

Review Article

Review of Salvage Therapy for Biochemically Recurrent Prostate Cancer: The Role of Imaging and Rationale for Systemic Salvage Targeted Anti-Prostate-Specific Membrane Antigen Radioimmunotherapy

Satyajit Kosuri,¹ Naveed H. Akhtar,¹ Michael Smith,²
Joseph R. Osborne,^{3,4} and Scott T. Tagawa^{1,4,5}

¹ Division of Hematology and Medical Oncology, Department of Medicine, Weill Cornell Medical College, New York, NY 10065, USA

² Department of Radiation Oncology, Weill Cornell Medical College, New York, NY 10065, USA

³ Division of Nuclear Medicine, Department of Radiology, Weill Cornell Medical College, New York, NY 10065, USA

⁴ Weill Cornell Cancer Center, New York, NY 10065, USA

⁵ Department of Urology, Weill Cornell Medical College, New York, NY 10065, USA

Correspondence should be addressed to Scott T. Tagawa, stt2007@med.cornell.edu

Received 15 December 2011; Accepted 30 March 2012

Academic Editor: Douglas S. Scherr

Copyright © 2012 Satyajit Kosuri et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Despite local therapy with curative intent, approximately 30% of men suffer from biochemical relapse. Though some of these PSA relapses are not life threatening, many men eventually progress to metastatic disease and die of prostate cancer. Local therapy is an option for some men, but many have progression of disease following local salvage attempts. One significant issue in this setting is the lack of reliable imaging biomarkers to guide the use of local salvage therapy, as the likely reason for a low cure rate is the presence of undetected micrometastatic disease outside of the prostate/prostate bed. Androgen deprivation therapy is a cornerstone of therapy in the salvage setting. While subsets may benefit in terms of delay in time to metastatic disease and/or death, research is ongoing to improve salvage systemic therapy. Prostate-specific membrane antigen (PSMA) is highly overexpressed by the majority of prostate cancers. While initial methods of exploiting PSMA's high and selective expression were suboptimal, additional work in both imaging and therapeutics is progressing. Salvage therapy and imaging modalities in this setting are briefly reviewed, and the rationale for PSMA-based systemic salvage radioimmunotherapy is described.

1. Prostate-Specific Antigen and Biochemical Relapse

Clinically localized prostate cancer (PC) may have a variable, often protracted course from first diagnosis to metastasis [1, 2]. Despite recent controversies, prostate-specific antigen (PSA) has not only revolutionized diagnosis but is also used to monitor disease recurrence after primary treatment options such as radical prostatectomy (RP) or local definitive radiotherapy (RT). An important aspect of monitoring is the concept of biochemical recurrence (BCR) which can be defined within the framework of PSA. A primary definition had proven elusive as there are considerable differences

between the primary therapies in regards to their PSA kinetics [3]. Following prostatectomy, absolute PSA values of 0.2–0.4 ng/mL are commonly used to define BCR, with a PSA of 0.4 ng/mL followed by another increase suggested for inclusion in clinical trials for men with BCR following RP [4, 5]. In the post-RT setting, an increase of 2 ng/mL from the patients' post-RT nadir is used as the marker for recurrent/persistent disease (biochemical failure) [6].

In many parts of the world, the majority of men diagnosed with PC are usually well suited for local curative attempts with RP or RT. In this population it has been shown that BCR occurs in 12–42% [7] and 22–69% [8], respectively, overall approximating 30% of patients treated with local

therapy for curative intent [5, 9, 10]. In the United States alone, it is estimated that approximately 50,000 patients are diagnosed with BCR annually [4, 11].

2. Salvage Therapy: Local Options

Once these patients experience BCR, the decision to start secondary or salvage therapy is a process for which may be as complicated as the decision about primary therapy. As at initial diagnosis, the range of outcomes after BCR is variable, with some men progressing to overt metastatic disease and death despite therapy and others dying of other causes even without further PC intervention [12]. As a concept akin to other solid tumors, those with local recurrence might be cured with local therapy; some with systemic recurrence may benefit from systemic therapy, though as with other solid tumors in general, only those with local recurrence tend to be cured with salvage therapy. There are many options that include salvage RP, brachytherapy, external beam radiation therapy, cryotherapy, androgen deprivation therapy (ADT), or a combination of these modalities.

For those with BCR following radiation therapy, salvage radical prostatectomy (SRP) after primary radiotherapy can offer an effective management option. Eastham and colleagues studied 146 patients who underwent SRP for biopsy-proven local recurrence of PC [13]. In this study BCR was defined as a serum PSA of 0.2 ng/mL or higher or the initiation of androgen deprivation therapy after radiotherapy. Over a period of 5 years the recurrence-free probability was 54%, and only one patient experienced a clinical local recurrence, with a 5-year cumulative incidence of death from PC of 4%. As all of the prior reported experience was retrospective, the Cancer and Leukemia Group B (CALGB) performed a multicenter prospective study of SRP in patients who had BCR after radiotherapy. In this study of 41 patients, the 5-year biochemical-free survival was 55% and overall survival (OS) was 85% [14]. The time to first incontinent-free rates at 3, 6, and 12 months after surgery were 90%, 18%, and 9%, and time to first erectile dysfunction-free rates following SRP at 3, 6, and 12 months were 87%, 25%, and 14%. Despite these potentially encouraging efficacy results, SRP is currently reserved for a highly select population based upon a number of factors, including real and/or perceived toxicity.

Salvage cryotherapy is an option which some see as less invasive approach to surgery with fewer side effects in the absence of prospective randomized studies. A retrospective analysis examined 76 patients over a 10-year period with a mean Gleason score of 7, who had prostate cryotherapy as salvage therapy before January 1999. At the end of this study, 43 of 76 men (56.6%) were still alive; 33 men (43.4%) had died but only 13.2% from prostate cancer and 22.4% from noncancerous causes, and 6.6% died from unknown causes [15]. A pooled analysis of salvage cryoablation demonstrated 54.5% 5-year actuarial biochemical disease-free survival with an incontinence rate of 4.4% and rectal fistula rate of 1.2% [16]. These and other investigators have concluded that cryosurgery is safe and effective treatment in selected patients

in whom radiation therapy fails [15–17]. Further study is necessary, including improvement and standardization of technique.

One option commonly offered to patients with BCR after primary RP is salvage radiation therapy (SRT). Most of the available data comes from retrospective series. Stephenson et al. analyzed data from 17 tertiary care centers, evaluating 1540 patients. The six-year progression-free probability was 32% overall, 48% for patients with a pre-SRT PSA less than or equal to 0.5, 40% with a PSA > 0.5–1, 28% for patients with a PSA 1–1.5, and 18% for PSA greater than 1.5. These findings suggest that delivering SRT at the earliest sign of recurrence, when the PSA is low, is optimal, as nearly half of patients may have a long-term PSA response, including some with other unfavorable prognostic factors, including a PSA doubling time of 10 months or less or with poorly differentiated (Gleason 8–10) histology. A nomogram is available utilizing independently significant variables, including PSA level before SRT, prostatectomy Gleason score, PSA doubling time, surgical margins, androgen-deprivation therapy before or during RT therapy, and lymph node metastasis [18].

A retrospective review from Johns Hopkins included 635 men who previously underwent RP and were subsequently observed (63%), underwent SRT (25%), or SRT + hormonal therapy (12%) for either a biochemical or local recurrence. SRT was associated with a threefold increase in prostate cancer-specific survival (CSS) compared to those not treated with SRT (HR 0.32, $P < 0.001$). The addition of hormonal therapy did not improve CSS. Without long-term followup this benefit in CSS was limited to those with a doubling time of less than 6 months and persisted after adjustment for other prognostic factors. SRT delivered greater than two years after recurrence or, for those men whose PSA never became undetectable after RP, did not result in improvement in CSS at the time of analysis [19].

Although there are limitations in the evaluation of retrospective data, these reports provide solid evidence for the benefit of early SRT. Important factors to consider in determining the need for SRT include preoperative and pre-RT PSA, postrecurrence doubling time, pathologic features suggestive of a local recurrence (e.g., positive margins), achievement or nonachievement of a nondetectable PSA post-operatively, pattern of rise of PSA (whether or not consistent with a local recurrence), long recurrence interval from surgery, as well as patient factors [18, 20, 21].

3. Imaging in the Setting of Biochemical Relapse

One of the major issues with local therapy (whether for newly diagnosed clinically localized disease or in the setting of BCR) is the lack of ability to accurately determine the presence or absence of distant metastatic disease. It is likely that the most significant reason for failure of most attempts at salvage therapy for biochemically recurrent PC is the presence of undetected metastatic disease. Conventional imaging techniques such as transrectal ultrasonography, magnetic resonance imaging (MRI), computed tomography

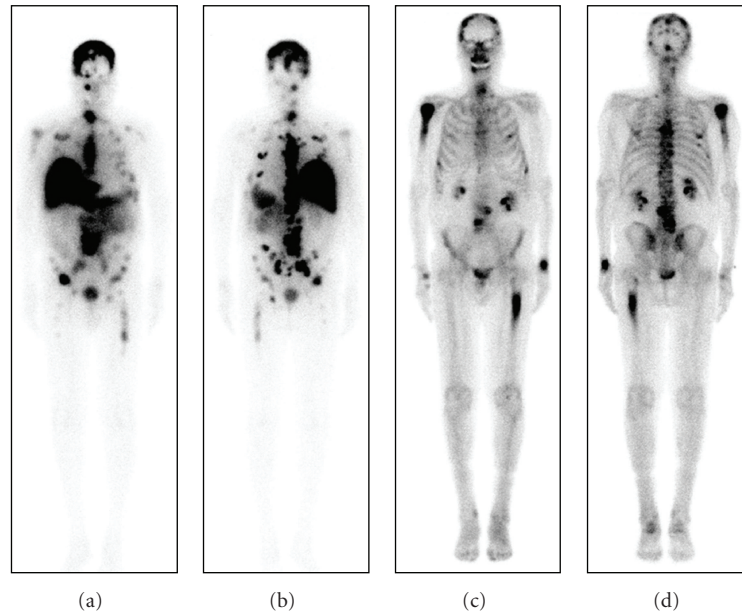


FIGURE 1: Anterior (a) and posterior (b) planar gamma camera images of radiolabeled J591. A greater number of lesions are apparent compared to anterior (c) and posterior (d) ^{99m}Tc -MDP bone scan. Hepatic clearance of radiolabeled mAb results in nonspecific uptake in the liver.

(CT), and ^{99m}Tc -MDP scintigraphy (bone scan) are usually not sensitive or specific enough to detect metastatic or recurrent prostate disease [22–28]. Therefore, an increase in PSA may precede a clinically detectable recurrent pelvic or metastatic cancer by months to years [29].

Though initial attempts using monoclonal antibodies (mAbs) to PSA and PAP were unsuccessful [30], more recently various and more specific markers of PC have been identified, including cell surface proteins, glycoprotein, receptors, enzymes, and peptides [31]. Prostate-specific membrane antigen (PSMA) is the most well established, highly specific prostate epithelial cell membrane antigen known [32–36]. The first and only approved agent for targeting PSMA in PC is ^{111}In -capromab [37].

An initial study utilizing capromab pentetide in men BCR after prostatectomy and lymphadenectomy demonstrated safety [38]. Kahn et al. performed a study in 32 men with BCR after prostatectomy prior to SRT; 61% of those with evidence of local disease only had a durable response to SRT versus 28% with durable response if they had evidence of distant disease on ^{111}In -capromab imaging [39]. However, while additional similar studies support these results [40], others have demonstrated no benefit with the use of capromab pentetide in selection of patients for local salvage therapy [41, 42]. Some efforts to improve ^{111}In -capromab imaging have added SPECT/CT fusion imaging, but results remain suboptimal [43–45].

A major reason for the suboptimal results with capromab pentetide lies with its targeting of the internal domain of PSMA, leading to the inability to bind to viable cells [32–35, 46]. Recognition of these features led to the development of mAbs by Bander et al. to the exposed, extracellular domain of PSMA [46–48]. J591, a deimmunized mAb against the

extracellular domain of PSMA, has been the lead clinical candidate [48, 49]. While no formal prostate imaging studies of J591 have been conducted, several therapeutic studies examining the clinical utility of radiolabeled J591 have been performed with built-in imaging components [49–51]. Radiolabeled J591 has successfully targeted (imaged) 89–100% osseous targeting and 69–100% soft tissue targeting [49–51], including cases where J591 demonstrated lesions that were not apparent on the bone scan but were identified on subsequent MR or conventional imaging as the lesion progressed (Figure 1) [52]. Current imaging work with anti-PSMA mAbs involves immune-PET imaging [53, 54]. Additional studies utilize small molecule inhibitors, including ^{123}I -MIP-1072, ^{123}I -MIP-1095, ^{99m}Tc -MIP-1404, and ^{99m}Tc -MIP-1405 [55, 56].

4. Systemic Therapy for Biochemical Relapse

The addition of hormonal therapy to primary RT has led to improvements for some men with clinically localized PC, possibly by radiosensitization and/or treating micrometastatic disease. This might be true with SRT as well, with several retrospective studies supporting this concept [57, 58]. Initial results of a large, prospective randomized study, RTOG 9601, in which SRT was compared with SRT + bicalutamide in patients with an elevated PSA after prostatectomy have been presented [57]. With a median followup of seven years, a statistically significant improvement in freedom from PSA progression with adjuvant bicalutamide versus RT alone has been reported (57 versus 40%) as well as incidence of metastatic disease (7 versus 13%). RTOG 0534, a Phase III Trial of short-term androgen deprivation

with pelvic lymph node or prostate bed only radiotherapy (SPPORT) in PC patients with a rising PSA after RP, is currently accruing (<http://www.clinicaltrials.gov/ct2/show/NCT00567580/>). Patients are randomly assigned to one of three arms: prostate bed RT only, prostate bed RT + neoadjuvant and concurrent ADT, or RT to the prostate bed and pelvic lymph nodes with neoadjuvant and concurrent ADT [59]. This study will help address the utility of the addition of ADT to SRT.

Though good local salvage options exist, not all patients qualify or agree to receive them, and most suffer disease progression despite local salvage therapy, likely because of micrometastatic disease outside of the prostate/prostate bed and pelvis that is not apparent on conventional imaging. Therefore systemic therapy is often employed. The most common management option for BCR after local therapy is ADT. While many studies have demonstrated that ADT does not prolong time to metastases and death in all comers, there are subgroups that likely benefit. Higher-grade disease and poorer PSA kinetics (i.e., short PSA doubling time) may predict improvement in outcome with early ADT [60, 61]. Additional evidence to support early ADT stems from the high-risk clinically localized or locally advanced settings [62–64]. However, while ADT may lead to some improvements, toxicity exists [65–70], and it is not curative in this situation. Chemotherapy is proven to improve survival and patient-reported outcomes in late stage disease but, as in most advanced solid tumors, is not able to overcome bulky disease and leads to cures in that setting [71, 72]. The addition of chemotherapy at an earlier stage has demonstrated a survival benefit in many solid tumors (i.e., neoadjuvant or adjuvant chemotherapy in combination with surgery/radiotherapy), presumably by eradicating micrometastatic sites of disease. We await the results of a study examining the use of chemotherapy in combination with hormonal therapy to treat micrometastatic disease in men with BCR after prostatectomy (<http://www.clinicaltrials.gov/ct2/show/NCT00514917/>) [73].

5. Prostate-Specific Membrane Antigen-Based Radioimmunotherapy

As discussed above, the concept of systemic therapy to eliminate micrometastatic disease has merit. “Targeted therapy” is designed to deliver agents to malignant cells and spare normal cells. PSMA is an ideal target for prostate cancer, based upon its near universal expression in PC. While the initial observations were that expression was limited to prostate cells, it is now known that there are low levels of expression in other tissues, including brush border of small intestine, renal proximal tubule lumen, and salivary glands. However, levels of expression are greatly increased in prostate cancer (as opposed to benign prostatic epithelial cells) and increase with grade, stage, and hormonal therapy [32–35]. Furthermore, alternative sites with low levels of expression have minimal or no exposure to circulating mAb, as they are protected by basement membranes and their luminal surface site of expression. Several studies

have demonstrated the ability of radiolabeled J591 to target and treat metastatic castration-resistant prostate cancer (CRPC).

Two independent phase I radioimmunotherapy (RIT) trials were performed using Yttrium-90 (^{90}Y) or Lutetium-177 (^{177}Lu) linked via a DOTA chelate to J591 in patients with metastatic CRPC. These trials defined the MTD and further refined dosimetry, pharmacokinetics, and immunogenicity (HAHA) of the radiolabeled mAb with some efficacy seen [50, 51]. Additional phase I and phase II studies utilizing ^{177}Lu -J591 have confirmed the ability of J591 to successfully target various sites of metastatic prostate cancer with the majority of subjects receiving full doses of radiolabeled antibody experiencing PSA declines and some measurable disease responses demonstrated [49, 74, 75]. As expected with radioimmunotherapy in general, dose-limiting toxicity is reversible myelosuppression, with a minority of patients also experiencing mAb-related infusion reactions (without pre-medication) or transient grade 1 transaminitis [49–51, 74–76].

Based on the physical properties of radionuclides, differential responses are expected depending upon radionuclide and tumor properties. ^{177}Lu is a low energy β emitter best for lesions 1–3 mm in diameter, while the higher β energy of ^{90}Y is best suited for 28–42 mm lesions [77]. An initial review of J591 RIT validated these properties in the clinical CRPC setting [76]. This leads to the hypothesis that ^{177}Lu -J591 should be less effective in the bulky metastatic CRPC setting but may lead to significantly more benefit in a micrometastatic disease setting. Indeed, RIT in general may have a higher impact in the minimal disease setting [78–80].

Prostate cancer is a radiosensitive disease, and BCR is common. Salvage local therapy may be successful but does not address disease sites outside of the prostate bed/pelvis, and most patients ultimately progress. Nearly all PC over-expresses PSMA; J591 is able to target metastatic disease sites. Full length anti-PSMA mAb has minimal to no access to other sites of low-level PSMA expression. Anti-PSMA-based RIT has demonstrated efficacy, and ^{177}Lu is optimal for 1–3 mm (i.e., micrometastatic) lesions.

Enrollment is ongoing in a multicenter Department of Defense and Prostate Cancer Foundation-sponsored study testing the concept of salvage targeted anti-PSMA-based RIT (<http://www.clinicaltrials.gov/ct2/show/NCT00859781/>). Men with high-risk CRPC (PSA doubling time <8 months and/or PSA > 20 [73]) and no evidence of disease on CT/MRI and bone scans are randomized in a 2:1 fashion to receive double-blinded ^{177}Lu -J591 versus ^{111}In -J591 (control) with a backbone of hormonal therapy (ketoconazole and hydrocortisone) and will undergo planar gamma camera imaging with SPECT following infusion. The primary endpoint of the study is 18-month metastasis-free survival with additional endpoints of median metastasis-free survival and overall survival. Secondary/exploratory endpoints include evaluation of radiolabeled J591 imaging to detect sites of metastases not apparent on standard CT/MRI and bone scan, validation of adrenal androgen levels as biomarkers for ketoconazole [81], and analysis of circulating tumor cells captured via CellSearch methodology as well as PSMA-GEDI capture [82]

for PSMA expression and counts to predict the appearance of radiographic metastases.

6. Conclusions

Biochemical relapse after local therapy for prostate cancer is common. While local salvage therapy is available, deficiencies in imaging currently lead to difficulties in selecting appropriate patients. For those with microscopic sites of disease outside of the prostate/prostate bed, targeted systemic salvage therapy is appealing. Prostate-specific membrane antigen-based diagnostics and therapeutics may lead to improvements in this disease setting.

Authors' Contribution

S. Kosuri and N. Akhtar contributed equally to this paper.

Acknowledgment

This paper is supported by Prostate Cancer Foundation, Department of Defense PC081664 (W81XWH-09-1-0596), NIH ULI RR024996, Robert H. McCooey Memorial Cancer Research Fund.

References

- [1] M. J. Zelefsky et al., "Cancer of the prostate," in *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*, V. T. DeVita Jr. et al., Ed., vol. 1, pp. 1392–1452, Lippincott Williams & Wilkins, Philadelphia, Pa, USA, 8th edition, 2008.
- [2] A. L. Potosky, B. B. Reeve, L. X. Clegg et al., "Quality of life following localized prostate cancer treated initially with androgen deprivation therapy or no therapy," *Journal of the National Cancer Institute*, vol. 94, no. 6, pp. 430–437, 2002.
- [3] A. J. Stephenson, M. W. Kattan, J. A. Eastham et al., "Defining biochemical recurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition," *Journal of Clinical Oncology*, vol. 24, no. 24, pp. 3973–3978, 2006.
- [4] H. I. Scher, M. Eisenberger, A. V. D'Amico et al., "Eligibility and outcomes reporting guidelines for clinical trials for patients in the state of a rising prostate-specific antigen: recommendations from the Prostate-Specific Antigen Working Group," *Journal of Clinical Oncology*, vol. 22, no. 3, pp. 537–556, 2004.
- [5] K. R. Han, J. K. Cohen, R. J. Miller et al., "Treatment of organ confined prostate cancer with third generation cryosurgery: preliminary multicenter experience," *Journal of Urology*, vol. 170, no. 4, part 1, pp. 1126–1130, 2003.
- [6] M. Roach, G. Hanks, H. Thames Jr. et al., "Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference," *International Journal of Radiation Oncology Biology Physics*, vol. 65, no. 4, pp. 965–974, 2006.
- [7] M. A. Khan, M. Han, A. W. Partin, J. I. Epstein, and P. C. Walsh, "Long-term cancer control of radical prostatectomy in men younger than 50 years of age: update 2003," *Urology*, vol. 62, no. 1, pp. 86–92, 2003.
- [8] W. U. Shipley, H. D. Thames, H. M. Sandler et al., "Radiation therapy for clinically localized prostate cancer: a multi-institutional pooled analysis," *JAMA*, vol. 281, no. 17, pp. 1598–1604, 1999.
- [9] A. L. Zietman, C. S. Chung, J. J. Coen, and W. U. Shipley, "10-Year outcome for men with localized prostate cancer treated with external radiation therapy: results of a cohort study," *Journal of Urology*, vol. 171, no. 1, pp. 210–214, 2004.
- [10] P. K. Agarwal, N. Sadetsky, B. R. Konety, M. I. Resnick, and P. R. Carroll, "Treatment failure after primary and salvage therapy for prostate cancer: likelihood, patterns of care, and outcomes," *Cancer*, vol. 112, no. 2, pp. 307–314, 2008.
- [11] S. J. Freedland and J. W. Moul, "Prostate specific antigen recurrence after definitive therapy," *Journal of Urology*, vol. 177, no. 6, pp. 1985–1991, 2007.
- [12] S. J. Freedland, E. B. Humphreys, L. A. Mangold et al., "Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy," *JAMA*, vol. 294, no. 4, pp. 433–439, 2005.
- [13] P. Paparel, A. M. Cronin, C. Savage, P. T. Scardino, and J. A. Eastham, "Oncologic outcome and patterns of recurrence after salvage radical prostatectomy," *European Urology*, vol. 55, no. 2, pp. 404–411, 2009.
- [14] M. H. Sokoloff, G. D. Steinberg, S. Halabi et al., "Management of recurrent prostate cancer after radiotherapy: results from CALGB 9687," in *Proceedings of the Annual Meeting of the American Urological Association (AUA '08)*, A Contemporary Prospective Multi-Institutional Salvage Radical Prostatectomy Series, May 2008.
- [15] P. Cheetham, M. Truesdale, S. Chaudhury, S. Wenske, G. W. Hruby, and A. Katz, "Long-term cancer-specific and overall survival for men followed more than 10 years after primary and salvage cryoablation of the prostate," *Journal of Endourology*, vol. 24, no. 7, pp. 1123–1129, 2010.
- [16] L. L. Pisters, J. C. Rewcastle, B. J. Donnelly, F. M. Lugnani, A. E. Katz, and J. S. Jones, "Salvage prostate cryoablation: initial results from the cryo on-line data registry," *Journal of Urology*, vol. 180, no. 2, pp. 559–564, 2008.
- [17] P. E. Spiess, A. E. Katz, J. L. Chin et al., "A pretreatment nomogram predicting biochemical failure after salvage cryotherapy for locally recurrent prostate cancer," *BJU International*, vol. 106, no. 2, pp. 194–198, 2010.
- [18] A. J. Stephenson, P. T. Scardino, M. W. Kattan et al., "Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy," *Journal of Clinical Oncology*, vol. 25, no. 15, pp. 2035–2041, 2007.
- [19] B. J. Trock, M. Han, S. J. Freedland et al., "Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy," *JAMA*, vol. 299, no. 23, pp. 2760–2769, 2008.
- [20] A. J. Stephenson, S. F. Shariat, M. J. Zelefsky et al., "Salvage Radiotherapy for Recurrent Prostate Cancer after Radical Prostatectomy," *JAMA*, vol. 291, no. 11, pp. 1325–1332, 2004.
- [21] S. E. Cotter, M. H. Chen, J. W. Moul et al., "Salvage radiation in men after prostate-specific antigen failure and the risk of death," *Cancer*, vol. 117, no. 17, pp. 3925–3932, 2011.
- [22] P. H. Smith, A. Bono, F. Calais da Silva et al., "Some limitations of the radioisotope bone scan in patients with metastatic prostatic cancer: a subanalysis of EORTC trial 30853," *Cancer*, vol. 66, no. 5, supplement, pp. 1009–1016, 1990.
- [23] F. Parivar, H. Hricak, K. Shinohara et al., "Detection of locally recurrent prostate cancer after cryosurgery: evaluation

- by transrectal ultrasound, magnetic resonance imaging, and three-dimensional proton magnetic resonance spectroscopy," *Urology*, vol. 48, no. 4, pp. 594–599, 1996.
- [24] K. K. Yu and H. Hricak, "Imaging prostate cancer," *Radiologic Clinics of North America*, vol. 38, no. 1, pp. 59–85, 2000.
- [25] J. Kurhanewicz, D. B. Vigneron, R. G. Males, M. G. Swanson, K. K. Yu, and H. Hricak, "The prostate: MR imaging and spectroscopy: present and future," *Radiologic Clinics of North America*, vol. 38, no. 1, pp. 115–138, 2000.
- [26] D. M. Nudell, A. E. Wefer, H. Hricak, and P. R. Carroll, "Imaging for recurrent prostate cancer," *Radiologic Clinics of North America*, vol. 38, no. 1, pp. 213–229, 2000.
- [27] F. May, T. Treumann, P. Dettmar, R. Hartung, and J. Breul, "Limited value of endorectal magnetic resonance imaging and transrectal ultrasonography in the staging of clinically localized prostate cancer," *BJU International*, vol. 87, no. 1, pp. 66–69, 2001.
- [28] H. Hricak, H. Schöder, D. Pucar et al., "Some limitations of the radioisotope bone scan in patients with metastatic prostatic cancer. A subanalysis of EORTC trial 30853. the EORTC urological group," *Seminars in Oncology*, vol. 30, no. 5, supplement, pp. 616–634, 2003.
- [29] C. R. Pound, A. W. Partin, M. A. Eisenberger, D. W. Chan, J. D. Pearson, and P. C. Walsh, "Natural history of progression after PSA elevation following radical prostatectomy," *JAMA*, vol. 281, no. 17, pp. 1591–1597, 1999.
- [30] A. Ghosh and W. D. W. Heston, "Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer," *Journal of Cellular Biochemistry*, vol. 91, no. 3, pp. 528–539, 2004.
- [31] J. S. Ross, K. E. Gray, I. J. Webb et al., "Antibody-based therapeutics: focus on prostate cancer," *Cancer and Metastasis Reviews*, vol. 24, no. 4, pp. 521–537, 2005.
- [32] J. S. Horoszewicz, E. Kawinski, and G. P. Murphy, "Monoclonal antibodies to a new antigenic marker in epithelial prostatic cells and serum of prostatic cancer patients," *Anticancer Research*, vol. 7, no. 5, pp. 927–935, 1987.
- [33] R. S. Israeli, C. T. Powell, W. R. Fair, and W. D. W. Heston, "Molecular cloning of a complementary DNA encoding a prostate-specific membrane antigen," *Cancer Research*, vol. 53, no. 2, pp. 227–230, 1993.
- [34] R. S. Israeli, C. T. Powell, J. G. Corr, W. R. Fair, and W. D. W. Heston, "Expression of the prostate-specific membrane antigen," *Cancer Research*, vol. 54, no. 7, pp. 1807–1811, 1994.
- [35] J. K. Troyer, M. L. Beckett, and G. L. Wright, "Detection and characterization of the prostate-specific membrane antigen (PSMA) in tissue extracts and body fluids," *International Journal of Cancer*, vol. 62, no. 5, pp. 552–558, 1995.
- [36] R. Sokoloff, K. C. Norton, C. L. Gasior, K. M. Marker, and L. S. Grauer, "A dual-monoclonal sandwich assay for prostate-specific membrane antigen: levels in tissues, seminal fluid and urine," *Prostate*, vol. 43, no. 2, pp. 150–157, 2000.
- [37] U. Elsässer-Beile, P. Wolf, D. Gierschner, P. Bühler, W. G. Schultze-Seemann, and U. Wetterauer, "A new generation of monoclonal and recombinant antibodies against cell-adherent prostate specific membrane antigen for diagnostic and therapeutic targeting of prostate cancer," *Prostate*, vol. 66, no. 13, pp. 1359–1370, 2006.
- [38] D. B. Sodee, R. Conant, M. Chalfant et al., "Preliminary imaging results using In-111 labeled CYT-356 (Prostascint(TM)) in the detection of recurrent prostate cancer," *Clinical Nuclear Medicine*, vol. 21, no. 10, pp. 759–767, 1996.
- [39] D. Kahn, R. D. Williams, M. J. Manyak et al., "111Indium-capromab pendetide in the evaluation of patients with residual or recurrent prostate cancer after radical prostatectomy," *Journal of Urology*, vol. 159, no. 6, pp. 2041–2047, 1998.
- [40] P. E. Levesque, P. T. Nieh, L. N. Zinman, D. W. Seldin, and J. A. Libertino, "Radiolabeled monoclonal antibody indium 111-labeled CYT-356 localizes extraprostatic recurrent carcinoma after prostatectomy," *Urology*, vol. 51, no. 6, pp. 978–984, 1998.
- [41] S. Wilkinson and G. Chodak, "The role of 111indium-capromab pendetide imaging for assessing biochemical failure after radical prostatectomy," *Journal of Urology*, vol. 172, no. 1, pp. 133–136, 2004.
- [42] C. T. Thomas, P. T. Bradshaw, B. H. Pollock et al., "Indium-111-capromab pendetide radioimmunoscintigraphy and prognosis for durable biochemical response to salvage radiation therapy in men after failed prostatectomy," *Journal of Clinical Oncology*, vol. 21, no. 9, pp. 1715–1721, 2003.
- [43] R. J. Ellis, E. Y. Kim, R. Conant et al., "Radioimmunoguided imaging of prostate cancer foci with histopathological correlation," *International Journal of Radiation Oncology Biology Physics*, vol. 49, no. 5, pp. 1281–1286, 2001.
- [44] J. K. DeWyngaert, M. E. Noz, B. Ellerin, E. L. Kramer, G. Q. Maguire, and M. P. Zeleznik, "Procedure for unmasking localization information from ProstaScint scans for prostate radiation therapy treatment planning," *International Journal of Radiation Oncology Biology Physics*, vol. 60, no. 2, pp. 654–662, 2004.
- [45] C. J. Schettino, E. L. Kramer, M. E. Noz, S. Taneja, P. Padmanabhan, and H. Lepor, "Impact of fusion of indium-111 capromab pendetide volume data sets with those from MRI of CT in patients with recurrent prostate cancer," *American Journal of Roentgenology*, vol. 183, no. 2, pp. 519–524, 2004.
- [46] H. Liu, P. Moy, S. Kim et al., "Monoclonal antibodies to the extracellular domain of prostate-specific membrane antigen also react with tumor vascular endothelium," *Cancer Research*, vol. 57, no. 17, pp. 3629–3634, 1997.
- [47] H. Liu, A. K. Rajasekaran, P. Moy et al., "Constitutive and antibody-induced internalization of prostate-specific membrane antigen," *Cancer Research*, vol. 58, no. 18, pp. 4055–4060, 1998.
- [48] N. H. Bander, E. J. Trabulsi, L. Kostakoglu et al., "Targeting metastatic prostate cancer with radiolabeled monoclonal antibody J591 to the extracellular domain of prostate specific membrane antigen," *Journal of Urology*, vol. 170, no. 5, pp. 1717–1721, 2003.
- [49] S. T. Tagawa, H. Beltran, S. Vallabhajosula et al., "Anti-prostate-specific membrane antigen-based radioimmunotherapy for prostate cancer," *Cancer*, vol. 116, no. 4, supplement, pp. 1075–1083, 2010.
- [50] N. H. Bander, M. I. Milowsky, D. M. Nanus, L. Kostakoglu, S. Vallabhajosula, and S. J. Goldsmith, "Phase I trial of 177Lutetium-labeled J591, a monoclonal antibody to prostate-specific membrane antigen, in patients with androgen-independent prostate cancer," *Journal of Clinical Oncology*, vol. 23, no. 21, pp. 4591–4601, 2005.
- [51] M. I. Milowsky, D. M. Nanus, L. Kostakoglu, S. Vallabhajosula, S. J. Goldsmith, and N. H. Bander, "Phase I trial of yttrium-90-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for androgen-independent prostate cancer," *Journal of Clinical Oncology*, vol. 22, no. 13, pp. 2522–2531, 2004.
- [52] N. H. Bander, "Technology Insight: monoclonal antibody imaging of prostate cancer," *Nature Clinical Practice Urology*, vol. 3, no. 4, pp. 216–225, 2006.

- [53] J. P. Holland, V. Divilov, N. H. Bander, P. M. Smith-Jones, S. Larson, and J. S. Lewis, "89Zr-DFO-J591 for immunoPET of prostate-specific membrane antigen expression in vivo," *Journal of Nuclear Medicine*, vol. 51, no. 8, pp. 1293–1300, 2010.
- [54] M. J. Evans, P. M. Smith-Jones, J. Wongvipat et al., "Non-invasive measurement of androgen receptor signaling with a positron-emitting radiopharmaceutical that targets prostate-specific membrane antigen," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 23, pp. 9578–9582, 2011.
- [55] R. E. Coleman, J. B. Stubbs, J. A. Barrett, M. De La Guardia, N. Lafrance, and J. W. Babich, "Radiation dosimetry, pharmacokinetics, and safety of ultratrace iobenguane I-131 in patients with malignant pheochromocytoma/paraganglioma or metastatic carcinoid," *Cancer Biotherapy and Radiopharmaceuticals*, vol. 24, no. 4, pp. 469–475, 2009.
- [56] J. R. Osborne, N. H. Akhtar, S. Vallabhajosula et al., "Tc-99m labeled small-molecule inhibitors of prostate-specific membrane antigen (PSMA): new molecular imaging probes to detect metastatic prostate adenocarcinoma (PC)," *Journal of Clinical Oncology*, vol. 30, supplement 5, 2012, Abstract no. 173.
- [57] C. R. King and M. T. Spiotto, "Improved outcomes with higher doses for salvage radiotherapy after prostatectomy," *International Journal of Radiation Oncology Biology Physics*, vol. 71, no. 1, pp. 23–27, 2008.
- [58] R. Cheung, S. L. Tucker, A. L. Lee et al., "Assessing the impact of an alternative biochemical failure definition on radiation dose response for high-risk prostate cancer treated with external beam radiotherapy," *International Journal of Radiation Oncology Biology Physics*, vol. 61, no. 1, pp. 14–19, 2005.
- [59] A Phase III Trial of Short Term Androgen Deprivation With Pelvic Lymph Node or Prostate Bed Only Radiotherapy (SPPORT) in Prostate Cancer Patients With a Rising PSA After Radical Prostatectomy—NCT00567580, 2007, <http://clinicaltrials.gov/ct2/show/NCT00567580>.
- [60] J. W. Moul, "Prostate specific antigen only progression of prostate cancer," *Journal of Urology*, vol. 163, no. 6, pp. 1632–1642, 2000.
- [61] C. J. Ryan and E. J. Small, "High risk biochemical relapse and the timing of androgen deprivation therapy," *Journal of Urology*, vol. 176, no. 6, part 2, pp. S61–S65, 2006.
- [62] C. A. Lawton, K. Winter, D. Grignon, and M. V. Pilepich, "Androgen suppression plus radiation versus radiation alone for patients with stage D₁/pathologic node-positive adenocarcinoma of the prostate: updated results based on national prospective randomized trial Radiation Therapy Oncology Group 85–31," *Journal of Clinical Oncology*, vol. 23, no. 4, pp. 800–807, 2005.
- [63] E. M. Messing, J. Manola, M. Sarosdy, G. Wilding, E. D. Crawford, and D. Trump, "Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer," *The New England Journal of Medicine*, vol. 341, no. 24, pp. 1781–1788, 1999.
- [64] T. B. Dorff, T. W. Flaig, C. M. Tangen et al., "Adjuvant androgen deprivation for high-risk prostate cancer after radical prostatectomy: SWOG S9921 study," *Journal of Clinical Oncology*, vol. 29, no. 15, pp. 2040–2045, 2011.
- [65] J. C. Smith, S. Bennett, L. M. Evans et al., "The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer," *The Journal of Clinical Endocrinology and Metabolism*, vol. 86, no. 9, pp. 4261–4267, 2001.
- [66] M. R. Smith, J. S. Finkelstein, F. J. McGovern et al., "Changes in body composition during androgen deprivation therapy for prostate cancer," *The Journal of Clinical Endocrinology and Metabolism*, vol. 87, no. 2, pp. 599–603, 2002.
- [67] M. Braga-Basaria, A. S. Dobs, D. C. Muller et al., "Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy," *Journal of Clinical Oncology*, vol. 24, no. 24, pp. 3979–3983, 2006.
- [68] S. Basaria, D. C. Muller, M. A. Carducci, J. Egan, and A. S. Dobs, "Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy," *Cancer*, vol. 106, no. 3, pp. 581–588, 2006.
- [69] M. R. Smith, H. Lee, and D. M. Nathan, "Insulin sensitivity during combined androgen blockade for prostate cancer," *The Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 4, pp. 1305–1308, 2006.
- [70] N. L. Keating, A. J. O'Malley, and M. R. Smith, "Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer," *Journal of Clinical Oncology*, vol. 24, no. 27, pp. 4448–4456, 2006.
- [71] I. F. Tannock, R. De Wit, W. R. Berry et al., "Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer," *The New England Journal of Medicine*, vol. 351, no. 15, pp. 1502–1512, 2004.
- [72] D. P. Petrylak, C. M. Tangen, M. H. A. Hussain et al., "Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer," *The New England Journal of Medicine*, vol. 351, no. 15, pp. 1513–1520, 2004.
- [73] A Randomized, Open Label, Multicenter, Phase III, 2-Arm Study of Androgen Deprivation With Leuprolide, +/- Docetaxel for Clinically Asymptomatic Prostate Cancer Subjects With a Rising PSA Following Definitive Local Therapy—NCT00514917, 2007, <http://clinicaltrials.gov/ct2/show/NCT00514917>.
- [74] S. T. Tagawa, M. I. Milowsky, M. Morris et al., "Phase II trial of ¹⁷⁷Lutetium radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody J591 (¹⁷⁷Lu-J591) in patients (pts) with metastatic castrate-resistant prostate cancer (metCRPC)," *Journal of Clinical Oncology*, vol. 26, article 284s, 2008, Abstract no. 5140.
- [75] S. T. Tagawa, S. Vallabhajosula, J. Osborne et al., "Phase I trial of fractionated-dose ¹⁷⁷lutetium radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody J591 (¹⁷⁷Lu-J591) in patients (pts) with metastatic castration-resistant prostate cancer (metCRPC)," *Journal of Clinical Oncology*, vol. 28, supplement 15, 2010, Abstract no. 4667.
- [76] N. H. Akhtar, D. M. Nanus, J. Osborne et al., "Anti-prostate specific membrane antigen (PSMA)-based radioimmunotherapy: a combined analysis of radiolabeled-J591 studies," *Journal of Clinical Oncology*, vol. 29, supplement 7, 2011, Abstract no. 136.
- [77] J. A. O'Donoghue, G. Sgouros, C. R. Divgi, and J. L. Humm, "Single-dose versus fractionated radioimmunotherapy: model comparisons for uniform tumor dosimetry," *Journal of Nuclear Medicine*, vol. 41, no. 3, pp. 538–547, 2000.
- [78] M. S. Kaminski, M. Tuck, J. Estes et al., "¹³¹I-tositumomab therapy as initial treatment for follicular lymphoma," *The New England Journal of Medicine*, vol. 352, no. 5, pp. 441–449, 2005.
- [79] J. P. Leonard, M. Coleman, L. Kostakoglu et al., "Abbreviated chemotherapy with fludarabine followed by tositumomab and iodine I 131 tositumomab for untreated follicular lymphoma,"

Journal of Clinical Oncology, vol. 23, no. 24, pp. 5696–5704, 2005.

- [80] O. W. Press, J. M. Unger, R. M. Braziel et al., “Phase II trial of CHOP chemotherapy followed by tositumomab/iodine I-131 tositumomab for previously untreated follicular non-Hodgkin’s lymphoma: five-year follow-up of Southwest Oncology Group protocol S9911,” *Journal of Clinical Oncology*, vol. 24, no. 25, pp. 4143–4149, 2006.
- [81] C. J. Ryan, S. Halabi, S. S. Ou, N. J. Vogelzang, P. Kantoff, and E. J. Small, “Adrenal androgen levels as predictors of outcome in prostate cancer patients treated with ketoconazole plus antiandrogen withdrawal: results from a Cancer and Leukemia Group B study,” *Clinical Cancer Research*, vol. 13, no. 7, pp. 2030–2037, 2007.
- [82] J. P. Gleghorn, E. D. Pratt, D. Denning et al., “Capture of circulating tumor cells from whole blood of prostate cancer patients using geometrically enhanced differential immunocapture (GEDI) and a prostate-specific antibody,” *Lab on a Chip*, vol. 10, no. 1, pp. 27–29, 2010.