient is not included, nor is the method of histologic confirmation (biopsy vs. dissection). Additionally, sites of uptake on the ProstaScint scan do not necessarily correlate with sites of pathological analysis, and not all sites of uptake were biopsied. In performing statistical analysis with regards to each patient, those with ProstaScint scans showing uptake anywhere and pathologic confirmation of any site were considered true positives. That is, the location of positive biopsy need not necessarily be a site of ProstaScint uptake for the scan results to have been considered accurate. The design of the study and the methods of statistical analysis severely limit the value of the data.

In another study, Haseman and colleagues (1996) reported on 14 patients, 10 of whom had undergone radical prostatectomy and 4 of whom had radiation therapy as primary treatment for prostate adenocarcinoma. Patients with prior chemotherapy or hormonal treatment were excluded. Inclusion criteria stated patients needed a PSA >1.0 ng/ml or a positive DRE, a negative bone scan, and a biopsy of the prostate bed scheduled within eight weeks of the ProstaScint scan. Biopsies were performed regardless of scan results. Biopsies were guided by ultrasound or DRE findings if abnormalities were evident. Compared to histological findings, ProstaScint yielded a sensitivity of 86%, specificity of 43%, PPV of 60%, NPV of 75%, and accuracy of 64%. In addition, PET scan was performed on 10 of the patients. Compared to histological findings, PET showed a sensitivity of 17%, specificity of 50%, PPV of 33%, NPV of
29%, and accuracy of 30%. The authors believe that there were 3 false negative biopsies, based on ProstaScint and PET correlation or response to treatment. Lymph nodes showed ProstaScint uptake in 8 of the 14 patients. However, none of the extraprostatic sites correlated with PET or CT findings, and therefore were unable to be biopsied.

The small population size limits the power of the findings. In addition, combining postprostatectomy patients with patients who had undergone radiation therapy limits the application of the findings. As suggested earlier, recurrence patterns may differ secondary to mode of curative therapy (Fang et al., 2000). Haseman et al. offer a second set of data, based on an assumption that 3 biopsies were falsely negative. As there was no histologic backing for these assumptions, the second set of data has not been included here. This study offers no histologic confirmation of lymph nodes positive on ProstaScint scans. The comparison of ProstaScint to PET imaging in this study is useful, however not all patients underwent PET and as such the data do not represent the entire population. No comparison is drawn to CT scans, though it seems a number of patients may have undergone such imaging.
Efficacy inferred from response to salvage radiotherapy

Studies discussed here express the effectiveness of ProstaScint scans with respect to patient’s reaction to salvage therapy. That is, there is no histological confirmation of metastatic lesions. Efficacy of the scan is inferred from patient response to salvage radiotherapy for suspected recurrence or residual disease.

A retrospective study by Kahn, Williams, Haseman, and colleagues (1998) looked at 32 postprostatectomy patients with PSA failure ≥0.4 ng/ml and no other evidence of prostate cancer. Patients underwent salvage radiotherapy to the pelvis after a ProstaScint scan; the decision for treatment, however, was not based on immunoscintigraphy results. Of the 32 patients, 21 experienced an initial complete response, defined as a PSA ≤0.3 ng/ml and remaining there for thirty days. Of those, 18 maintained a durable complete response, that is a serum PSA remaining at or below 0.3 mg/ml for at least six months before the final follow-up. As this was a retrospective study, the final follow-up varied by patient. Comparing treatment response to scan results, the authors determined that 70% of men with normal scans or scans positive only in the prostate fossa had a durable complete response to salvage radiotherapy. Contrarily, only 22% of patients with antibody reactivity beyond the prostate fossa achieved durable complete response. A three-year follow-up on these patients showed similar results (Kahn, Austin, & Miller, 1999). This significant difference (p=0.0225) between treatment response in patients with uptake beyond the pelvis and those with normal scans or uptake in the prostatic fossa only suggests that ProstaScint scan can help predict a patient’s response to salvage radiotherapy of the pelvis. Additionally, no other variable measured showed significant correlation with achieving a durable complete response, including pretreatment PSA (p=0.13), pathologic stage (p=0.87), and positive prostate biopsy (p=0.96) (Kahn, Williams, Haseman, et al.).
Some series on postprostatectomy patients demonstrate similar findings. Levesque et al. (1998) described 13 men with rising PSA who received radiation regardless of their scan results. A PSA dropping to and remaining $\leq 0.2$ ng/mL was considered a good response. Of 6 patients that had monoclonal antibody uptake beyond the field of radiation, only 2 showed a good response. In those patients without ProstaScint reactivity beyond the radiation field, 5 of 7 were responders. Similarly, Proaño et al. (2006) found that patients with a negative ProstaScint scan prior to radiation had a lower rate of PSA progression following salvage radiotherapy than patients with positive scans.

However, the literature varies on the predictive value of ProstaScint results on PSA response to salvage radiotherapy. In a study of 58 men receiving local radiotherapy for rising PSA, 20 experienced biochemical relapse after treatment. Nagda et al. (2007) saw no correlation ($p=0.51$) between ProstaScint results and biochemical relapse after radiation, defined as PSA $>0.2$ ng/ml or an increase to greater than the nadir PSA. Moreover, a pre-radiation PSA below 1.0 ng/mL seemed the only indicator of decreased biochemical relapse. Notably, the median follow-up was 41 months following onset of radiotherapy, much longer than other studies of its kind. Similarly, a retrospective study by Thomas and colleagues (2003) found no difference in positive or negative scans in the prediction of biochemical response to salvage radiotherapy for PSA failure after prostatectomy. However, only 5 patients in their study showed ProstaScint uptake beyond the prostate fossa, limiting the power of the findings.
Conclusion

As evidenced above, the effectiveness of the ProstaScint scan has varied amongst clinical studies. Most studies reviewed indicate the scan has a respectable sensitivity but lacks specificity. Interestingly, the opposite was true in the FDA trial performed by Kahn, Williams, and Manyak et al. (1998), as the scan showed a decent specificity but the sensitivity was lacking. This study indeed has a much greater population size. However, with the exception of the study by Bermejo et al., the designs of the other studies are relatively similar. The differences in results are most likely due to random error resulting from a number of factors influencing the statistical calculations. Foremost is the lack of a perfect standard. While histologic confirmation via biopsy offers high specificity, its sensitivity is limited by sampling error. Data suggest that 20% of prostate carcinoma may be missed on initial biopsies (Ellis & Brawer, 1995). Furthermore, ProstaScint scans can be difficult to interpret and readings may vary by radiologist (Howell & Hailey, 1999). As such, a confounding variable exists between all studies discussed. On another note, small tumor volume and inadequate uptake or distribution of the monoclonal antibody may result in false negative scans. Additionally, prostate specific membrane antigen (PSMA) expression has been seen in variety of tissue samples. Samples of normal tissue from prostate, bladder, kidney, testis, ovary, fallopian tube, breast, sweat glands, adrenal gland, liver, esophagus, stomach, duodenum, colon, heart, skeletal muscle, and brain have shown ProstaScint uptake (Kinoshita et al., 2006; Lopes, Davis, Rosenstraus, Uveges, & Gilman, 1990; Silver, Pellicer, Fair, Heston, & Cordon-Cardo, 1997). Samples of cancerous tissue from bladder, kidney, testis, esophagus, stomach, small intestine, colon, adrenal gland, and lung have also expressed the protein (Kinoshita et al.). Expression of PSMA in other tissues may decrease scan
specificity. Conversely, some lines of prostate cancer do not express PSMA, potentially decreasing scan sensitivity (Israeli, Powell, Corr, Fair, & Heston, 1994).

Despite inconsistent results, the ProstaScint scan does offer clinicians an additional tool to assist in treatment planning for patients with prostate cancer. However, as with any medical test, the potential benefit of the scan must be weighed against its negative side effects and financial cost. According to the package insert, adverse side effects of ProstaScint infusion were seen in 4% of patients (Cytogen, 1997). Most common reactions included hypotension, hypertension, elevated bilirubin, and elevated liver enzymes. Less often, itching, stinging at infusion site, fever, chills, headache, myalgia, chest pain, and shortness of breath have been seen. No deaths have been attributed to ProstaScint administration. In addition, as the monoclonal antibody is a foreign protein developed from mice, patients can develop a response known as human anti-mouse antibody (HAMA). This response, while uncommon, could change the efficacy of future murine-based diagnostic and therapeutic procedures as well as increase the risk of adverse reactions (Cytogen; Howell & Hailey, 1999). While relatively safe, a ProstaScint scan costs an estimated $2500 and may not be a cost-effective option for all patients (Howell & Hailey).

The role of ProstaScint in the post treatment population is to aid in finding the cause of a rising PSA. It is not indicated for screening or assessment of response to treatment. It is unclear if ProstaScint results can help predict a patient’s response to salvage radiotherapy. While ProstaScint seems to be more effective in detecting residual or recurrent disease than CT, MRI, or PET, the literature is lacking in direct comparisons of these more conventional imaging studies and ProstaScint to biopsy confirmation. Currently, the data regarding the efficacy of ProstaScint do not provide convincing evidence such that clinicians can comfortably trust its
findings. Given the metastatic patterns of prostate cancer, ProstaScint scan should only be considered after bone scan and CT of the pelvis/abdomen have been ineffective in guiding treatment. As no study indicates treatment plans should be determined solely on findings of a ProstaScint scan, using these conventional tests first may be a more cost effective approach to guiding treatment. However, as with our patient, the ProstaScint scan can be invaluable in those without evidence of disease on such conventional scans. More convincing data showing histologic confirmation of distant metastasis are necessary to fully appreciate the usefulness of the ProstaScint scan. However, distant biopsies can be difficult to perform and invasive. Clinicians would benefit from long term follow up of sites unable to be initially confirmed by biopsy. Recently, ProstaScint scans have been combined with CT or MRI images in a technique called ProstaScint Fusion imaging (Kipper, 2003). This method hopes to enhance the detection of metastatic disease, but evidence of the effectiveness is currently limited. Future research should also assess the effectiveness of ProstaScint scan compared to conventional imaging at identifying distant metastatic lesions on large populations.
References


## Table 1

*Outcomes Comparison for ProstaScint Studies, in the Order Discussed in this Project*

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
<th>False (+) rate</th>
<th>False (-) rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahn, Williams, Manyak et al., 1998</td>
<td>158</td>
<td>49</td>
<td>71</td>
<td>50</td>
<td>70</td>
<td>63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burgers, Hinkle, &amp; Haseman, 1995</td>
<td>35</td>
<td>94</td>
<td>65</td>
<td></td>
<td></td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kahn et al., 1994</td>
<td>13</td>
<td>100*</td>
<td>40*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fang et al., 2000</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50</td>
<td>24</td>
<td>67</td>
</tr>
<tr>
<td>Elgamal, Troychak, &amp; Murphy, 1998</td>
<td>33</td>
<td>89</td>
<td>67</td>
<td>89</td>
<td></td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bermejo, Coursey, Basler, Austenfeld, &amp;</td>
<td>41</td>
<td>94</td>
<td>42</td>
<td>53</td>
<td>92</td>
<td>65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thompson, 2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haseman, Reed, &amp; Rosenthal, 1996</td>
<td>14</td>
<td>86</td>
<td>43</td>
<td>60</td>
<td>75</td>
<td>64</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(n\) indicates the number of confirmatory biopsies performed. That is, some patients in some series had more than one site biopsied.

* Kahn et al., 1994 did not calculate the sensitivity or specificity. These calculations have been made for the sake of comparison.
Figure 1: Full body ProstaScint scan of the patient.
Figure 2: ProstaScint scan of patient’s chest. Isolated lung metastasis marked.
Abstract

**Objective.** ProstaScint is a monoclonal antibody that reacts with a protein expressed by prostate epithelial cells. ProstaScint should only react with normal or malignant prostate cells throughout the body. However, studies have shown varied sensitivities, specificities, and accuracies. We summarize studies on ProstaScint’s effectiveness at detecting local recurrence or distant metastasis. A case report is also described. **Methods.** The review includes articles found through MEDLINE, PubMed, and Science Citation Index that compare ProstaScint to histologic confirmation in patients with suspicion of treatment failure. **Results.** The effectiveness of ProstaScint varied amongst clinical studies; however most describe respectable sensitivity with low specificity. **Conclusion.** ProstaScint is an additional tool to aid treatment planning for patients with recurrent prostate cancer. ProstaScint should be considered after bone scan and pelvic/abdominal CT have been ineffective in guiding treatment. More convincing data showing histologic confirmation of distant metastasis are necessary to fully appreciate ProstaScint’s usefulness.