

Managed Care Implications in Castration-Resistant Prostate Cancer

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Abstract

The management of prostate cancer (PrCa) and especially castration-resistant disease can be complex, challenging, and costly. Significant developments in the field of oncology have led to the further development of safe and effective therapies that are better targeted to particular tumor types and to individual patients. This is evident in castration-resistant prostate cancer (CRPC), where 5 new therapies proved to increase overall survival have debuted in just the past few years. With new therapies, however, come new treatment paradigms and new potential costs. It is vital that managed care clinicians and providers analyze the burden and the costs of cancer in the United States, especially those relating to PrCa and especially CRPC. This will allow a better understanding of how costs and issues relating to healthcare utilization affect the treatment of patients with CRPC, and impact individualized therapy and management decisions.

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For author information and disclosures, see end of text.

The Burden and Costs of Cancer in the United States

Significant and rapid clinical progress has been made in the field of oncology over the past 2 decades, mainly due to the development of effective targeted therapies for numerous different types of cancer. With these developments, the overall incidence of cancer has declined since the 1990s, with survival improving for many types of cancer, including prostate cancer (PrCa).^{1,2} It has been estimated that as of 2010, there were approximately 13.8 million men and women in the United States still alive who had a history of cancer.² The prevalence of cancer survivorship is expected to be even greater in the future, with the population of survivors projected to reach 18.1 million in 2020, due to the aging and growth of the US population as well as improved survival following diagnosis consequent to advances in screening, detection, and treatment.^{2,3} This increasing number of cancer survivors will receive continuous medical care throughout the trajectory of their disease, starting with diagnosis, and including short-term side effects, late or lasting impacts of disease, and its treatment. Because the incidence of cancers is highest among elderly patients, with people 65 years or older accounting for 8 million of the 13.8 million cancer survivors who were alive in 2010, the impact of this population growth on cancer prevalence may be greater than the declining incidence rates for some forms of cancer. Overall, the number of cancer survivors and cancer-related expenditures is likely to increase substantially in the United States.¹ Trends toward a greater intensity of healthcare service utilization and increasing costs of cancer care are expected to result in an increased general cancer-related burden in this country. Estimating and projecting the economic burden of cancer, including healthcare expenditures, loss of productivity, and morbidity and mortality, for patients and their families is an increasingly important issue for healthcare policy makers, health systems, physicians, employers, and society overall.³

Along with incidence and survival, practice patterns for the management of cancer have been constantly evolving for the majority of tumor types, and it is especially important to assess the cost burden in this particularly dynamic facet of healthcare. One recent study published in 2011 evaluated the costs of cancer care in the United States by utilizing cancer incidence and survival models from the Surveillance, Epidemiology and End Results (SEER)

program data. Taking into account the assumptions of constant incidence, survival, and associated costs, the study projected 13.8 and 18.1 million cancer survivors in 2010 and 2020, respectively. Based on the growth and aging of the US population, medical expenditures for cancer in the year 2020 were projected to reach at least \$158 billion (in 2010 dollars), which represents an increase of 27% over 2010, according to an analysis by the National Institutes of Health.¹

Identifying phases of care, including the initial period following diagnosis, the last year of life, and the interim between these 2 milestones, the average annualized costs of care were highest in the last year of life among all cancer types. However, the largest increases in costs between 2010 and 2020 were estimated to be in the continuing phase of care for PrCa (42% estimated increase from approximately \$6.02 billion to \$8.81 billion [in 2010 US dollars]), followed by female breast cancer (32% estimated increase from approximately \$6.85 billion to \$8.90 billion [in 2010 US dollars]). It was also estimated that if costs of care increase annually by 2% in the initial and last year of life phases of care, the total costs of cancer care in 2020 would actually reach \$173 billion, a massive 39% increase over 2010 costs.¹ With PrCa associated with such a substantial clinical and cost utilization burden, it is important to explore the healthcare utilization and economic burden related to PrCa and its implications for managed care practice and cost management.

The Costs Associated With PrCa in the United States: Different Study Foci and Different Data

Determining the actual cost burden of PrCa and its management can be challenging, and analyses may vary depending on the focus and the parameters researched. Various analyses have evaluated the economic burden of PrCa by examining the costs associated with different phases of care, the short- and long-term costs of various treatment modalities, and estimates of the potential lifetime economic burden associated with the disease. While analyses may vary in focus, each provides a valuable set of data and insights into the costs of disease management and the potential impact of these expenditures on patients and providers.³⁻⁵

Costs Related to Phase of Care

The various costs associated with cancer care are often reported from the time of initial diagnosis or from the time of a specific cancer-related event for a select group of patients with cancer, defined by clinical characteristics (ie, incidence costs), or for all survivors of that cancer type in a specific year (ie, prevalence costs).³ Costs and expenditures may vary

depending upon the phase of care. In a study by Yabroff et al, which evaluated the economic burden of cancer in the United States, it was estimated that the prevalence costs of care for PrCa was \$11.9 billion in 2010, which reflected the absolute number of cancer survivors by phases of care and by annualized phase-specific cost estimates. A larger proportion of prevalence costs was found in the continuing phase of care, as opposed to the initial phase of care or within the last year of life, since PrCa is a tumor type associated with longer survival than other cancer types (ie, lung and pancreatic cancers). Costs tend to be concentrated during the initial treatment phase and end-of-life care. Although the annual costs accumulated during the continuing phase tend to be lower, those costs may exceed the costs associated with early and late treatment, especially in cancers associated with long-term survival.^{1,3}

Short- and Long-Term Costs: The Impact on Disease Management

A retrospective, longitudinal cohort study published in 2010 by Snyder et al sought to compare the incremental short- and long-term costs of PrCa based on the initial treatment strategy chosen. Using the SEER-Medicare linked database, investigators were able to follow and compare 13,769 patients with clinically localized PrCa diagnosed in 2000 with 13,769 matched control patients without PrCa for 5 years. The 5 treatment groups in the study were based on the treatment received by the patient during the first 9 months following diagnosis: (1) watchful waiting (no treatment in the first 9 months); (2) radiation therapy only (including external beam and/or brachytherapy); (3) hormonal therapy only; (4) hormonal plus radiation combination; and (5) surgery (may have also received other treatments). The investigators found that, while the costs for the treatment strategies varied widely, for most cases of PrCa, costs were highest in the initial year of treatment and then dropped sharply, remaining steady over the next several years. Watchful waiting incurred the lowest 1-year and 5-year total mean overall incremental costs of \$4270 ($P < .0001$) and \$9130, respectively. First-year mean overall incremental costs were highest for patients who had received hormonal therapy plus radiation (\$17,474; $P < .0001$), followed by those who had undergone surgery (\$15,197; $P < .0001$), radiation therapy only (\$12,120; $P < .0001$), and then hormonal therapy only (\$11,034; $P < .0001$). While hormonal therapy alone had the second-lowest cost following the first year of treatment, it incurred highest 5-year total costs at \$26,896, followed closely by hormonal therapy plus radiation (\$25,097), then surgery (\$19,214), radiation therapy only (\$15,589), and

watchful waiting (\$9130).⁴ Patterns of care can vary significantly by treatment choice, and analyses of cost data better inform the patients and providers who are considering their various treatment options, along with policy makers who have interest in patterns of costs.

With the recent development and approval of 5 new therapies that improve survival in patients with CRPC and are specifically indicated for use in that patient population, cost of disease management will likely become an even greater issue. To date, no randomized controlled trials have directly compared the activity of these newer agents. As such, clinicians must rely on measures of drug effectiveness and side effect profiles to guide therapeutic decisions. A “rational approach” to the selection of therapy is warranted and should account for overall costs and improvements in patient quality of life (QOL). Further clinical trials are necessary to address the best use of these novel agents, including the sequencing of use to improve time-to-disease progression and survival, and to address which agents will offer the optimal cost-to-benefit ratio with regard to maintaining QOL.⁶ Future evaluations of therapeutic cost-effectiveness for various treatment strategies, particularly of newer biologic and/or immune-based therapies that are designed to treat more advanced disease and may be associated with increased costs, should take into consideration that lower initial costs of treatment do not necessarily translate into lower overall costs of care in the long term.

The Lifetime Economic Burden of Prostate Cancer

While healthcare claims databases are frequently used to estimate disease-related costs, they often do not provide an adequate number of years of patient follow-up to truly estimate lifetime costs. This issue is particularly problematic with PrCa, as 5-year survival rates for the disease can approach 100%, and there are limited data available that discern the total costs accumulated over the full course of disease. A study by Stokes et al was designed to estimate the total and disease-related per patient lifetime costs using a phase-based model of care in a group of patients who had been diagnosed with PrCa at 65 years or older. Patients were selected from the SEER database, and using estimated SEER survival times, the researchers extrapolated survival times for patients with PrCa from diagnosis until death. The periods of time that patients contributed to clinically relevant phases of treatment (ie, initial, continuing, terminal care) were determined using an algorithm that was designed to mimic the natural course of PrCa. Phase-specific monthly costs were combined with data for the number of months that patients with PrCa were alive during each phase of care to estimate total and

PrCa-related lifetime costs. The results of this study model, reported in inflation-adjusted 2004 US dollars, estimated that patients with PrCa accumulated a lifetime cost of \$110,520 per patient (95% confidence interval \$110,324-\$110,739). PrCa-related costs totaled \$34,492, comprising approximately 31% of total costs for medical care per patient. Total medical costs were highest for patients with Stage I disease, with costs lowering sequentially with each advancing stage of PrCa; the cost associated with advanced stage IV PrCa was approximately \$73,587, which reflected shorter periods of survival compared with patients who had been diagnosed at earlier stages of disease. However, after adjusting PrCa-related costs by the length of follow-up, annual costs for Stage IV disease (\$8118) were much higher than Stages I, II, and III (\$2740, \$2128, and \$1590, respectively). This finding reflects the higher usage of medical resources among patients with more advanced PrCa. Long-term cost estimates, such as those provided by this study, may be useful for improving the current understanding of potential treatment costs and their upper limits.⁵

Honing the Focus: The Economic Impact and Burden of CRPC

Estimations of the Economic Burden of Castration-Resistant Disease

The treatment of patients with CRPC continues to be a substantial clinical challenge that may be associated with high cost burden.^{7,8} An analysis published in 2010 focused on a retrospective analysis of claims and enrollment information from a large US database, through which laboratory data could be obtained. The analysis examined patients who were male, 40 years or older, diagnosed with PrCa, and received surgical or medical castration. Patients with CRPC were initially identified based on having at least 2 increases in serum prostate-specific antigen (PSA) levels. As there were a small number of patients with PSA data available, logistic regression modeling that used characteristics of patients with known CRPC was applied to identify a likely patient population with castration-resistant disease. Per patient monthly healthcare utilization and costs were determined through medical and pharmacy claims data. The final sample encompassed 349 patients with known CRPC identified by serum PSA increases and an additional 2391 patients with likely CRPC.⁸

In patients with confirmed CRPC and likely CRPC, there was a per patient, per month average of 1.43 PrCa-related ambulatory visits, 0.04 PrCa-related inpatient hospital stays, and 0.01 cancer-related emergency department (ED) visits. The average per patient, per month PrCa-related

costs were \$1152 for ambulatory outpatient visits, \$559 for inpatient stays, \$72 for pharmacy costs, and \$1 for ED visits. On average, total per patient, per month PrCa-related costs amounted to \$1799, and these costs comprised approximately 50% of all healthcare costs for this patient population. The authors concluded that CRPC is indeed a costly disease, with ambulatory care and inpatient hospitalization encompassing the bulk of the economic burden for these patients. However, the study was limited by the paucity of actual laboratory data that proved, definitively, CRPC status, thereby creating a need for a broader sample of patients with CRPC who have been identified via a prediction model that uses logistic regression to relate baseline patient characteristics with known CRPC status. To note, the actual status for CRPC among these patients was not known, and non-specific markers of CRPC, including data such as medical claims for bone scans and oncologist office visits, were used to select some patients within this broader population. As such, the “over-identification” of patients with CRPC may have occurred, and future research should better rely upon specific medical chart data to appropriately identify eligible patient and PrCa-related characteristics.⁸

Utilization of Resources by Practice Type: Oncology Versus Urology

Patients receiving treatment for CRPC may be managed by oncologists and/or urologists, and treatment patterns within these 2 types of clinical specialties may vary. One retrospective claims data analysis published in 2011 examined the treatment patterns, healthcare resource utilization, and cost-utilizing claims from a US managed care plan. The analysis focused on patients with CRPC who solely visited either a urologist or an oncologist for their cancer care, with variable follow-up data collected from a 6-year period. Results demonstrated that, of the 2585 patients who were included in the analysis, those within the oncologist cohort (n = 1590) were significantly more likely than patients within the urologist cohort (n = 995) to have insurance claims for hormone therapy (74.5% vs 61.1%, respectively; $P < .001$), with luteinizing-hormone-releasing hormone agonists being the most commonly prescribed hormone among both cohorts (oncology, 65.4% vs urology, 54.6%; $P < .001$). Patients who were managed by oncologists were also more likely than those who were managed by urologists to have insurance claims for chemotherapy (46.9% vs 10.2%; $P < .001$), radiation therapy (22.3% vs 3.7%; $P < .0001$), and treatments for other conditions (83.9% vs 63.0%; $P < .001$), such as anemia (42.8% vs 16.6%; $P < .001$), neutropenia (16.0% vs 2.3%; $P < .001$), and pain (67.4% vs 49.9%; P

$< .001$). Mean-adjusted healthcare costs were also higher among the patients in the oncologist group compared with those in the urologist cohort (\$31,896 vs \$15,318, respectively; $P < .001$). Predicted cumulative total adjusted CRPC-specific costs after 6 years was significantly higher among the patients treated by oncologists versus urologists with chemotherapy (\$86,706.26 vs 168,793.50, respectively; $P < .001$) and without chemotherapy (\$86,706.26 vs \$114,179.69, respectively; $P < .01$). Higher percentages of patients treated by oncologists, when compared with urologists, experienced inpatient stays (35.7% vs 12.2%, respectively; $P < .001$) and ambulatory visits (98.0% vs 93.1%; $P < .001$). However, patients treated by oncologists who did not receive chemotherapy demonstrated treatment patterns and costs that were similar to those within the urologist group, suggesting that the differences in costs between oncology and urology practice for patients with CRPC may be driven primarily by differences in the severity of illness, with the oncologists potentially managing more patients with more severe disease. As such, it is difficult to fully assess the differences in cost impact in these cases.⁹

The Potential Economics and Costs of Managing CRPC in Post Docetaxel Patients

Previous therapeutic options for CRPC were primarily palliative until 2004, when clinical trials demonstrated the survival benefit associated with docetaxel therapy. Since then, additional chemotherapeutic agents, immunotherapy, and targeted therapies have emerged and gained approval from the US Food and Drug Administration (FDA) for the treatment of CRPC and its associated metastatic disease, and have demonstrated improved overall survival in patients.¹⁰⁻¹² With the development of these new agents and their proven survival benefits, the treatment paradigm for PrCa has been revolutionized. However, further complicating these already complex treatment strategies is the research and emergence of new biomarkers that are meant to evaluate treatment efficacy, assess prognosis, and assist in patient management.¹¹

As a testament to today's constantly evolving therapeutic pipeline, multiple treatment options that were unavailable as little as 2 years prior now exist and have already received approval for use in patients with CRPC. While these new agents do provide specific disease and survival benefits, appropriate healthcare utilization and management of associated expenditures is a growing concern. Recent estimates of the costs that are associated with the use of those 5 newer, “post docetaxel” treatments over their approved courses of therapy are notably high^{10,12,13}:

Reports

- Sipuleucel-T: approximately \$93,000 for a standard course of 3 treatments
- Cabazitaxel: approximately \$50,000 for a typical 6 cycles
- Abiraterone acetate: approximately \$47,000 for an 8-month course of treatment
- Enzalutamide: approximately \$60,000 for an 8-month course of treatment
- Radium Ra-223 dichloride (for bone metastases): approximately \$70,000 to \$75,000

The metastatic spread of PrCa to bone also merits consideration with regard to healthcare utilization and costs. Bone metastases place a significant economic burden on the United States, adding approximately \$1.9 billion in associated expenditures (in 2004 US dollars). Skeletal-related events, including pathological fracture, spinal cord compression, bone surgery, and radiation, affect approximately 50% of patients with metastatic disease and negatively impact QOL as well as healthcare costs. For example, a study that examined the cost-effectiveness of 2 earlier approved treatments for bone metastases, zoledronic acid and denosumab, found that the total per patient costs incurred over 1 year were estimated at \$27,528 for those treated with zoledronic acid and \$35,341 for patients who had received denosumab (dollar values inflation-adjusted to December 2010).¹⁴ As radium Ra-223 dichloride is a newly approved agent, additional data and research will be needed to truly ascertain its costs; however, 1 insurer did estimate that the total cost of treatment ranged from \$70,000 to \$75,000.^{13,15} It should be noted that all of the agents that are designed to treat bone metastases will require further evaluation regarding clinical and cost-effectiveness over time.

Payers are preparing for the increasing costs of managing patients with CRPC, including the possibility that many of these patients may eventually require treatment with 1 or more of these new agents, perhaps due to new sequencing of therapies or the combination of multiple agents. A significant quandary for providers attempting to best manage the use of these agents is the virtual lack of comparative data for these new therapies in CRPC. It will be difficult for payers to gauge the appropriate use of new agents until clinically meaningful data that compares the treatments becomes available. Managing access to these drugs will need to be based on their FDA-approved indications and compendium arrangements/guidelines, at least until additional data become available. As such, further comparative research for these agents will help to guide future treatment decisions and resource utilization in the clinical space for CRPC.¹³

The expansion of treatments for patients with CRPC presents an additional need to adapt drug utilization among patients to better individualize therapy for CRPC. Multidisciplinary collaboration between radiation oncologists, medical oncologists, urologists, and various other healthcare professionals will be vital to formulate the best clinical practices and optimal therapeutic strategies, to monitor efficacy and safety, and to adapt treatment protocols. The combination of newer agents, emerging drugs, and specific biomarkers for providing therapeutic guidance requires improved clarification of the roles of the various clinical specialists, such as oncologists and urologists, and other members of the patient care team, to ensure that each patient receives the best possible care at the most opportune time to potentially obtain the best possible outcomes.¹¹

Conclusion

The management of PrCa and especially castration-resistant disease has led to new complexities and additional costs in disease management and patient care. With multiple new therapies proved to increase overall survival arriving rapidly at the forefront of treatment, managed care and healthcare providers must carefully evaluate the burdens and costs of PrCa, especially in castration-resistant disease, and must develop a better understanding of how conventional and novel treatment strategies may have far-reaching implications, both clinically and economically. Data in this area are continually expanding and evolving, and new challenges will likely present as additional information on the efficacy, safety, and appropriate utilization of newer therapeutic strategies comes to light. Individualizing treatments, tailoring disease management, and approaching patient care through multidisciplinary teams for PrCa or CRPC are central to delivering the most clinically and cost-effective treatments at the best time to ensure optimal patient and economic outcomes.

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