# Chapter 5
# Prostate Cancer

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## Introduction

Prostate cancer is one of the most common malignancies in American men, second only to non-melanoma skin cancer. In 2009, an estimated 192,280 new cases of prostate cancer were diagnosed in the United States, and about 27,360 men died of this disease [1]. The median age at diagnosis is 68 years, and the risk of developing the disease increases in men with advancing age, in those with an affected first-degree relative, and in African American men. The behavior of prostate cancer can vary from a microscopic, well-differentiated cancer with a slow clinical course to an aggressive, poorly differentiated cancer with the potential to invade and spread. Men with prostate cancer can be broadly staged as having localized disease (confined to the prostate), regional disease (i.e., spread to periprostatic fat, seminal vesicles, or pelvic lymph nodes), or distant disease (which metastasizes most commonly to distant lymph nodes and bone).

Current American Joint Committee on Cancer staging definitions for the extent of disease are outlined in Table 5.1. Since the introduction of serum prostate-specific antigen (PSA) testing in the 1990s, most cases of prostate cancer have been diagnosed while the disease is confined to the prostate. "Localized" (i.e., nonmetastatic) prostate cancer is further categorized into "low-risk," "intermediate-risk," and "high-risk"

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**Table 5.1** Prostate cancer staging by 2009 American Joint Committee on Cancer staging system

| | |
|---|---|
| *Primary tumor (T)* | |
| *Clinical* | |
| Tx | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Clinically inapparent tumor neither palpable nor visible by imaging |
| T1a | Tumor incidental histologic finding in 5% or less of tissue resected |
| T1b | Tumor incidental histologic finding in more than 5% of tissue resected |
| T1c | Tissue identified by needle biopsy (e.g., because of elevated PSA) |
| T2 | Tumor confined within the prostate |
| T2a | Tumor involves one-half of one lobe or less |
| T2b | Tumor involves more than one-half of one lobe but not both lobes |
| T2c | Tumor involves both lobes |
| T3 | Tumor extends through the prostatic capsule |
| T3a | Extracapsular extension (unilateral or bilateral) |
| T3b | Tumor invades the seminal vesicle(s) |
| T4 | Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles and/or pelvic wall |
| *Pathologic (pT)* | |
| pT2 | Organ confined |
| pT2a | Unilateral, involving one-half of one side or less |
| pT2b | Unilateral, involving more than one-half of side but not both sides |
| pT2c | Bilateral disease |
| pT3 | Extraprostatic extension |
| pT3a | Extraprostatic extension |
| pT3b | Seminal vesicle invasion |
| pT4 | Invasion of rectum, levator muscles, and/or pelvic wall |
| *Regional lymph nodes (N)* | |
| *Clinical* | |
| Nx | Regional lymph nodes were not assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastases in regional lymph node(s) |
| *Pathologic (pN)* | |
| pNx | Regional lymph node not sampled |
| pN0 | No positive regional lymph nodes |
| pN1 | Metastases in regional lymph node(s) |
| *Distant metastasis (M)* | |
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| M1a | Non-regional lymph node(s) |
| M1b | Bone |
| M1c | Other site(s) with or without bone disease |

*PSA* prostate-specific antigen

**Table 5.2** National Comprehensive Cancer Network categorization of recurrence risk (v.1.2010)

| Category | Tumor characteristics |
|---|---|
| Very low risk | T1a; Gleason score ≤6; PSA <10 ng/mL; fewer than 3 biopsy cores positive, ≤50% cancer in each core; and PSA density <0.15 ng/mL/g |
| Low | T1-T2a, Gleason score 2–6, and PSA <10 ng/mL |
| Intermediate | T2b-T2c, Gleason score 7, or PSA 10–20 ng/mL |
| High | T3a, Gleason score 8–10, or PSA >20 ng/mL |
| Very high | T3b-T4 |
| Metastatic | Any T, N1, M0; or any T, any N, M1 |

*PSA* prostate-specific antigen

groups on the basis of the extent of local disease, Gleason score, and PSA level. These groups, which reflect the potential (or actual) spread beyond the prostate and the likelihood of recurrence after treatment, are commonly used to guide pretreatment evaluations and treatment recommendations. The current National Comprehensive Cancer Network risk categories are listed in Table 5.2.

In this chapter, we present six decades of the MD Anderson Cancer Center prostate cancer experience.

## Historical Perspective

Diagnosing and staging of prostate cancer have evolved over the past six decades. Historically, prostate cancer was diagnosed when men developed obstructive or irritative urinary symptoms, palpable soft tissue metastases, or symptomatic bony metastases (i.e., back or hip pain). The introduction of PSA testing in the 1990s, however, dramatically changed the stage at which prostate cancer was diagnosed [2], in most cases shifting from an advanced metastatic stage at diagnosis to an asymptomatic, localized, and highly curable stage.

Radiologic advances over the past six decades have led to improved methods of identifying men with only local disease or with disease that has spread only to local lymph node basins. In the 1940s and 1950s, plain radiographs were available for diagnostic purposes. Plain radiographs can visualize bone changes but cannot visualize pelvic lymph node involvement. Lymphangiograms were introduced in the 1960s and used throughout the 1990s to image pelvic lymph nodes [3]. Computed tomographic scans were developed in the 1970s, adopted in the 1980s, and continue to be used to evaluate pelvic lymph nodes. Bone scans, introduced in the 1970s, are still used to evaluate men for bone metastases. In addition, endorectal magnetic resonance imaging is used in selected cases to visualize tissue planes and to define the local extent of disease. These imaging advances have improved the accuracy of identifying disease extent at presentation and have no doubt led to stage migration.

Along with advances in scanning technologies, surgical techniques have been refined as well. The anatomic radical prostatectomy technique, described in the

early 1980s [4], improved urinary continence and sexual function after surgical resection based on enhanced visualization and precise dissection in a relatively bloodless field. Radical prostatectomy subsequently became a more common treatment for prostate cancer, and a nerve-sparing radical prostatectomy technique was introduced at MD Anderson Cancer Center in the 1990s. The administration of novel therapeutic strategies, such as targeted molecular systemic agents, before radical prostatectomy among patients with high-risk prostate cancer was established in the late 1990s as a mechanism with which to rapidly evaluate both tissue and molecular effects of new potential agents affecting prostate cancer [5]. Recently, less invasive robotic prostatectomy techniques have been adopted that provide enhanced magnification for even greater precision.

The introduction of urologic oncology fellowships provided an opportunity for physicians to refine their surgical technique and enhance their oncologic knowledge base before practicing independently [6]. The first urologic oncology fellowship at MD Anderson Cancer Center was in the early 1970s, and we continue to train four urologic oncology fellows annually.

Radiotherapeutic techniques have also evolved over the past several decades. The introduction of three-dimensional computed tomography-based planning in the 1990s improved targeting in radiotherapy. The development of intensity-modulated radiation therapy improved dose delivery in the 2000s and permitted the escalation of radiation dose [7]. These dose-escalated treatments led to improved treatment outcome in localized prostate cancer, as shown in a randomized trial at MD Anderson Cancer Center [8]. In addition, the integration of hormone therapy with radiotherapy for men with localized and locally advanced prostate cancer led to improved prostate cancer survival rates [9, 10]. Currently, altered radiation fractionation to improve prostate cancer outcome is being investigated at MD Anderson.

Androgen ablative therapy was introduced in the 1940s and remains the primary systemic therapy for men with metastatic or locally advanced prostate cancer [11]. The methods of delivering androgen ablative therapy have changed over time and include maximum androgen blockade and intermittent androgen ablation. Systemic treatment options for men with castrate-resistant prostate cancer are limited; however, improved survival rates after administration of docetaxel were established in 2004 [12]. Clinical trials at MD Anderson are investigating cytotoxic agents, targeted agents, and immunotherapy to improve outcome for men with castrate-resistant prostate cancer.

Currently, in a large portion of men diagnosed with prostate cancer, the disease is still localized to the prostate. There are several treatment options for these men that offer similar efficacy but have different side effect profiles. Therefore, increased attention is being focused on the long-term sequelae of treatment and the impact of treatment on quality of life during treatment selection and treatment evaluation [13]. Ongoing clinical trials at MD Anderson are evaluating the effects of prostate cancer diagnosis and treatments on quality of life. In addition, active surveillance (frequent monitoring with no immediate cancer-directed treatment) is being studied at MD Anderson in men with early disease who may not require intervention and can therefore be spared the adverse effects of treatment and in those with comorbidities that render prostate cancer therapy unnecessary.

## The MD Anderson Cancer Center Experience

In total, 28,891 men presented to MD Anderson with a diagnosis of prostate cancer from March 1944 through December 2004. Of this group, 13,711 had no prior treatment for their cancer. Excluding men treated elsewhere and those diagnosed with other primary cancers (except superficial skin cancers), 6,675 men received definitive primary treatment for prostate cancer at MD Anderson and made up the cohort for analysis. Survival was calculated from the date of initial presentation to MD Anderson.

The number of patients presenting by decade is shown in Table 5.3. This number increased considerably over time, from 59 in 1944–1954 to 3,979 in 1995–2004, reflecting both the growth of MD Anderson and the national increase in prostate cancer diagnoses. Diagnoses increased nationally because of improved cancer detection, population growth, longer life expectancies, and the aging population. Of note, the number of prostate cancer patients tripled between 1975–1984 ($n=529$) and 1985–1994 ($n=1{,}631$), when serum PSA testing became more widespread. Awareness of the potential benefits of early detection with use of PSA testing led to its adoption in early detection programs in the late 1980s at MD Anderson Cancer Center. The widespread use of PSA testing in the 1990s is also reflected in the larger proportion of men with localized disease in later decades; this proportion had remained stable at about 30% through 1984 but increased to 73% in the 1995–2004 period. The proportion of men with localized disease is smaller than that seen nationally, however, because MD Anderson is a referral center that draws men with more advanced cancer.

Over the 60-year period, survival rates after prostate cancer diagnosis have improved significantly at MD Anderson ($P<0.0001$). As illustrated in Fig. 5.1, 5-year survival rates increased from 18.6% to 92.5%, and 10-year survival rates increased from 8.5% to 82.5%. Lengthened survival was the result of both the larger proportion of men being diagnosed with localized disease, when cure is more likely, and the improvements in prostate cancer treatment at MD Anderson, particularly for men with localized and regional disease. Stage migration was a consequence of implementing improved imaging at MD Anderson that could better distinguish men with localized

**Table 5.3** Prostate cancer stage distribution by decade

| | SEER stage at presentation | | | | |
|---|---|---|---|---|---|
| | Local | Regional | Distant | Unstaged | Total |
| Decade | [No. (%) of men diagnosed] | | | | |
| 1944–1954 | 18 (30.5) | 2 (3.4) | 34 (57.6) | 5 (8.5) | 59 (100.0) |
| 1955–1964 | 74 (33.9) | 26 (11.9) | 104 (47.7) | 14 (6.4) | 218 (100.0) |
| 1965–1974 | 73 (28.2) | 60 (23.2) | 119 (45.9) | 7 (2.7) | 259 (100.0) |
| 1975–1984 | 174 (32.9) | 203 (38.4) | 147 (27.8) | 5 (0.9) | 529 (100.0) |
| 1985–1994 | 760 (46.6) | 642 (39.4) | 171 (10.5) | 58 (3.6) | 1,631 (100.0) |
| 1995–2004 | 2,914 (73.2) | 770 (19.4) | 172 (4.3) | 123 (3.1) | 3,979 (100.0) |
| *Total* | *4,013 (60.1)* | *1,703 (25.5)* | *747 (11.2)* | *212 (3.2)* | *6,675 (100.0)* |

*SEER* Surveillance, Epidemiology, and End Results program

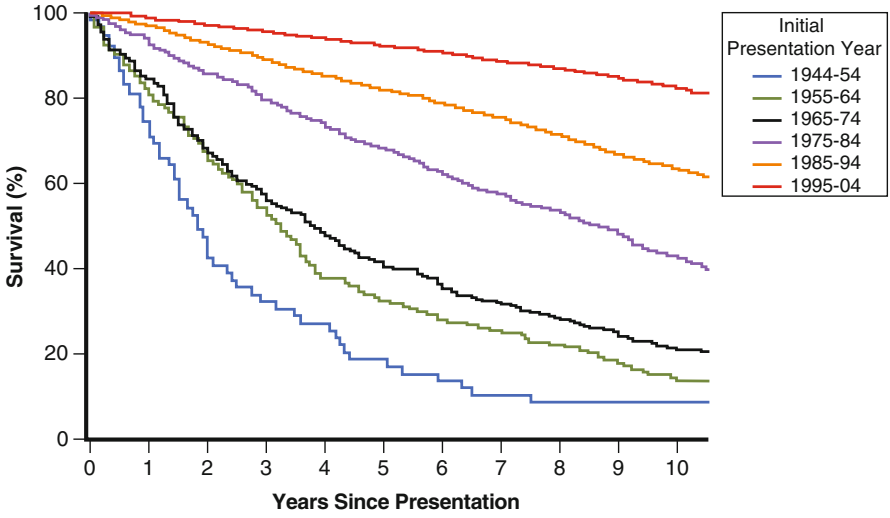


**Fig. 5.1** Overall survival rates for patients with prostate cancer (1944–2004) ($P < 0.0001$, log-rank test for trend).

disease and regional disease while identifying men with earlier metastatic disease. This contributed to increased survival rates among all groups over time. In addition, improvements in overall health contributed to men living longer over time.

In men with localized disease at diagnosis, 5-year survival rates increased from 38.9% to 96.0%, and 10-year survival increased from 22.2% to 87.3% (Fig. 5.2; $P < 0.0001$). Significant improvements were also seen in men with regional disease (Fig. 5.3; $P < 0.0001$) and in men with distant disease at diagnosis (Fig. 5.4; $P < 0.0001$). In men with distant disease at diagnosis, 5-year survival rates increased from 11.8% to 38.8%, and 10-year rates increased from 2.9% to 16.9%. Androgen deprivation therapy was the mainstay of systemic treatment throughout this period. The benefit of docetaxel for castrate-resistant prostate cancer was not established until 2004; therefore, improvements from docetaxel are not reflected in this analysis.

The significant improvements in prostate-cancer survival over the past six decades reflect the development and implementation of advances in imaging, surgery, radiotherapy, and medical oncology at MD Anderson. In addition, the adoption of routine PSA testing and subsequent earlier diagnosis of prostate cancer have contributed to improved prostate cancer survival.

## Current Management Approach

Our current approach to the management of prostate cancer is stratified by using "risk group" criteria and anticipated life expectancy. After initial diagnosis by PSA and prostate biopsy, pelvic imaging and a bone scan are obtained for selected men at

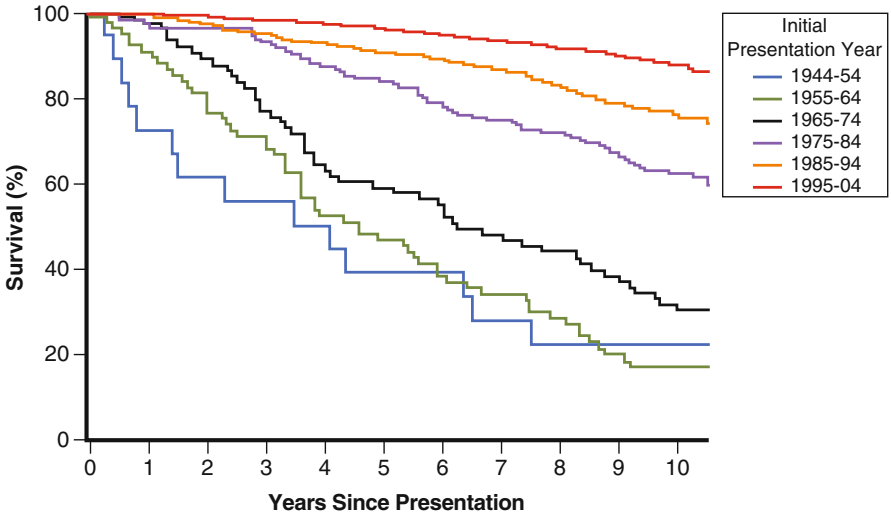


**Fig. 5.2** Survival rates for patients with local (SEER stage) prostate cancer (1944–2004) ($P < 0.0001$, log-rank test for trend).

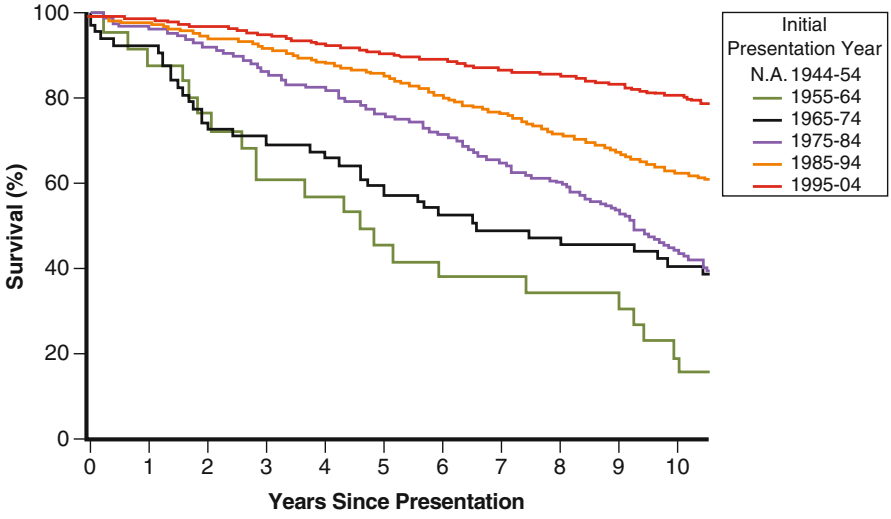


**Fig. 5.3** Survival rates for patients with regional (SEER stage) prostate cancer (1944–2004) ($P < 0.0001$, log-rank test for trend). Because of the very small number of individuals with regional prostate cancer seen from 1944 to 1954, data from this period were excluded. N.A., not applicable.

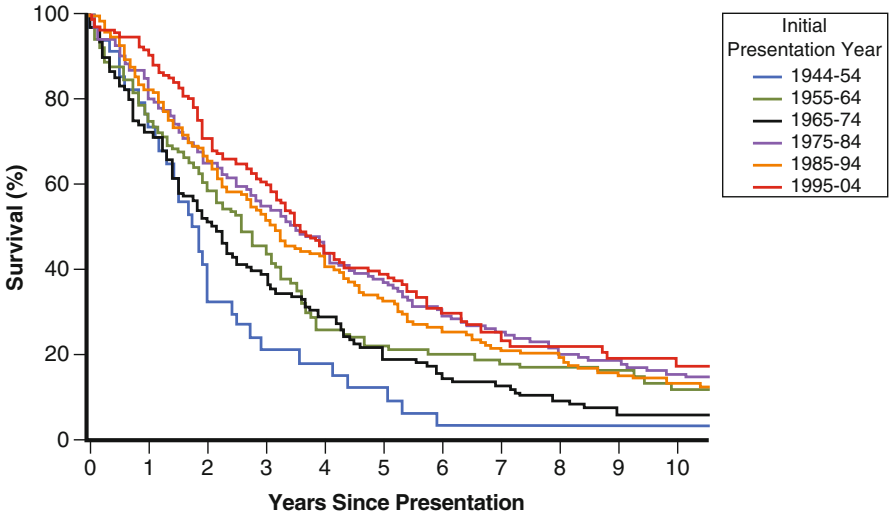


**Fig. 5.4** Survival rates for patients with distant (SEER stage) prostate cancer (1944–2004) ($P < 0.0001$, log-rank test for trend).

increased risk of disease spread beyond the prostate. Men with localized prostate cancer are offered treatment options on the basis of their overall health, prostate size, pubic bone geometry, and urinary function; these patients can often select from several suitable treatment choices, which include active surveillance, external beam radiotherapy, radical prostatectomy, brachytherapy, and cryotherapy.

Men with low-risk disease or those with a short life expectancy may forgo treatment and instead be monitored for progression of symptoms. For men with high-risk disease and for some men with intermediate-risk disease, androgen deprivation therapy is administered along with external beam radiotherapy. Men with nodal involvement are treated with androgen ablation, and locoregional radiation therapy is administered to some men. Men with metastatic disease are treated with systemic therapy. When appropriate, patients are offered enrollment in clinical trials.

To help patients assimilate all of the complex data associated with their disease process, treatment options, and quality-of-life effects, the Multidisciplinary Prostate Cancer Clinic was established at MD Anderson in 2004. In this setting, patients with localized prostate cancer are seen simultaneously by a urologist and radiation oncologist with a medical oncology consultation as appropriate. Patient visits are facilitated by an advanced practice nurse who helps patients navigate through the treatment selection process [14].

In the future, driven by new knowledge gained through the MD Anderson Cancer Center Prostate Cancer Specialized Program of Research Excellence (SPORE) Program, we anticipate that molecular classifications of prostate cancer will be used to define prognosis and guide management. This move toward personalized medicine should reduce the number of cases of overtreatment and undertreatment in men with prostate cancer.

Among those requiring treatment strategies to reduce the morbidity of local therapies, maintaining quality of life is paramount. Ongoing investigations at MD Anderson will help elucidate the appropriate length of androgen deprivation therapy, the optimal fractionation of radiotherapy, and the optimal time for administration of radiotherapy after prostatectomy. In addition, ongoing laboratory and clinical studies of cytotoxic, targeted, and immunotherapeutic agents will lead to the development of more effective systemic therapies for men with castrate-resistant prostate cancer, the type that presents the greatest threat to life.

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