Multidisciplinary Treatment for Prostate Cancer

Edited by

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Cover image description: cancer cell division. Coloured scanning electron micrograph (SEM) of two prostate cancer cells in the final stage of cell division (cytokinesis). During this stage the cells' cytoplasm divides. Here the cells are joined by a thin cytoplasmic bridge. Cancer cells divide rapidly in a chaotic, uncontrolled manner. They may clump to form tumours, which invade and destroy surrounding tissues. Prostate cancer affects the prostate gland of the male reproductive system, located below the bladder. It can cause difficulty in passing urine and an increased need to urinate. Magnification unknown. Credit: Steve Gschmeissner/Science Photo Library
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Textbook

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About the Activity

The CME activity is based on the information learned from reading this book, *Multidisciplinary Treatment for Prostate Cancer*. It was developed from an identified educational need for information about practical management issues in the practice of medical, surgical, and radiation oncology.

This activity has been developed and approved under the direction of Beam Institute.

Activity Learning Objectives

After reading *Multidisciplinary Treatment for Prostate Cancer*, participants should be able to:

- Explain the contributions of both systemic and local treatment modalities to optimal management of locally advanced prostate cancer.
- Understand the utility, advantages, and disadvantages of various surgical options currently being used to excise tumors of the prostate.
- Describe currently available radiotherapeutic methods of treating localized prostate cancer, considering the benefits and drawbacks of each.
- Discuss reasons why androgen deprivation may be used with other prostate cancer treatments and why patient selection is critical for its optimal benefit.
- Review the results of recent prostate cancer therapy trials and appreciate the promise of treatments currently being tested alone and in combination against the disease.
Target Audience
This activity targets physicians in the fields of oncology, hematology, radiation, and urology.

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This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Beam Institute and The Oncology Group. Beam Institute is accredited by the ACCME to provide continuing medical education for physicians.

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Financial Disclosure

Dr. George serves on the speakers’ bureau for Sanofi-Aventis. Dr. Kantoff is a consultant for Amgen, Celgene, Dendreon, GPC, Novacea, and Sanofi-Aventis; he is also an investigator for Amgen, Bayer, Bristol Myers Squibb, Genentech, Genzyme, GlaxoSmithKline, Novartis, Pfizer, Therion Biologics, and Wilex. Dr. Roach is a consultant for AstraZeneca and receives honorarium from Siemens and TAP. Dr. Sartor is a consultant for Dendreon, GPC Biotech, GlaxoSmithKline, Novartis, and Sanofi-Aventis. Dr. Febbo and Dr. Hu have indicated they have no financial relationships.

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Introduction

The prostate cancer field has been changing rapidly over the past two decades since the introduction and widespread use of the prostate-specific antigen (PSA). The increase in the number of cases diagnosed with prostate cancer that occurred as a result of screening necessitated refinements of existing therapies and the development of novel approaches. More recently, a greater appreciation of a role for active surveillance for selected patients has also developed. The primary oncologist should play a central role in helping patients make educated decisions about therapy (to treat or not and what is optimal therapy for the individual patient). The changes in the field have been staggering, and the literature can be confusing. This monograph updates the reader on developments in the field, providing a balanced, state-of-the-art assessment of treatment of early prostate cancer. It updates the reader on established forms of therapy, including external beam radiotherapy (EBRT) and brachytherapy, the evolving role of minimally invasive surgery and combination therapies, and, finally, on future directions.

In his chapter, Dr. Mack Roach from the University of California at San Francisco gives us his perspective on the role of brachytherapy in early prostate cancer; in particular, in the area of patient selection. In his comprehensive discussion of external beam radiation, he focuses his attention on trials that have demonstrated that survival and/or biochemical (PSA) control rates are improved with the addition of either short-term or long-term androgen-deprivation therapy (ADT) to EBRT, on trials that have demonstrated that biochemical control rates can be improved with the use of higher doses of radiation, and on the emerging role of three-dimensional conformal radiation or intensity-modulated radiotherapy techniques, which permit the delivery of high doses of radiation safely. Dr. Hu and colleagues from the Brigham and Women’s Hospital review the latest in different techniques for performing radical prostatectomy, including minimally invasive surgery, an increasingly popular approach. Although this is a rapidly evolving field, the oncologist needs to be aware of the latest in these approaches.

The next two chapters explore integrated approaches. Dr. Sartor from the Dana-Farber Cancer Institute builds on Dr. Roach’s chapter with a thorough review of the different forms of ADT, the evolving appreciation of side effects of ADT, and the role of ADT in early disease in particular when used in conjunction with radiation. He points out, however, the failure of ADT to provide a benefit when used before surgery. Finally, he discusses the potential role of adjuvant ADT in high-risk patients; currently the subject of clinical trials. Drs. Febbo and George from Duke University review the integration of
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chemotherapy into early prostate cancer treatment. Many small trials have been conducted, and we await the results of the trials that are well outlined in this chapter. Finally, looking to the future of therapy for prostate cancer, the last chapter reviews some of the agents under investigation, which, if they prove to be efficacious, may find their way into the multimodality management of early disease.

It is hoped that this monograph gives the practicing oncologist useful and current information to help guide patients through the difficult decision-making process surrounding the diagnosis of early prostate cancer.
Surgical Therapy for Localized Prostate Cancer: 
A Comparison of Open, Laparoscopic, and Robotic-Assisted Techniques

Heidi J. Rayala, MD, PhD, Glen W. Barrisford, MD, 
Steven B. Williams, MD, and James C. Hu, MD, MPH

Excluding nonmelanoma skin cancer, prostate cancer is the most commonly diagnosed malignancy and the third leading cause of cancer-specific death among men in the United States, with 218,890 new diagnoses and 27,050 prostate cancer–related deaths estimated to occur in 2007 (1). The advent of prostate-specific antigen (PSA) screening in the early 1990s resulted in an overall downstaging of newly diagnosed prostate cancer, and presently, approximately 77% of diagnosed disease is limited to the prostate (stage T1–T2) (2). Radical prostatectomy remains the most popular treatment option for men with localized prostate cancer (3). This chapter delineates the three most common surgical approaches for localized prostate cancer: (a) open retropubic radical prostatectomy; (b) laparoscopic radical prostatectomy (LRP); and (c) robotic-assisted LRP (RALRP). The authors describe the evolving surgical approach and review the functional and oncologic outcomes for each of these surgical therapies.

Evolution of Radical Prostatectomy

Young performed the first radical prostatectomy through a perineal incision between the scrotum and the rectum in 1905 (4). In 1949, Millen first described the retropubic approach
to the prostate via a small infraumbilical incision, which over the years has become the most familiar open surgical approach. A prostatectomy, regardless of approach, can be associated with excessive blood loss, incontinence, and erectile dysfunction, and for these reasons, external beam radiotherapy became a popular alternative for treating prostate cancer during the 1970s. In the 1980s, Walsh was instrumental in defining the surgical anatomy of the prostate. His study of cadavers revealed that the nerves innervating the penile corpus cavernosum, which allow erectile function, travel along the posterior-lateral aspect of the prostate, outside of the prostatic fascia, but within the visceral layer of the overlying pelvic/levator fascia. By careful dissection of the pelvic fascia and neurovascular bundles from the prostate, the nerves responsible for erectile function could be preserved, resulting in reduced morbidity (5,6). Presently, retropubic radical prostatectomy remains the gold standard surgical therapy for localized cancer of the prostate (7).

Schuessler performed the first LRP in 1992 (8). Rather than obtaining exposure through an abdominal incision with metal retractors to spread the muscle and soft tissues, the laparoscopic approach relies on small incisions through which several small (<12 mm) working ports are placed. In addition, carbon dioxide is used to insufflate the abdomen, creating space and exposure between the abdominal wall and the bowel. A lighted magnified scope is used to visualize the internal organs, providing ten times the magnification of the naked eye. Schuessler performed nine LRPs; however, due to long operative times of 9.4 hours and overall technical difficulty, he concluded that the approach was not a feasible alternative to the open approach (8). Less than a decade later, Guillonneau et al. published their initial series of 28 LRPs, reporting similar oncologic and functional efficacy to Schuessler, but a reduced operative mean time of 270 minutes (9). Subsequently, several surgeons demonstrated several consistently reproducible advantages of LRP, including minimal scarring, reduced blood loss, and decreased postoperative analgesic requirements (10–14).

The next evolutionary step in radical prostatectomy was the use of Intuitive Surgical’s da Vinci robot (Intuitive Surgical, Sunnyvale, Calif.) to perform a laparoscopic prostatectomy (15–17). The da Vinci robot was developed by the Stanford Research Institute under contract by the Department of Defense, with the original intent of robotic surgical intervention in the battlefield using a remotely located surgeon. The da Vinci robot was approved by the Food and Drug Administration for medical use in 2000. Similar to the LRP, small ports and a camera system are used; however, slave robotic instruments inserted through the laparoscopic ports are controlled by a surgeon seated at a master console. Unlike traditional laparoscopic instruments, the robotic instruments have 7 degrees of freedom (similar to the human wrist), which is particularly useful during the sewing required to reconstruct the bladder to the urethra. The computer-based technology filters out intrinsic surgeon hand tremors as well as allowing for scaling of motion when meticulous dissection is required. In addition, the surgeon has a three-dimensional view of the operative field, in contrast to the two-dimensional display in conventional laparoscopy. Finally, the robotic console provides ergonomic advantages for the seated surgeon when compared with surgeons performing conventional laparoscopy with a fixed gaze on the monitor and
arms and shoulders placed in fixed positions for several hours. Though technologic advances have ushered in minimally invasive approaches to surgical removal of the prostate, the surgical goals of cancer control remain the same: removal of the prostate and seminal vesicles with preservation of continence and potency.

**Patient Selection**

Reduction in surgical morbidity begins with patient selection. Appropriate surgical candidates have biopsy-proven prostate cancer, clinically and/or radiologically established localized disease (T1–T2), a life expectancy of at least 10 years, and a limited number of comorbidities. The authors prefer a 12-core prostate needle biopsy that provides information such as the percent involvement of each core, the number of core needle biopsies involved, and the Gleason grade. This information, along with a patient’s baseline sexual function, determines whether unilateral or bilateral nerve sparing should be offered versus a wide resection of the neurovascular bundles. Men with severe coronary artery disease or respiratory difficulties must be evaluated and medically optimized before surgery. Anticoagulants, including aspirin and other nonsteroidal antiinflammatory medications, must be stopped before surgery.

Anesthesia is an important consideration in performing a radical prostatectomy. Most centers administer general anesthesia with open radical prostatectomy; however, a spinal anesthetic may be used, avoiding the need for intubation and general anesthesia. In contrast, general anesthesia must be used for LRP and RALRP to achieve muscle relaxation and control of ventilation in the face of abdominal insufflation with carbon dioxide gas. During laparoscopy, the absorption of carbon dioxide may result in hypercarbia, and the abdominal insufflation results in a reduced tidal volume, factors that need to be carefully considered in patients with severe chronic obstructive pulmonary disease or other lung disease.

Due to high intraoperative blood loss, approximately 20% of men undergoing open radical prostatectomy require blood transfusion perioperatively (18), compared with a transfusion rate approaching 0% using an RALRP approach (19,20). In addition, open radical prostatectomy requires more intravenous fluid volume expansion to compensate for the higher blood loss and also the insensible fluid loss associated with an open incision. Finally, intraoperative hypotension is preferred by many open surgeons to lessen the amount of bleeding encountered during pelvic surgery. Many centers offer the option of autologous blood donation several weeks before an open radical prostatectomy, and these are important factors to consider when selecting between an open and laparoscopic approach in patients with cardiac comorbidities.

**Surgical Technique**

At the authors’ institution, bowel preparation and autologous blood donation are not performed routinely. Perioperative pain control is established with intravenous narcotics
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and ketorolac. Most patients can be transitioned to oral narcotics in the first 24 hours. Expected length of stay is 2 days.

For an open prostatectomy, the patient is placed in a supine position, and the operating table flexed to allow maximal exposure to the lower abdomen below the umbilicus. A lower midline or Pfannenstiel’s incision is made through the fascia and access gained into the extraperitoneal space. When indicated, obturator lymph nodes are sampled for staging purposes. The endopelvic fascia overlying the prostate is opened, and the superficial and deep dorsal veins traveling just superior to the urethra are ligated and divided. Careful attention is paid to the dissection of the prostatic apex from the anterior urethra, as this is where positive surgical margins are often found. If indicated, preservation of the neurovascular bundle is performed by incising the levator fascia and releasing the bundles away from posterior-lateral aspect of the prostate. The urethra is divided, followed by the underlying recto-urethralis muscle so that the prerectal fat is exposed. The prostate is then dissected off of the rectum in a retrograde fashion. Clips are used to divide the lateral pedicles, which contain the primary arterial blood supply to the prostate. At the base of the prostate, the vas deferens are transected, and the seminal vesicles are dissected free from underlying tissue, becoming part of the specimen. The bladder neck is transected from the cephalad aspect of the prostate and the specimen removed. Finally, the continuity is reestablished between the urethra and bladder by performing a vesicourethral anastomosis over a Foley catheter. To perform the anastomosis, the urethra and bladder need to be in proximity; thus, the retractors are first removed. Interrupted sutures are preplaced under direct vision, but the actual anastomotic knots are tied without visualization. A closed suction drain is placed near the urinary anastomosis, and the operative site is closed appropriately.

For LRP and RALRP, five to six incisions, ranging in size from 5 mm to 12 mm, are made over the lower abdomen for insertion of laparoscopic ports. The periumbilical port accommodates the laparoscope, and two of the trocars are manipulated by an assistant surgeon, whose role is that of aiding in retraction, providing suction in the field, and applying surgical clips. For both minimally invasive approaches, the patient is placed in Trendelenburg’s position to displace the bowel cephalad away from the pelvis, thereby improving exposure to the prostate. For RALRP, the freestanding da Vinci robot is then moved in over the patient, the robotic arms interfaced to the ports, and the instruments inserted through the ports into the abdomen. Currently, the da Vinci has a camera arm and three additional arms to accommodate robotic instruments.

The LRP and RALRP surgical dissections are largely the same, and surgery may be performed either via a transperitoneal or extraperitoneal approach. Though both LRP and RALRP were first performed via a transperitoneal approach (8,21), the extraperitoneal approach has the advantage of decreased risk for bowel injury. The transperitoneal approach has the advantage of a larger working space and ease of taking lymph nodes. However, the transperitoneal approach oftentimes requires the patient to be in a steep Trendelenburg’s position to allow the bowel contents to descend out of the working field. Such a position may be poorly tolerated in obese men and those with chronic
obstructive pulmonary disease. Though choice of extra-versus transperitoneal approach for laparoscopic approaches is currently based on surgeon preference and training, as experience in field matures, the ultimate goal will be to tailor the procedure to the specific needs of the patient. The authors limit their description to the transperitoneal approach, which is favored at the majority of high-volume centers.

The original Montsouris approach to LRP involves an antegrade dissection of the prostate, proceeding from the cephalad base to caudal apex of the gland (22). Once the abdomen is entered, access to the extraperitoneal space is gained via an incision posterior to the bladder. This allows access to the seminal vesicles, which are dissected free from surrounding tissue before dividing the vas deferens. Denonvilliers fascia is opened to identify the prerectal fat, and the prostate is dissected off of the underlying rectum. Next, the bladder is separated from its attachments to the anterior abdominal wall, allowing entry into the retropubic space of Retzius. The prostate is visualized, the overlying endopelvic fascia opened, and the puboprostatic ligaments partially divided. The dorsal vein complex is ligated with suturing or an endovascular stapler. Ahlering et al. reported that the enhanced visualization provided by the staple technique during RALRP decreased the rate of positive surgical margins from 27% to 4.7% in organ-confined (pT2) disease (23).

Next, the bladder neck is transected from the prostate. Defining the border between the bladder and prostate may be the most difficult step for converts from open to the minimally invasive approaches because visual anatomic cues must be used to define the border, in lieu of palpation, which is used during an open approach. The levator fascia is then incised to define the contour of the prostate. If indicated, the neurovascular bundles are dissected from the prostatic capsule. The lateral pedicles of the prostate are ligated with clips and divided. Finally, the urethra is divided and the prostate freed completely. In contrast to open surgery, the vesicourethral anastomosis is performed under direct camera vision. A potential advantage of the laparoscopic approaches is the ability to identify anastomotic leaks by filling the bladder with irrigation, and repairing any visualized leaks. Absence of exposure when the bladder is dropped behind the pubic bone precludes this approach with open radical prostatectomy.

**Perioperative Complications**

Hemorrhage is the most common intraoperative complication for radical prostatectomy, and in this respect, the laparoscopic approach has a clear advantage over the open approach. A prospective study of eight high-volume centers demonstrated that median blood loss was 700 mL for open, 350 mL for LRP, and 150 mL for RALRP. In addition, 19% of men receiving open radical prostatectomy required blood transfusions, compared with no transfusion requirements for men who underwent minimally invasive approaches (19). Rectal injury is a rare complication of open radical prostatectomy (0–5.3%) (6,24–26) and typically occurs during the apical dissection of the prostate from
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the underlying rectum. Similarly, the incidence of rectal injury in LRP and RALRP ranges from 0.7% to 1.9% (10,27,28). If recognized intraoperatively, a rectal injury can easily be repaired during open radical prostatectomy (6,24) or laparoscopic approaches (29) with a two-layer closure of the defect with absorbable sutures. However, unrecognized rectal injuries often result in formation of rectal-urethral fistulas and require additional surgeries to repair (28,29).

Late complications associated with open radical prostatectomy include bladder neck contracture, urinary incontinence, and erectile dysfunction. Although these complications are not life-threatening, they may require additional surgical procedures to correct. Bladder neck contracture (anastomotic stricture) has been reported in 0.8%–20% of patients (7,30). It can occur weeks to months postoperatively and typically presents with a weak or splayed urinary stream, dribbling, urgency, and occasionally urinary retention. Risk factors for developing bladder neck contracture relate to surgical technique (31–33)—that is, bladder mucosal eversion and tension-free apposition to the mucosa of the urethra—and are technically the most demanding portion of LRP (34). Reported bladder neck contracture rates for LRP versus RALRP range from 2.2% (28) to 5% (10) versus 0.6% (12) to 0.8% (28). Surgical procedures to correct a bladder neck contracture include mechanical dilation or incision of the contracture, both via an endoscopic approach.

Oncologic Outcomes

Operative outcomes with regard to complete excision of the cancerous tissue are based on a variety of clinical and pathologic factors. The clinical factors include preoperative PSA, Gleason score, and clinical stage (35,36). More recently, the percent of positive prostate biopsies has been included (37). Based on these clinical factors, patients can be stratified into low (cT1–T2a, Gleason 2–6, PSA <10 ng/mL), intermediate (cT2b, Gleason 7, PSA 10–20 ng/mL), and high (cT2c, Gleason 8–10, PSA >20 ng/mL) risk groups with regard to likelihood of recurrence following surgery. Pathologic prognostic indicators include pathologic stage, surgical margin status, and pathologic Gleason score. A number of preoperative and postoperative nomograms have been developed based on the pathologic factors that predict outcomes associated with open radical prostatectomy (35,38,39). Radiologic imaging, including computed tomography and magnetic resonance imaging with coil, is generally reserved for those individuals with advanced disease or high-risk clinical factors (40).

Positive surgical margins are associated with a four-fold annual increase in cancer recurrence when compared with men with negative surgical margins (41). Swindle et al. reported PSA recurrence–free probability at 10 years post–open radical prostatectomy was 58% for patients with a positive surgical margin and 81% for patients with negative surgical margins (42). In this open radical prostatectomy series of 1,389 patients, the overall positive surgical margin rate was 12.9%, including 6.8% for pT2 disease and
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23% for pT3 disease. A prospective evaluation at a high-volume laparoscopic center in patients followed for 4 years found a positive surgical margin rate of 6.9% in pT2a, 18.6% in pT2b, 30% in pT3a, and 34% in pT3b patients undergoing LRP (43). Similarly, LRP and RALRP positive margin rates range from 12–15% for surgeons who served as their own controls when performing both minimally invasive approaches (44,45). Finally, a prospective multicenter study of high-volume centers did not show differences in positive margin rates by surgical approach (19).

A theoretical concern regarding the laparoscopic excision of prostate cancer is the lack of tactile sensation that may assist in obtaining a negative margin in patients with extracapsular (T3) disease. Ahlering et al. reviewed their positive surgical margins for open versus RALRP, finding no statistical difference in positive margin rate regardless of tumor stage (46). Tewari et al. found an overall higher positive surgical margin rate with open radical prostatectomy in a series of men with T2a–T3a disease (23% vs. 9%) (47). Factors that have been shown to increase the risk of positive surgical margins in both open and laparoscopic approaches include high preoperative PSA, high clinical stage, high pathologic stage, and high Gleason score (43).

Biochemical recurrence after surgical excision of the prostate has been variably defined but generally encompasses a PSA value of more than 0.1 or 0.2 mg/dL with two sequential increases. As with positive surgical margins, the biochemical recurrence rates in large series are similar among the three surgical approaches, with reports of 13% 5-year recurrence rates for open radical prostatectomy (48), 10% 3-year recurrence rate for LRP (43), and a 17-month recurrence rate of 6.9% for RALRP (49).

Continence

Three mechanisms are responsible for the maintenance of urinary continence: bladder neck, prostatic smooth muscle, and the striated urinary sphincter. After radical prostatectomy, the urinary sphincter remains with the bladder neck if bladder neck sparing is performed. Most men experience substantial improvement in urinary function in the months after surgery. Though there is wide variation in defining continence, it is generally defined as either completely “dry” or the requirement for one pad per day for stress-related incontinence.

When comparing high-volume institutions, the continence rates after open, LRP, and RALRP are 93%–95% (33,50,51), 87%–97% (52,53), and 92%–96% (49,54), respectively. In two prospective studies comparing open to RALRP, both Tewari and Ahlering et al. found no difference in overall continence rates (46,55). However, Tewari found that return of continence was significantly shorter for RALRP versus open radical prostatectomy, 44 versus 166 days.

Risk factors for increased urinary incontinence include old age (56–58), higher tumor stage (greater operative dissection), and surgeon experience/technique (33). In a study examining preoperative factors that predict return to continence after RALRP, Ahlering et al. found a body mass index of 30 or greater versus less predicted a worse outcome.
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(47% vs. 91.4% pad-free at 6 months) (59). Surgical therapies for resolution of incontinence include injection of bulking agent, suburethral sling procedure (male sling), and artificial urinary sphincter placement.

Erectile Function

Diminished sexual function is a common complication after radical prostatectomy. Factors associated with recovery of sexual function include younger age, lower tumor stage, and nerve-sparing technique (60,61). Erectile dysfunction is defined as inability to initiate and maintain an erection sufficient for penetration during sexual intercourse. For open radical prostatectomy, Catalona et al. demonstrated that bilateral versus unilateral nerve-sparing resulted in better preservation of sexual function (68% vs. 47%) (32). Moreover, Walsh reported significant improvement in overall sexual function when the preservation of the neurovascular bundles was combined with the routine use of phosphodiesterase inhibitors (50,51). Catalona et al. reported that 47% of men in their 70s, 60% in their 60s, 80% in their 50s, and 90% of men in their 40s were potent after open radical prostatectomy (32). Regardless of the surgical approach, initial approaches to boost sexual function should be conservative because recovery often takes more than 2 years postoperatively. In the event that potency does not return, a stepwise approach can be undertaken, including oral phosphodiesterase inhibitor, vacuum erectile device with compression ring, intraurethral/intracavernosal agents, and finally, placement of a penile prosthetic device.

Surgical Volume and Outcomes

Higher open radical prostatectomy surgeon volume, or number of cases performed over time, is associated with lower perioperative complications, shorter lengths of stay, and late urinary complications (62–64). Similarly, high open radical prostatectomy surgeon volume is associated with lower rates of positive surgical margins (65). Furthermore, it is estimated that at least 100 open radical prostatectomies per year should be performed achieve desirable outcomes (66). Although a volume outcome effect has not been described for LRP with or without robotic assistance, steep learning curves have been estimated for LRP, ranging from 60 to 150 cases (10,67), and the learning curve is estimated to be less steep for RALRP, with estimates of 8 to 30 cases required to achieve proficiency (68,69). However, in 2005, Herrell et al. estimated that 150 RALRPs were required to achieve similar outcomes to open radical prostatectomy, and surgeon confidence was established after 250 cases (70). In addition, Atug et al. found that the surgical positive margin rate fell from 21.2% to 11.7% between their 66th and 100th RALRP (71).

A recent survey indicated 37% of urologists performing radical prostatectomy reported doing less than 11 per year, whereas 84% reported doing less than 31 per year.
Consequently, the learning curve may be extended for years (69). Paradoxically, no formal certification process exists, and considerable variation exists among hospitals for attaining LRP privileges; surgeons may perform the procedure after completing brief courses lasting 2 days or less (34,69).

**Cost Analysis**

It is generally understood that new technologies carry with them additional costs. The hope is that incorporation of the new technology will ultimately transmute into an economic benefit. For many laparoscopic surgeries, the associated shortened hospital stay makes up for the higher equipment costs when compared with an open approach. Indeed, for laparoscopic versus open radical prostatectomy, the shorter hospital stay and decreased transfusion rate transmute into a very similar cost ($9,378 vs. $8,030, respectively) (73). At a purchase price of $1.4 million, an annual maintenance contract of $100,000, and a single case equipment charge of $1,700, RALRP can be quite cost-prohibitive. This is due in large part to the monopoly that the robot manufacturer currently holds. When comparing hospital cost estimates based on theoretical operative times and lengths of stay, Lotan et al. found open versus LRP versus RALRP costs to be $5,554 versus $6,041 versus $7,280 (74). This difference was much more striking when comparing actual hospital charges for open versus RALRP, $31,518 versus $39,315 (75). However, it is difficult to measure the economic impact of earlier return to work and activities of daily living associated with LRP with or without robotic assistance. Additionally, the cost and maintenance of the robot will fall with time as other surgical robot device manufactures enter the market.

**Conclusion**

For many disease processes, laparoscopic surgery offers distinct, consistently reproducible advantages over open approaches; laparoscopic surgery shortens hospital stays and may increase the number of outpatient versus inpatient procedures, resulting in lower costs. However, open radical prostatectomy is performed through a relatively small incision that is infrequently associated with significant pain, and lengths of stay are relatively short, averaging 2 days at high-volume referral centers (19). However, many patients intuitively perceive minimally invasive approaches to reduce complications as more advantageous than conventional open operations and prefer them due to smaller incisions requiring less analgesics and shorter hospital stays, even at greater cost (76). Distinguishing hype from reality may be difficult for novel procedures such as LRP (77), and the absence of randomized, control trials to provide cancer control and long-term functional data limits the ability to discern differences in open, laparoscopic, and RALRP outcomes. In addition, marketing of the robotic approach by the manufacturer and health care providers, particularly via the internet, has resulted in growing, wide-
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spread use of RALRP (77). Consequently, it becomes imperative for practicing surgeons to quickly adopt laparoscopic techniques or be forced to withdraw from treating the disease process (78). Given the rapid adoption, increased patient demand, steep learning curves, and low radical prostatectomy volumes for the majority of practicing urologists, men undergoing minimally invasive approaches to radical prostatectomy may face hidden risks. Further studies are needed to determine thresholds for surgeon proficiency in achieving good outcomes for LRP with and without robotic assistance.

References

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Surgical Therapy for Localized Prostate Cancer

Radiation Therapy: 
External Beam Radiotherapy and 
Brachytherapy for Clinically 
Localized Prostate Cancer

Mack Roach III, MD

Radiotherapy has been used to treat prostate cancer for nearly 100 years, with the earliest forms of treatment being in the form of brachytherapy (1,2). The early results were hampered by a number of major limitations. First, many patients had very extensive locoregional and systemic disease, such that the opportunity for cure via treatment directed only at the prostate was limited. Second, the technology required to design radiation treatment fields that accurately encompassed the prostate while accurately shielding normal tissues did not exist. As a result, it was not safe to give the doses (we now know) that are required for a high probability of local control. There were also no online imaging systems to allow corrections to be made for treatment errors due to daily setup and organ movement. This chapter touches on some of the key issues regarding the role of radiation in the treatment of localized prostate cancer.

Advances in the Use of External Beam Radiotherapy

Over the past 10–15 years, there have been a number of major advances in our understanding of the role of external beam radiotherapy (EBRT) in men with clinically localized disease (Table 1). These advances can be divided into four general areas:
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Table 1. Selected studies involving external beam radiotherapy (EBRT) for clinically localized prostate cancer

<table>
<thead>
<tr>
<th>Clinical question</th>
<th>Author(s), year, reference number</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role of androgen-deprivation therapy (ADT)</td>
<td>D’Amico et al. 2004; Denham et al. 2005; Bolla et al. 2002; Hanks et al. 2003; Roach et al. 2003; Pilepich et al. 2005 (4,6–8,47,76)</td>
<td>Short-term ADT (3–8 mos) beneficial in patients with intermediate- to high-risk disease when combined with EBRT. Long-term adjuvant ADT beneficial in patients with high- to very high-risk disease when combined with EBRT.</td>
</tr>
<tr>
<td>Role of intensity-modulated radiation therapy (IMRT) vs. three-dimensional conformal radiation therapy (3D CRT)</td>
<td>Zelefsky et al. 2000; Wang-Chesebro et al. 2006 (77,78)</td>
<td>There appear to be clear-cut advantages to IMRT over 3D CRT when limited to the prostate or when treating pelvic lymph nodes.</td>
</tr>
<tr>
<td>Role of postoperative radiation</td>
<td>Bolla et al. 2005; Thompson et al. 2006 (69,70)</td>
<td>Adjuvant EBRT reduces the risk of clinical progression and need for ADT in men who have undergone radical prostatectomy and have adverse pathologic features.</td>
</tr>
</tbody>
</table>

1. Several phase III trials have demonstrated that survival and/or biochemical (prostate-specific antigen [PSA]) control rates are improved with the addition of either short-term or long-term androgen-deprivation therapy (ADT) to EBRT.
2. Several phase III trials have demonstrated that biochemical control rates can be improved with the use of higher doses of radiation.
3. To deliver high doses of radiation safely, three-dimensional conformal radiation (3D CRT) or intensity-modulated radiotherapy (IMRT) techniques are required.
4. Postoperative radiotherapy given in the adjuvant setting reduces the risk of clinical recurrences of prostate cancer after a radical prostatectomy.

Androgen-Deprivation Therapy and External Beam Radiotherapy

Based on the phase III trials completed to date, there is a growing body of evidence that patients with intermediate-risk prostate cancer have a better survival and/or biochemical
(PSA) failure when short-term ADT is combined with EBRT (3–6). There is also a growing body of evidence that high-risk patients [typically characterized by having one or more of the following: (a) palpation T stage T2c–T3, (b) Gleason 8–10, or (c) PSA >20 ng/mL] benefit from the addition of long-term ADT (7–9). Based on the best available data, there is no evidence that low-risk patients (e.g., Gleason scores ≤6, a PSA ≤10 ng/mL, and being T stage T1–T2) benefit from the addition of hormonal therapy to EBRT. Thus, given the adverse physiologic consequences of ADT, it should be avoided in low-risk patients (10,11).

The challenge to the appropriate use of ADT is precisely identifying which patients should be considered “low,” “intermediate,” and “high” risk. Even more challenging is selecting the appropriate treatment for patients who are “tweeners” (patients falling on the borderline between “low” and “intermediate” risk or between “intermediate” and “high” risk). It is clear that occasionally patients who might be considered “low” risk should be treated as an “intermediate” risk patient. For example, patients with a Gleason score of 6 or less, a PSA of 10 ng/mL or less, and T1–T2 but with more than 50% of their biopsies positive do not behave the way that most low-risk patients do (12). Similarly, patients who would otherwise be characterized as being “intermediate” risk do not behave as such if more than 50% of their biopsies are positive (13). For example, D’Amico et al. studied the impact of the percentage of positive prostate biopsies provides on the end points of prostate cancer–specific survival and overall survival after EBRT in 381 men who underwent EBRT for localized prostate cancer. They concluded that the presence of 50% or lower positive biopsies versus more than 50% positive biopsies stratified intermediate-risk patients into favorable and unfavorable subgroups (100% vs. 57%, \( P = .004 \), 7-year estimates of prostate cancer–specific survival). Although intuitively it would seem logical to “bump” patients up to the next risk group if a large number of their biopsy positive cores are noted, to date there are no prospective data to support this policy. At the other extreme, there may be patients with high-grade disease (Gleason scores of 8–10) who do well without the use of long-term ADT when treated with higher doses of radiation (14).

It is hoped that in the near future, the staging system will be modified such that one day soon physicians will be able to refer to stages rather than risk groups (15). Going forward, it is also hopeful that more rational ways to design trials will be developed so that new agents can be introduced into the management of patients with high-risk disease that will allow physicians to guide therapeutic interventions targeting a survival end point (16).

**Defining Recurrences after External Beam Radiotherapy with and without Androgen-Deprivation Therapy**

The widespread adoption of ADT has not only changed the standard of care, it also resulted in a need to change the definition of biochemical failure following EBRT (17). The American Society for Therapeutic Radiology and Oncology (ASTRO) originally sponsored a consensus conference in 1996 to establish a definition of biochemical failure
after EBRT. The “ASTRO definition” defined PSA failure as occurring after three consecutive PSA rises following a nadir, with the date of failure as the point halfway between the nadir date and the first rise or any rise great enough to provoke initiation of therapy. However, this definition was not linked to clinical progression or survival; it performed poorly in patients undergoing ADT.

Recent studies have shown that when compared with patients treated with radiation alone the ASTRO consensus definition tends to cause an increased number of false-positives for biochemical failure. This phenomenon probably occurs because when men discontinue ADT, the PSA may rise due to the recovery of testosterone even if the patient is cured. The ASTRO definition was also problematic because (a) it violates some basic statistical principles; (b) it has a relatively low sensitivity and specificity; and (c) due to backdating it is extremely sensitive to the duration of follow-up. As a result of these shortcomings, a second consensus conference was sponsored by ASTRO and the Radiation Therapy Oncology Group in Phoenix on Jan. 21, 2005. An expert multidisciplinary panel recommended the following: (a) a rise by 2 ng/mL or more above the nadir PSA be considered the standard definition for biochemical failure after EBRT with or without HT and (b) the date of failure be determined “at call” (not backdated). They also recommended that investigators be allowed to use the ASTRO consensus definition after EBRT alone (no hormonal therapy), with strict adherence to guidelines as to “adequate follow-up.” To avoid the artifacts resulting from short follow-up, the reported date of control should be listed as 2 years short of the median follow-up. Thus, for example, if the median follow-up is 5 years, control rates at 3 years should be cited. Retaining a strict version of the ASTRO definition would allow comparisons with a large existing body of literature. These new criteria taken as a whole have come to be called the “Phoenix definition”; this definition is strongly recommended with regard to all patients undergoing combination therapy with ADT and EBRT (17).

“Conventional” versus “Three-Dimensional” versus Intensity-Modulated Radiation Therapy
Over the last 20 years, the doses of external beam radiation have gradually increased from 60–70 Gy to doses exceeding 77 Gy. The justification for administering higher doses comes from a plethora of retrospective and prospective studies demonstrating that higher doses of radiation resulted in better biochemical (PSA) control rates (see Table 1) (18–20). These studies taken as a group support the notion that doses of 78 Gy or higher are required to control most patients who require definitive EBRT.

Although 3D CRT appeared to reduce the expected rate of complications at conventional or slightly higher doses, at 78 Gy or higher, complications were noted to increase rapidly (21,22). For example, Kuban et al. noted that 5 years after therapy, the grade 2–3 rectal complication rate was twice as high for patients treated to 78 Gy than to 70 Gy, 26% versus 12%. In an attempt to extend the principles learned from 3D CRT (more dose is better and sparing normal tissues is a good thing), various investigators began to apply IMRT to the treatment of prostate cancer. IMRT is a more sophisticated form of 3D CRT. The fact that there is a continuum from the simplest form of complicated 3D
CRT to more complicated forms of IMRT has confused discussions about how 3D CRT and IMRT should be distinguished. To address these issues, the NCI-IMRT Collaborative Working Group (NCI-IMRT-CWG) set out to define an agreed-on set of jargon, standards for quality assurance, and a clinical context through which this technology might be viewed (23). Table 2 summarizes the timeline over which 3D CRT overtook conventional radiotherapy as standard of care and over which IMRT replaced 3D CRT. Table 3 lists and compares the four major forms of IMRT available at the time the NCI-IMRT-CWG consensus paper was written.

The most widely adopted form of IMRT is dynamic multileaf IMRT, a complex delivery approach in which the gantry and leaves move simultaneously and inverse planning is incor-

Table 2. Summary of American College of Radiology appropriateness treatment planning guidelines for prostate cancer (modified)

<table>
<thead>
<tr>
<th>Treatment planning</th>
<th>Appropriateness rating</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment planning 1996 (79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Computed tomography (CT)-based 2D treatment plan</td>
<td>6</td>
<td>Standard in 1996</td>
</tr>
<tr>
<td>2.5D treatment plan</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>3D treatment plan</td>
<td>6</td>
<td>Only a handful of institutions had this in 1996</td>
</tr>
<tr>
<td>Non-CT–based computerized treatment plan</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Hand calculation</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Treatment planning 2000 (31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3D conformal radiation therapy (CRT)</td>
<td>8</td>
<td>Standard in 2000</td>
</tr>
<tr>
<td>2.5D treatment plan</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Intensity-modulated radiation therapy (IMRT)</td>
<td>6</td>
<td>Only a handful of institutions had this in 2000</td>
</tr>
<tr>
<td>Nonconformal treatment approaches</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Treatment planning 2006b (80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMRT</td>
<td>8</td>
<td>Standard in 2007</td>
</tr>
<tr>
<td>3D treatment plan</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>2D CT–based plan</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Nonconformal treatment approaches</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*a1 = least appropriate; 9 = most appropriate.
bModified to exclude discussion of proton beam radiotherapy.
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Table 3. Conformal and intensity-modulated therapy techniques

<table>
<thead>
<tr>
<th>Type of conformal therapy</th>
<th>Minimum dose calculation requirements</th>
<th>Minimum imaging requirements</th>
<th>Treatment delivery requirements</th>
<th>Degree of conformality $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional three-dimensional conformal radiation</td>
<td>3D with DVHs</td>
<td>Full set of CT or MRI images</td>
<td>Cerrobend blocks or MLC</td>
<td>2H</td>
</tr>
<tr>
<td>Forward planned SMLC IMRT</td>
<td>3D with DVHs</td>
<td>Full set of CT or MRI images</td>
<td>Computer-controlled MLC</td>
<td>3H</td>
</tr>
<tr>
<td>Inverse planned SMLC IMRT</td>
<td>3D with DVHs</td>
<td>Full set of CT or MRI images</td>
<td>Computer-controlled MLC</td>
<td>2–4H</td>
</tr>
<tr>
<td>DMLC IMRT</td>
<td>3D with DVHs</td>
<td>Full set of CT or MRI images</td>
<td>DMLC</td>
<td>2–4H</td>
</tr>
<tr>
<td>Tomotherapy IMRT</td>
<td>3D with DVHs</td>
<td>Full set of CT or MRI images</td>
<td>Tomotherapy device or a Linac with binary MLC</td>
<td>2–4H</td>
</tr>
</tbody>
</table>

CT = computed tomography; DVH = dose-volume histogram; DMLC = dynamic multileaf collimator; IMRT = intensity-modulated radiation therapy; MLC = multileaf collimator; MRI = magnetic resonance imaging; SMLC = segmental multileaf collimator.

$^a$ Conformality is subjectively rated on a scale of 1–5H (with the higher number indicating a higher degree of conformality). This is to point out to the readers that inverse-planned IMRT can either be better or worse than forward-planned techniques depending on the objective function and/or the input parameters used in the inverse-planning process and on technical details related to the various delivery techniques. Note that no attempt was made to distinguish how well the three inverse-planned IMRT methods would compare against each other.


Tomotherapy is a second type of inverse planning–based IMRT and involves the use of a rotating multisegmented delivery system. Tomotherapy involves radiation delivered by using either sequential or continuous arcs much like a computed tomographic (CT) scanner does. Sequential tomotherapy was the first common IMRT system and delivered radiation using the so-called MiMic device (27,28). More recently, a spiral tomotherapy–based approach has become available (29).

It is a common misconception that IMRT requires inverse treatment planning to generate the best plans. However, inverse planning algorithms have not been proved to be
able to select the optimal number of beams or beam angles, so occasionally the inverse plan may not be as good as one generated using forward planning if the beam arrangement favors the latter. Regardless of whether IMRT is performed using forward or inverse planning, elegant dose distributions can be generated such that sites of dominant intraprostatic disease or a so-called dominant intraprostatic lesion (or “DIL”) can be treated to 90 Gy or more (28). There are advantages and disadvantages to each form of IMRT, but all can deliver very complex dose distributions (23). The major advantages associated with the forward-planning approach are that planning is more intuitive and manual editing of blocks can be carried out more readily.

**Challenges of Day-to-Day Setup Variation and Organ Movement and Intensity-Modulated Radiotherapy**

The advantages of IMRT over 3D CRT are critically dependent on the accuracy of reproducing the planned dose distribution in the patient. If the dose distribution is delivered 5 mm posterior to the intended location, it can have a major impact on the dose delivered to surrounding normal tissues (28,30). It is now clear that the use of weekly port films is probably inadequate for the accurate delivery of highly conformal dose distributions because organ movement and day-to-day setup variations can result in significant treatment errors (31–35). Intrarectal balloon, ultrasound localization, and the use of an electronic portal imaging device in conjunction with implanted markers are common options for allowing online corrections to be made during IMRT (36–38). At the University of California, San Francisco, physicians have chosen to adopt the electronic portal imaging device–based approach because it is reproducible, fast, convenient, and accurate. Intrafraction movement and seed migration appear to be extremely uncommon (39,40).

**Hypofractionated External Beam Radiotherapy**

Over the last several years, there has been an increase in the enthusiasm for hypofractionated EBRT (the use of larger fraction sizes and fewer treatments) supported by theoretical radiobiologic advantages resulting from the notion that the alpha-beta value for prostate cancer may be as low as 1.5 Gy (41–45). These estimates were generated based on a review of papers published from 1995 to 2000 and estimated PSA control rates after EBRT, iodine 125, or palladium 103 permanent prostate implants. Although a number of investigators have concluded that a hypofractionated regimen appears to be most logical, not all experts agree that this is a clinically relevant observation (43–46). Arguments against the use of hypofractionation include the fact that the control rates used for the calculation of alpha and beta significantly overestimated control rates due to the inadequacy of follow-up because the ASTRO consensus definition was used (17).
Another argument against hypofractionated regimens is the fact that intermediate- and high-risk patients appear to benefit from pelvic radiotherapy and it is unlikely that a hypofractionated regimen would be well tolerated by the gut (47).

**Contemporary Brachytherapy**

The popularity of prostate brachytherapy, in its two major forms, has waxed and waned for nearly 100 years. Prostate brachytherapy (placement of radioactive material directly into the prostate) was first reported by Barringer in 1917, but it did not become more widespread until the 1970s (2,48,49). In those early days, it was applied as a transurethral or it was administered as an open retropubic approach. Over the last 10–15 years, there has been a tremendous surge in transrectal ultrasound–guided prostate brachytherapy, first described by Holm in 1983 (50,51). Brachytherapy offers potential biologic advantages over radiation administered via the external approach. Compared with EBRT, brachytherapy is potentially more localized and provides higher total biologic doses and higher dose rates.

According to Kuban et al., the optimal definition of biochemical failure after brachytherapy may be similar to the definition recommended after EBRT (52). They compared PSA failure definitions in 2,693 patients with stage T1–T2 prostate cancer treated by permanent prostate seed implants and concluded that the definition nadir + 2 ng/mL definition performed the best, similar to patients treated by EBRT, and recommended the same PSA failure definition for both modalities. They also concluded that for patients treated by brachytherapy who had follow-up of at least 6 years, defining failure as exceeding an absolute PSA level in the 0.5 ng/mL was also reasonable.

**Patient Selection for Brachytherapy**

Suitability for brachytherapy is based on the cancer status and the risk of morbidity. Patients with clinical stage T1–T2 are usually considered to be good candidates for brachytherapy (either permanent or temporary), as long as they do not have a contraindication. Patients with clinical stage T3 disease are usually considered better candidates for high-dose rate (HDR) than for permanent implants (53). There is a small but real risk of severe long-term complications with brachytherapy, including rectal ulceration, irritative urinary symptoms, retention, strictures, and incontinence. Patients with large prostates (e.g., >50 mL) appear to be at risk for inadequate anterior coverage of their gland due to pubic arch interference and are at higher risk of acute postimplant retention, but it is usually short-lived (54). Preimplant urinary retentive symptoms (high American Urological Association score) are also usually considered a relative contraindication to brachytherapy. Urodynamic studies, postvoid residual urine volume, maximum flow rate, and cystoscopy are not accurate predictors of postimplant retention, however. Although early reports suggested
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that approximately 50% of patients with transurethral resection of the prostate developed postimplant incontinence, more recent series suggest the presence of a transurethral resection of the prostate should probably be considered a relative but not absolute contraindication (55–57). Even a patient who has had prior radiation may be a candidate for brachytherapy administered as a “salvage” approach, with encouraging preliminary results (58–61).

Although temporary implants (HDR) are performed less frequently, there is a body of evidence that suggests that this approach is also an effective treatment option for men with early localized prostate cancer. Each catheter is sequentially loaded with a radioactive source (iridium Ir 192), and treatment-planning software is used to ensure the optimal duration a radioactive source is left in a given position. By controlling the amount of time the source spends at points along the catheter (dwell time), a variety of dose distributions can be generated. Temporary prostate implants are usually administered using multiple fractionated treatments delivered over one to three outpatient or inpatient visits. The radiation exposure to personnel is minimized because the radioactive sources are loaded outside of the treatment room. The ability to load the sources after placement of the catheters and to use computer control to place the radioactive source makes HDR brachytherapy extremely flexible. Fractionation schemes have been as aggressive as 9.5 Gy × 2 to 5.0 Gy × 3 combined with EBRT from 45 to 50 Gy (62). Although most of the published reported results of HDR brachytherapy involves its application in combination with EBRT, at least one report compared (and favored) the results of HDR monotherapy versus permanent implants (63). It is unclear whether the technical aspects of how the permanent implants were done could explain the investigators’ observations.

Evidence of a Biologic Advantage to Brachytherapy

There are three major lines of support for favoring brachytherapy over EBRT. First, it appears that patients who would otherwise be expected to do quite poorly if treated with EBRT (or surgery for that matter) do quite well with brachytherapy in either form (53,64). Second, it appears that the response of the prostate to brachytherapy as measured by magnetic resonance spectroscopy is more dramatic than after EBRT (65,66). In addition, the PSA response appears to be more dramatic (lower nadir), and failure rate may be lower after brachytherapy than after EBRT (67,68).

Adjuvant and Salvage Radiotherapy after Radical Prostatectomy

The role of adjuvant EBRT after a radical prostatectomy has become more evidence-based with the recent completion of two major phase III trials (69,70). The European Organization for Research and Treatment of Cancer conducted a phase III randomized controlled trial comparing immediate EBRT after prostatectomy for patients with positive margins or
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pT3 disease (69). Just over 1,000 patients were randomized to immediate postoperative EBRT (60 Gy) or observation. With a median follow-up of 5 years, the biochemical progression-free survival was 74% for immediate compared with 53% for the observed group ($P < .0001$), and the clinical progression-free survival was also improved ($P = .0009$). The authors concluded that immediate EBRT after prostatectomy improved progression-free survival in patients with positive margins or pT3 prostate cancer.

The Southwest Oncology Group conducted a phase III trial including 425 men with pathologically advanced prostate cancer who had undergone radical prostatectomy and randomly assigned them to receive 60–64 Gy of EBRT to the prostatic fossa or “usual care plus observation” (70). The primary end points included metastasis-free survival or death due to any cause; secondary end points included PSA relapse, recurrence-free survival, overall survival, freedom from ADT, and postoperative complications. With a median follow-up of 10.6, years the metastasis-free survival favored immediate adjuvant EBRT, 36% compared with 43% in the observation group (hazard ratio, 0.75; $P = .06$). The freedom from PSA relapse was 10.3 years for immediate EBRT, compared with only 3.1 years for observation (hazard ratio, 0.43; $P < .001$). The median recurrence-free survival was 13.8 years for EBRT versus 9.9 years for the observation group (hazard ratio, 0.62; $P = .001$). The authors concluded adjuvant radiotherapy resulted in significantly reduced risk of PSA relapse and disease recurrence in men who had undergone radical prostatectomy for pathologically advanced prostate cancer. Although the improvements in metastasis-free survival and overall survival did reach statistical significance, it is likely that with a larger study these end points would probably have been reached as well.

The role of “salvage” radiotherapy after a radical prostatectomy has not yet been subjected to a phase III trial, but retrospective data strongly support its use (71). Better targeting and the inclusion of ADT in this setting may result in further improvements over the results compared with EBRT alone (33,72–74). Investigators from the University of California, San Francisco, studied interfraction prostate bed motion, setup error, and total positioning error in 10 consecutive patients undergoing postprostatectomy radiotherapy using daily electronic portal imaging of gold seed fiducials implanted into the prostate bed (75). They showed that total positioning errors of more than 5 mm occurred in 14.1%, 38.7%, and 28.2% of all fractions in the lateral, superior-to-inferior, and anterior-to-posterior directions, respectively, and there was no significant migration of the gold marker seeds. This study validates the use of daily image-guided target localization and alignment using electronic portal imaging of implanted gold seed fiducials in the postoperative setting as a method to correct for interfraction target motion and to improve precision in the delivery of EBRT.

Extrapolating from the findings from trials combining ADT with EBRT, it is not surprising that preliminary findings of neoadjuvant ADT before EBRT in the postoperative setting are promising (72–81). Only a randomized trial can definitively answer this question, and such a trial is currently in the planning stages within the Radiation Therapy Oncology Group.
Conclusion

After 100 years of progress, a point has now been reached where it is clear that radiotherapy is one of the most viable options for men with clinically localized prostate cancer.

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Androgen-Deprivation Therapies in Combination with Radiation or Surgery

Oliver Sartor, MD

Androgen-deprivation therapy (ADT) for prostate cancer has been a valued addition to the clinician’s armamentarium since the Nobel Prize–winning work of Huggins was first published in 1941 (1). Primarily used initially in patients with symptomatic metastases, data supporting the use of ADT have evolved to the point that it is now considered a standard of care for selected patients with nonmetastatic disease. This brief synopsis covers those areas where androgen deprivation has now become an integral part of the therapeutic approach in combination with other therapeutic modalities.

One of the key issues with regard to prostate cancer staging is that the traditional anatomic staging system has limited prognostic significance. To better understand and apply ADTs in appropriate settings, it is also necessary to understand risk classification in some detail, as this concept is critical in the appropriate selection of patients expected to benefit from these approaches.

Because ADT comes in a variety of distinct forms and formulations, a portion of this chapter is devoted to the various methods of androgen deprivation and their mechanisms of action.

When examining studies related to prostate cancer, it is also critical to evaluate what end points are reported, as these are highly variable from study to study and have frequently changed over time. Some treatments have been linked to pathologic end points such as extracapsular invasion or extension or margin positivity. These end points may or may not correlate with subsequent clinical events. Others factors are linked to biochemical progression post-treatment and/or the development of radiographically detected metastatic disease, whereas others are linked explicitly to either overall or cancer-specific survival. Understanding end points in clinical trials is critical to understanding and interpreting the literature regarding prostate cancer and for understanding ADT.
in particular. As is well known, androgen deprivation decreases PSA production in a manner that may or may not be related to clinically relevant end points.

This review emphasizes appropriately powered randomized trials with end points and follow-up adequate to make conclusions for the practicing clinician. Several distinct patient groups are discussed herein. Emphasis is placed on the patient initially treated with radical prostatectomy and the patient initially treated with radiation therapy.

Risk Classification

Nonmetastatic prostate cancer is an extremely heterogeneous disease, with some patients at high risk for progression and death and others unlikely to have any clinical consequences from their disease despite long-term follow-up. Understanding this heterogeneity is of considerable interest to clinicians, as treatment decisions are inextricably linked to understanding and predicting prognosis in individual patients. Because prostate cancer is one of the leading causes of cancer death in men, it is critical to provide aggressive treatment for men at risk of death. However, because of the high prevalence of prostate cancer in older men, it is also important to carefully risk-stratify patients so that treatments are not administered to men whose quality and quantity of life are not threatened by their prostate cancer.

The anatomic tumor, nodal, metastatic (TNM) staging system has been in use and under refinement for over 50 years since the International Union against Cancer introduced the concept; however, traditional anatomic tumor staging is only one of several variables now known to determine prognosis in prostate cancer. Though still relevant today, particularly in patients with clear evidence of locally advanced or metastatic disease, increasingly, prostate cancer patients are being diagnosed and treated with cancers that are not palpable. Additional tools are clearly necessary to provide important prognostic information under these circumstances.

From a historical perspective, the contributions of Gleason (2) are unquestioned with regard to prognosis. Microscopic evaluation of prostate tissue and careful histologic grading, via Gleason scoring or one of several alternatives, are among the most important factors in understanding clinically relevant outcomes in this heterogeneous disease. Every method of risk stratification for patients with localized prostate cancer incorporates Gleason score or a proxy as one of the most important variables in determining prognosis.

In addition to Gleason score, a number of pathologic variables available on prostate needle biopsies have been studied as determinants of prognosis. These markers include DNA ploidy, microvessel density, perineural invasion, and neuroendocrine differentiation. To date, these additional pathologic variables have been of relatively minor importance in the typical patient. Neuroendocrine differentiation, particularly a small cell variant, is an exception. This distinct form of prostate cancer is better treated as a highly aggressive disease, and treatment approaches should mirror those taken in small cell carcinomas diagnosed in other anatomic regions. Perineural invasion on prostate needle biopsies has been associated with increased biochemical relapse rates after radiation therapy in several single institutional trials (3,4), and some clinicians take this variable into consideration when considering treatment options.
Androgen-Deprivation Therapies in Combination with Radiation or Surgery

Shortly after the advent of prostate-specific antigen (PSA) testing, a number of investigators linked measurement of PSA to both anatomic staging and prognosis after various treatments, and this biochemical marker continues to provide important information in certain settings. PSA has been repeatedly confirmed as an independent prognostic marker predictive of various clinical outcomes, a fact recognized relatively early in the course of investigation (5) and confirmed on numerous subsequent occasions. PSA elevations are known to have prognostic significance for survival in patients treated with radiation (6).

Combining clinical stage, PSA, and Gleason score to determine pathologic finding post–radical prostatectomy in a systematic and quantitative fashion was initially performed by Partin and colleagues (7,8). This method of risk stratification was restricted to patients undergoing radical prostatectomy, and the end points were restricted to pathologic findings. Regardless, the impact of this approach has been substantial, as it helped to clearly quantify prognostic factors beyond the conventional anatomic TNM staging system. Partin’s classification methodologies have now been verified in multiple settings both in the United States and Europe (9,10); however, performance in the community setting does not appear as robust as that in academic/referral settings (11).

D’Amico and colleagues have incorporated PSA, Gleason sum, and clinical stage into a simple (low, intermediate, and high) assessment of risk that has been used initially to stratify patients both for biochemical recurrence (12) and prostate cancer–specific mortality (13). The D’Amico methods for classifying risk are operative in both the postradiation as well as postsurgical settings.

Roach and colleagues (14) have also published a risk-classification system based on PSA, Gleason sum, and clinical stage using data derived from mature Radiation Therapy Oncology Group (RTOG) trials. These studies have demonstrated that each of these factors contributes to prediction of disease-specific survival.

Kattan and colleagues have successfully incorporated PSA, Gleason score, and clinical stage into nomograms that quantitatively predict not only pathologic staging but also PSA recurrence-free survival in patients after various types of prostate cancer treatments, including surgery, external beam radiation, and brachytherapy (15). These nomograms have been evaluated in both academic and community settings and clearly provide important and broadly applicable pretherapy prognostic information. One caveat has been raised in these validation studies; these nomograms may overestimate the likelihood of relapse-free survival in the community setting, especially among patients with relatively low-risk tumors (16). Overall, however, the model is robust and provides important information, when managing prostate cancer, regarding prognosis and treatment options. More work is needed to create nomograms that predict disease-specific survival as opposed to PSA relapse. Such models are currently under development.

Types of Androgen-Deprivation Therapies

A number of potential options exist for a patient undergoing ADT today. These potential options can include surgical orchiectomy, a variety of luteinizing hormone–releasing hor-
mone (LHRH) agonist formulations, an LHRH antagonist, several antiandrogens, estrogens, and 5α-reductase inhibitors.

Surgical orchiectomy is the oldest and most established form of ADT. Though the surgical procedure is in itself relatively minor and the overall costs comparatively low, studies have demonstrated that surgical orchiectomy is less likely to be chosen by patients when other options are available (17).

LHRH analogues are also the product of Nobel Prize–winning work. Andrew Schally shared the Nobel Prize for his discoveries concerning hypothalamic control of pituitary function, and his laboratory was the first to isolate LHRH (18). Shortly thereafter, the paradoxical effect of continuous LHRH on testosterone was discovered. Initial injections of LHRH caused increases in luteinizing hormone and testosterone, but continued administration was associated with LH suppression and testosterone declines. From this fundamental observation, the concept of treating prostate cancer with this approach was readily apparent. Of note, LHRH itself had a very short half-life and was poorly suited as a drug; thus, the development of LHRH agonists (19) was a critical step in this therapeutic approach.

Today, a number of U.S. Food and Drug Administration (FDA)-approved LHRH agonists are available to clinicians, and these compounds have been formulated in distinct ways to allow sustained release of the agonists in a variety of durations (Table 1). Each of these agents downregulates LH and testosterone secretion and leads to castrate levels of serum testosterone (<50 ng/dL). In terms of proven distinctions between these agents, none exists. Each has achieved an FDA-approved end point of testosterone suppression, and each is considered a viable option for the treatment of prostate cancer.

Estrogens are primarily of historic interest. These agents are also highly effective in suppressing testosterone and have been used in clinical studies that date back to the early 1940s. Several problems became apparent in the randomized Veterans Administration studies performed in the 1960s (20). First and foremost, men receiving higher doses of estrogens (5 mg oral diethylstilbestrol [DES]) died from cardiovascular disease at a more frequent rate. In addition, serious thromboembolic disease such as deep vein thrombosis

### Table 1. Luteinizing hormone–releasing hormone agonists approved by the U.S. Food and Drug Administration for use in the United States

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Formulations</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leuprolide acetate</td>
<td>Lupron</td>
<td>1, 3, 4 mos</td>
<td>Injection</td>
</tr>
<tr>
<td>Goserelin acetate</td>
<td>Zoladex</td>
<td>1, 3 mos</td>
<td>Injection</td>
</tr>
<tr>
<td>Leuprolide acetate</td>
<td>Eligard</td>
<td>1, 3, 4, 6 mos</td>
<td>Injection</td>
</tr>
<tr>
<td>Histrelin</td>
<td>Vantas</td>
<td>1 yr</td>
<td>Implant</td>
</tr>
<tr>
<td>Leuprolide acetate</td>
<td>Viadur</td>
<td>1 yr</td>
<td>Implant</td>
</tr>
<tr>
<td>Triptorelin pamoate</td>
<td>Trelstar</td>
<td>1, 3 mos</td>
<td>Injection</td>
</tr>
</tbody>
</table>
and pulmonary emboli is clearly increased in frequency in comparison with no-treatment controls. These data resulted in a significant decline in the use of oral estrogens, and subsequent randomized trials comparing oral DES with LHRH agonists demonstrated a better safety profile for the LHRH agonists compared with 1 mg oral DES (21). More recent data demonstrate that transdermal estrogen approaches are less thrombogenic than oral estrogens. Efficacy studies are relatively limited, and consequently comparative effects of transdermal estrogens on clinically relevant outcomes have yet to be ascertained.

One LHRH antagonist (abarelix) has been approved by the FDA, but extreme limitations on the label were imposed as a consequence of allergic reactions. This compound was approved for use by the FDA only in those patients in whom LHRH agonist therapy was not appropriate and who refuse surgical castration, and who had one or more of the following: (a) risk of neurologic compromise due to metastases, (b) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (c) severe bone pain from skeletal metastases persisting with narcotic analgesia. Given these labeling limitations and poor sales, the company has ceased distributing the drug.

Three nonsteroidal antiandrogens (flutamide, bicalutamide, and nilutamide) have been approved for use in the United States. These agents serve as competitive antagonists by blocking ligand interaction at the level of the androgen receptor. Though these agents have been used in a number of studies in combination with LHRH agonists, no randomized trials have demonstrated that this class of agents adds to the effects observed by LHRH agonists alone when these agents are given in combination with radiation or surgery. Adjuvant studies with bicalutamide monotherapy after external beam radiation have been published, and discussion of these results ensues below.

Two 5α-reductase inhibitors (finasteride and dutasteride) are approved for use in the United States in patients with benign prostatic hyperplasia. These agents block the conversion of testosterone to dihydrotestosterone via inhibition of 5α-reductases. This enzyme exists in two forms: Finasteride selectively inhibits the type II enzyme, whereas dutasteride inhibits both the type I and II enzymatic isoforms. Neither is approved for use in prostate cancer patients, and there are no randomized trials in patients with prostate cancer that indicate their usefulness either with or without other agents. Monotherapy studies in prostate cancer have demonstrated minor decreases in PSA (22), but clinical benefits have not been demonstrated in patients with cancer.

### Risks of Androgen-Deprivation Therapy

It is important to recognize that FDA-approved LHRH agonists may have adverse effects capable of affecting survival. It is well known that hot flashes, declines in libido, and osteoporosis can result from these agents, but more recent data (23) suggest that LHRH agonists can increase risk of diabetes, coronary heart disease, myocardial infarction, and sudden cardiac death. Consequently, it is necessary to balance both risks and benefits in making clinical decisions.
One factor often neglected is that duration of administered drugs designed to induce androgen deprivation (LHRH agonists) and actual duration of effects on testosterone may or may not be identical. Several factors may influence return of testosterone to pretreatment baseline, including duration of ADT, age, and baseline testosterone. A fixed duration of an LHRH agonist may be expected to have more profound effects in older patients and in those with lower baseline serum testosterone than in those who are younger or in those with higher baseline serum testosterone levels (24,25). Thus, it is readily conceivable that shorter durations of administered LHRH agonists in older patients may be equivalent to longer durations in younger patients.

Clinicians treating prostate cancer need to be aware of both the risks and benefits of ADT. More research is needed in this area, particularly in understanding the consequences of ADT in those patients who are older and/or those with cardiovascular disease. The toxicities of ADT may be more consequential in older patients and/or those with underlying cardiovascular disease, making shorter durations of ADT especially desirable in these populations. Furthermore, these new data on the risks of ADT make it especially important that ADT use be regarded in the context of an overall risk-to-benefit ratio, as cardiovascular disease remains one of the leading causes of death in men with prostate cancer.

### Androgen-Deprivation Therapy in Combination with Radiation

A multiplicity of large randomized studies support the use of ADT in combination with radiation (Table 2). A number of these trials are sufficiently mature to be of substantial interest. The cooperative groups have been active in these studies, including the European Organization for Research and Treatment of Cancer (EORTC), the RTOG, and the Trans-Tasman Radiation Oncology Group (TROG). It is instructive to examine the design and outcomes from these well-controlled trials, as they have been particularly informative.

The first trial to demonstrate an overall survival benefit of ADT and radiation was EORTC 22863 (26), using radiation alone versus 3 years of ADT in combination with radiation therapy in patients with T1–T2 lesions and high-grade disease (World Health Organization [WHO] grade 3) or T3–T4 N0–N1 disease of any grade. A total of 415 patients were randomized between 1987 and 1995. ADT was administered for 3 years and consisted of 1 month of cyproterone acetate (starting 1 week before radiation) and 3 years of goserelin beginning on the first day of radiation. In the control group, hormonal therapy was allowed at the time of progression. Radiation was given to a total of 70 Gy, beginning with a 50-Gy whole-pelvic field and finishing with a 20-Gy field designed to include both the prostate and seminal vesicles.

Of the patients enrolled in the trial, 82% in each arm had T3 disease and only 8%–9% had T1–T2 and WHO grade 3 disease. Baseline PSAs were available in nearly 90%
<table>
<thead>
<tr>
<th>Trial</th>
<th>Clinical stages (Tx)</th>
<th>ADT duration</th>
<th>Radiation (pelvic +/−) and dose</th>
<th>Median follow-up</th>
<th>Overall survival</th>
<th>Prostate cancer–specific survival</th>
<th>Metastasis-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 8531</td>
<td>T3 primarily T3</td>
<td>0 vs. forever</td>
<td>Pelvic + 65–70 Gy</td>
<td>91.2 mos</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Tx N1 28%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>RTOG 8610</td>
<td>T3–T4 70% Tx N1 8%</td>
<td>0 vs. 4 mos</td>
<td>Pelvic + 65–70 Gy</td>
<td>80.4 mos</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>RTOG 9202</td>
<td>T2 45% T3 51%</td>
<td>4 vs. 28 mos</td>
<td>Pelvic + 65–70 Gy</td>
<td>69.6 mos</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Trans-Tasman Radiation Oncology Group 9601</td>
<td>T2b/c 60% T3/4 40%</td>
<td>0, 3, 6 mos</td>
<td>Pelvic – 66 Gy</td>
<td>71 mos</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>European Organization for Research and Treatment of Cancer 22863</td>
<td>T3 82% T4 9%</td>
<td>0 vs. 3 yrs</td>
<td>Pelvic + 70 Gy</td>
<td>66 mos</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dana-Farber/Harvard Cancer Center</td>
<td>T1 48% T2 52%</td>
<td>0 vs. 6 mos</td>
<td>Pelvic – 70.35 Gy</td>
<td>54 mos</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

RTOG = Radiation Therapy Oncology Group.
Androgen-Deprivation Therapies in Combination with Radiation or Surgery

of the patients, and slightly over 50% of the patients in each arm had PSAs greater than 20 ng/mL. Median follow-up of all patients at the last report was 66 months (27). Five-year survival was 78% in the combined treatment arm and 62% in the radiotherapy alone arm (Figure 1). For disease-specific survival, the 5-year rates were 94% and 79% for the combined and single-modality arms, respectively. These statistically significant and clinically relevant differences helped to establish combined modality treatment as the standard of care for patients with locally advanced prostate cancer but left many additional questions unanswered. What was the optimal duration of ADT? What other subsets of prostate cancer patients might have clinical benefit?

Radiation Therapy Oncology Group 8610

RTOG studies of ADT and radiation date back to the mid 1980s, when RTOG 8531 and RTOG 8610 were designed. For RTOG 8610, patients with bulky T2–T4 tumors...
were randomized to receive radiation alone or radiation with 4 months of ADT consisting of flutamide (250 mg by mouth tid) and goserelin (28). To be eligible for RTOG 8610, the cross-sectional area of the tumor had to be estimated at 25 cm$^2$ or more by digital rectal examination. Nodal disease was allowed, provided it was detected only below the level of the common iliac vessels. The hormonal treatments were started 2 months before radiation and continued during the (approximately) 2 months of radiation therapy. Radiation consisted of a regional lymph node field of 44–50 Gy, followed by a total prostatic dose of 65–70 Gy given 4–5 times per week, with 1.8–2.0 Gy per fraction. The radiation field went as high as L5–S1 in those without pelvic nodes but was extended to the L2–3 interspace for those with positive nodes.

After a median follow-up of 6.7 years for all patients (and 8.6 years for alive patients), this short-term androgen ablation successfully impacted a variety of potential end points but not overall survival in the intent-to-treat analysis. There were, however, improvements in locoregional control, metastasis-free survival, and disease-specific survival. Subset analysis indicated that this short duration of ADT had no effect on either locoregional control or mortality in patients with Gleason 7–10 disease but that within the subset of patients with Gleason disease of 6 or less, overall survival was improved to 70% versus 52% (Figure 2). Clinicians agree that 4 months of ADT plus radiation is not adequate for control of bulky T2–T4 lesions that contain high-grade disease.

![Figure 2](image-url)

**Figure 2.** Overall survival in Radiation Therapy Oncology Group 8610 patients with Gleason 2–6 disease treated with radiation and 4 months of androgen-deprivation therapy versus radiation and no androgen-deprivation therapy. RT = radiation therapy.
Radiation Therapy Oncology Group 8531

RTOG 8531 took a different approach from many other trials using ADT in combination with radiation. In this trial, which accrued between 1987 and 1992, patients with non-bulky T3 disease or clinical stage T1–T2 with lymph node involvement were randomized to radiation alone or radiation plus ADT, with the ADT administered indefinitely beginning in the last week of radiation (29). Lymph node involvement could be documented by computed tomography, lymphadenectomy, or lymphangiogram. Patients postprostatectomy were also allowed in the trial if seminal vesicles or extracapsular extension were histologically documented. ADT (goserelin monotherapy) was given adjuvantly rather than neoadjuvantly/concomitantly. A total of 997 patients were entered onto the trial, and at the last report, median follow-up was 7.6 years for all patients and 11 years for alive patients. Radiation was given up to 50 Gy to the nodal regions, with the exact nodal region radiated being dependent on where involved lymph nodes were detected. The prostate region received an additional 20–25 Gy up to a total dose of 65–70 Gy in men with an intact prostate. For men postprostatectomy, the nodal field could be excluded if the lymphadenectomy had no positive nodes and the total radiation to the prostate fossa was limited to 60–65 Gy.

Approximately 15% of the patients in 8531 were postprostatectomy, and slightly more than 70% had node-negative disease. Results from RTOG 8531 were positive for multiple end points. Both overall survival and prostate cancer–specific survival were improved in the adjuvant arm. At 10 years, overall survival was improved from 39% to 49%. Prostate cancer–specific survival was improved from 16% to 22%. Local failure rates and distant failure rates were also statistically significantly better in the adjuvant treated patients. These data established that adjuvant ADT could prolong survival in patients with T3 or node-positive disease. RTOG 8531 is analogous to the Messing trial postprostatectomy (see “Androgen-Deprivation Therapy in the Radical Prostatectomy Patient”) in that therapy was administered adjuvantly after a local definitive therapy. Interestingly, additional analyses on this trial regarding duration of hormonal therapy are pending, as the “indefinite” use of early adjuvant ADT was, in fact, variable in length.

Radiation Therapy Oncology Group 9202

RTOG 9202 included patients with T2c–T4 disease, but all patients had to be clinically and radiographically negative for nodal disease. Given that RTOG 8610 had demonstrated a survival advantage in similarly staged patients with Gleason disease of 6 or less but not in patients with higher Gleason score, the trial was designed to combine radiation and ADT for 4 months and compare that treatment with two additional years (28 months total) of hormonal therapy in patients with T2c or locally advanced disease. For the radiation, up to 50 Gy of whole-pelvis radiation was combined with a total prostate dose of 65–70 Gy for T2c lesions or 67.5–70 Gy for T3–T4 lesions.
For ADT, the first 4 months consisted of goserelin and flutamide. ADT treatment for the patients randomized to receive two additional years included goserelin alone. ADT was started 2 months before radiation, continued concomitantly with radiation, and then either discontinued or continued for two additional years depending on the arm of the trial. A total of 1,554 patients were enrolled in the study, and approximately 55% had T3–T4 disease. The median age was 70 years, median PSA was approximately 20 ng/mL, and 40% of the patients had Gleason disease of 6 or less. Gleason 8–10 disease was present in approximately one-fourth of patients, and Gleason 7 disease was present in one-third of patients. Median follow-up was 5.8 years at the time of reporting.

Overall survival was not distinct between the two arms of the trial in the intent-to-treat analysis, though disease-specific survival favored the two additional years of adjuvant ADT. Excess numbers of non–prostate cancer deaths counterbalanced the decreases in prostate cancer–specific deaths. In a nonplanned subset analysis, both overall and disease-specific survival favored the patients who were enrolled with a Gleason 8–10 disease (Figure 3). Though several interpretations are possible, the simplest explanation would be that the patients with the highest grade cancers (Gleason 8–10) were the only ones who benefited from the 24 additional months of adjuvant hormonal therapy and that patients with

**Figure 3.** Overall survival rate for patients with Gleason 8–10 disease treated in Radiation Therapy Oncology Group 9202 with long-term (28 months) androgen deprivation plus radiation therapy (LTAD+RT) versus short-term androgen deprivation (4 months) plus radiation therapy (STAD+RT).
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T2c–T4 disease that was Gleason 7 or lower did not benefit from the additional ADT administered postradiation. Both local progression and distant metastases were also decreased in the Gleason 8–10 subset by using the longer-term adjuvant ADT. This trial helps to frame the question, how does the optimal duration of ADT vary according to baseline tumor characteristics?

Dana-Farber/Harvard Cancer Center Randomized Trial

D’Amico and colleagues were the first to report a trial of 6 months of ADT in combination with radiation therapy (30). This trial was conducted solely at the Dana-Farber/Harvard Cancer Center; thus, this is the only randomized trial using ADT/radiation with a survival outcome conducted in a single institution. Eligible patients had a PSA of at least 10 ng/mL (maximum PSA of 40 ng/mL), a Gleason score of 7 or more, and TNM staging of T1b–T2b. “Low-risk” patients according to the D’Amico classification scheme (PSA <10 ng/mL, Gleason <7, and less than T2A disease) could be included if an endorectal coil magnetic resonance image indicated that either extracapsular extension or seminal vesicle invasion was present. ADT was administered for a total of 6 months of continuous therapy (2 months neoadjuvantly, 2 months concomitantly, and 2 months adjuvantly) and consisted of both leuprolide acetate and oral bicalutamide for the entire duration of 6 months. Radiation consisted of a prostate field plus a 1.5-cm margin. Nodal fields were not included. Total dose to the prostate was 70.35 Gy.

A total of 206 patients were randomized; median duration of follow-up was 4.5 years at the time of reporting. Median age was approximately 72, Gleason was 7 or less in approximately 85% of patients, and median PSA was 11 ng/mL. Only 3% of patients were low-risk but had an endorectal coil magnetic resonance image showing extracapsular or seminal vesicle involvement. Approximately 45% of the patients had nonpalpable prostate cancer (T1c). Clearly, this is a distinct subset of patients as compared with the earlier RTOG trials such as 8531, 8610, and 9202.

Overall survival and prostate cancer–specific survival were both improved in the ADT arm, though the data were still relatively immature at the time of reporting. A total of four deaths were attributed to prostate cancer in the radiation-alone arm, and no prostate cancer deaths were recorded in the combination arm.

Trans-Tasmanian Radiation Oncology Group 9601

The Trans-Tasmanian Radiation Oncology Group (TROG), a cooperative group located in Australia and New Zealand, randomized 818 men with T2B–T4 prostate cancer to radiation and one of three hormonal treatment schemes in TROG 9601 (31). Lymph node involvement was an exclusion. ADT was given for 0, 3, or 6 months. ADT consisted of goserelin and flutamide and was started either 2 months before the radiation (for the 3-month arm) or
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5 months before the radiation (for the 6-month arm). Radiation did not include a pelvic field; only the prostate and seminal vesicles were treated. The radiation was administered in 33 fractions, 2 Gy per fraction, for a total of 66 Gy. Median follow-up was 5.9 years.

Median age was 68 years, median PSA was approximately 15, and approximately 60% of the patients had stage T2 disease. Overall survival was not presented in this study but was noted not to be distinct among the three arms of the study. Compared with the no-ADT treatment arm, 6 months of hormonal therapy was associated with improved rates of local recurrence, metastasis-free survival, and a borderline improvement in prostate cancer-specific survival \((P = .072; \text{hazard ratio}, 0.58; \text{but 95\% confidence interval, 0.33–1.05})\). Careful examination of the overall deaths indicated no excess deaths from non–prostate cancer causes. It is conceivable that longer follow-up will change these initial statistics, but these preliminary data seemingly indicate that 6 months of ADT do not increase non–prostate cancer deaths. More follow-up in this study is needed to be confident that overall mortality is favorably impacted. It is noted that this trial has been criticized because of the low radiation doses used (66 Gy).

Early Prostate Cancer Program Studies of Radiation and Bicalutamide

Recent results have been announced for the radiation therapy component of the ongoing bicalutamide early prostate cancer (EPC) program sponsored by Astra-Zeneca (32). In this program, the efficacy and safety of adding bicalutamide 150 mg once daily to standard care (radical prostatectomy, radiotherapy, or watchful waiting) were evaluated in patients with localized or locally advanced prostate cancer. This program was not a typical clinical trial but rather was designed to reflect standard care worldwide. Radiation techniques and dose fractionations were not specified. Eligible patients had clinically localized (T1–T2, N0/Nx) or locally advanced (T3–T4, any N; or any T, N+) prostate cancer with no evidence of distant metastases. Patients were randomized in a 1:1 ratio to receive oral bicalutamide 150 mg or placebo once daily after radiation.

The majority of patients enrolled in the EPC program after radiation \((N = 1,370)\) had clinical stage T1–T2 disease \((1,065/1,370)\); the remainder \((305/1,370)\) (approximately 22%) had T3–T4 disease. Clearly node-positive patients comprised only 1% of patients. Gleason 7–10 cancers were present in approximately 24% of the patients. Taken together, most patients had clinically localized disease and Gleason 6 or less disease. Slightly over 30% of patients had prior unspecified neoadjuvant therapy. Specified duration of bicalutamide was variable in the various components of the EPC program, but in the reported results, median duration of placebo or bicalutamide treatment was 1.9 years. Patients were recruited between 1995 and 1998.

After a median follow-up of 7.2 years, overall survival was similar between the two arms; however, in the T3–T4 tumors, overall survival was improved in those patients receiving adjuvant bicalutamide \((\text{hazard ratio}}, \ 0.65; \text{95\% confidence interval 0.44–0.95})\);
In this subgroup of patients, 30% of patients receiving bicalutamide 150 mg had died, and 42% in the radiotherapy alone population had died. The significant overall survival benefit with bicalutamide 150 mg adjuvant to radiotherapy was driven by a lower risk of prostate cancer–related deaths compared with radiotherapy alone (16.1 vs. 24.3%, respectively). There was no significant difference in overall survival in patients with localized disease nor were an excess number of non–prostate cancer–related deaths encountered. Toxicity varied from that of the typical LHRH agonist trial. Breast pain (75%) and gynecomastia (67%) were common, and 31% of patients withdrew from study treatment as a consequence of adverse events. Erectile dysfunction was noted only in a minority of the bicalutamide-treated patients, but this potential adverse event was not directly quantified. Overall, these results are similar to those of the RTOG 9202 trial.

Other Androgen-Deprivation Therapy/Radiation Studies of Note

RTOG 9413 examined radiation and ADT in patients at high risk for positive lymph nodes. Two distinct radiation fields and two distinct ADT schema were used in a randomized fashion; all patients received 4 months of goserelin/flutamide. Eligible patients were required to have an estimated risk of lymph node involvement of more than 15% using the following equation: [% nodal positivity = (2/3)PSA + (GS–6) – 10]. Patients with clinical stage T2c–T4 disease were also eligible if they had a Gleason score of 6 or less, even if their calculated risk of lymph node involvement did not reach 15% by the equation. Radiation fields were either whole pelvis or prostate. Maximum radiation dose was 70.2 Gy. ADT was administered for 4 months either in a neoadjuvant/concomitant dosing schema or as adjuvant only. Thus, an overall 2 × 2 design was used. The primary end point of the study was progression-free survival rather than overall or disease-specific survival. A total of 1,323 patients were accrued between 1995 and 1999. The initial report (33) indicated that one arm of the 2 × 2 design was superior to the others; 4 months of neoadjuvant/concomitant radiation using a pelvic radiation field was superior to other ADT or radiation approaches using progression-free survival. PSA was included as part of the analysis, and most progression events were driven by PSA. The median follow-up at the time of reporting was 59.5 months. Overall survival data were not distinct among the various arms of the trial at the time they were reported.

RTOG 9408 is another important trial, but results are not yet reported. This trial accrued more than 2,000 patients (N = 2,028) between 1994 and 2001 with a PSA of 20 ng/mL or less and T1b–T2b prostate cancer. Patients with nodal metastases were excluded. The trial design was simple and involved radiation plus or minus 4 months of neoadjuvant/concomitant ADT consisting of goserelin/flutamide. The treatment schema is similar to RTOG 8610; however, the patients have predominantly early-stage disease, and more than 60% of the patients have a Gleason score of 6 or less. The primary end point is prostate cancer–specific survival. The trial has yet to be reported, implying that no differences to date have been detected between the two treatment groups with regard to the primary end point.
RTOG 9601 is likewise an interesting trial but is too immature to report. In this trial, patients’ status post–radical prostatectomy with recurrent disease and a PSA level of 0.2–4.0 ng/mL were randomized to 64.8 Gy of prostate fossa radiation plus or minus 2 years of 150 mg of bicalutamide. The primary end point is overall survival. Between 1988 and 2003, a total of 810 patients were accrued, and no results have been reported to date, again implying no differences between arms with respect to the primary end point.

EORTC 22961 compares various durations of hormonal therapy in a randomized fashion. Results have been reported in abstract form but not yet in peer reviewed publications. Radiation plus 6 months of LHRH agonist/antiandrogen were evaluated versus radiation plus 6 months of an LHRH agonist/antiandrogen plus an additional 2.5 years of an LHRH treatment (total of 3 years ADT). Entry criteria were restricted to those with T2c–T4 disease (with or without positive pelvic nodes) or stage T1c–T2b disease associated with pelvic nodes. Thus, these patients are expected to be more advanced than those treated in the Dana-Farber/Harvard Cancer Center trial published by D’Amico and colleagues. More than 950 patients were accrued between 1997 and 2002. Initial results have now been reported at ASCO 2007 (34). The data were analyzed with a non-inferiority analysis; 970 patients were randomized, and at 5.2 years median follow-up, 173 patients had died. An Independent Data Monitoring Committee recommended disclosure of results based on an interim analysis showing futility. Patient characteristics were well balanced: median age was 69 years; most patients had T2c-T3 N0 disease. The 5-year overall survival rate was 85.3% for the 3 years of ADT and 80.6% on the 6-months of ADT (HR = 1.43). The 5-year clinical progression-free survival rate was 81.8% on the 3-year arm versus 68.9% on the 6-month arm, and the 5-year biochemical progression-free survival rate was 78.3% on 3 years versus 58.9% on the 6-month arm, HR = 1.93 and HR = 2.29, respectively. Though as yet not peer-reviewed, careful attention to subsets will be needed as necessary. This trial calls into question using 6 months of ADT for patients with clinical T3 or higher disease at the time of diagnosis. It should be emphasized that the TROG trial is immature with regards to survival, thus the data supporting use of 6 months of hormones in the setting of the T3 or higher disease is minimal at this time.

**Androgen-Deprivation Therapy in the Radical Prostatectomy Patient**

Given the success of neoadjuvant and adjuvant ADT in patients treated with radiation, the role of ADTs in patients treated with surgical approaches is distinctly more limited. After neoadjuvant ADT, multiple studies have demonstrated that margin status in the pathologic postoperative specimen may be improved, but studies have not demonstrated that these improved pathologic outcomes translate into an improved disease-free interval or prolonged survival (35).
One prospective randomized trial in the post–radical prostatectomy setting provides clear evidence of overall and disease-specific survival benefit (36,37). This trial warrants a careful examination. From 1988 to 1993, 100 patients were randomized in 23 institutions to “early” versus “late” ADT. In this trial, “late” ADT was defined as ADT on symptomatic relapse or after the diagnosis of metastatic disease. “Early” ADT was defined as ADT within 12 weeks after surgery. Eligibility was restricted to patients undergoing a radical prostatectomy and lymphadenectomy and found to have node-positive disease after the surgery. Lymphadenectomy was restricted to the obturator and external iliac nodal regions in most cases. PSA values were determined postoperatively in the vast majority of patients and found to be undetectable in approximately 80% of the patient population enrolled in the trial. The typical patient was relatively young (median age of 65), which might be expected from a surgical series of patients. Though overall comorbidities were not discussed, most patients having a radical prostatectomy have 10 or more years of expected survival. This relatively young group of patients would also be expected to have limited comorbidities. Additional baseline characteristics included the following: Most patients had positive margins and seminal vesicle invasion, and the median number of positive nodes was two. A baseline computed tomographic scan was done in 80 of the randomized patients, and none had evidence of nodal metastases. As expected for a group of patients with aggressive disease, the majority of the patients had a Gleason sum of 7 or higher.

ADT was administered continuously in the Messing study; in the immediate-treatment group, 13 patients had orchiectomy, and 33 had long-term goserelin acetate. Median follow-up was 11.9 years at the time of the last study report. Outcomes in the Messing study were measured by PSA, disease-specific survival, and overall survival. Each of these end points was positive in patients treated with early as opposed to deferred ADT. Long-term outcomes were provided in a follow-up to the original study (37). The median overall survival (Figure 4) in the deferred-treatment group was 11.3 years, and the median overall survival for the early-treatment group had yet to be reached (hazard ratio, 1.84). Median prostate cancer–specific survival was 12.3 years in the deferred-treatment group and not yet reached in the immediate-treatment group (hazard ratio, 4.09). Progression-free survival, including PSA progression, was 2.4 years in the deferred-treatment group and 13.9 years in the early-treatment group (hazard ratio, 3.42). Thus, all end points are positive in this small but important randomized trial in patients with node-positive cancer after radical prostatectomy. After adjustment of baseline treatment characteristics for centrally graded Gleason sum, all outcomes continued to be positive.

Clinical trials attempting to demonstrate clinical benefit in patients given neoadjuvant ADT before surgery have not been successful in improving either quantity or quality of life. As noted previously, pathologic and biochemical end points are surrogates for clinical end points due to the long natural history of prostate cancer. Taken together, the lack of clinical benefit using new-adjuvant ADT before surgery leads to the conclusion that this approach should not be used in clinical practice.
Conclusion

Risks and benefits of ADT must be carefully assessed in prostate cancer patients scheduled to undergo definitive therapy with surgery or radiation. There is no currently accepted role for ADT before radical prostatectomy. In the postprostatectomy setting, the only evidenced-based indication for ADT is for the patient with node-positive disease after surgery. Regardless, many questions remain; node-positive disease is only one marker for relapse in the postsurgical setting. Other postoperative risk factors for progression (e.g., seminal vesicle invasion, residual PSA) have not been studied. What is the optimal duration of ADT? Which patients may be safely treated for less than 3 years? Is lifetime ADT really necessary? Further, no comparisons between adjuvant ADT and salvage ADT have been performed. Given that PSA recurrences typically find disease recurrences quite early, it is conceivable that treatment with salvage ADT is comparable to adjuvant therapy. Studies examining this comparison are now under way.

In patients considering external beam therapy, multiple evidence-based opportunities exist for improving long-term patient outcomes. Clearly, for patients with locally advanced cancers (T3–T4) and/or node-positive disease, radiation plus 3 years of con-
Androgen-Deprivation Therapies in Combination with Radiation or Surgery

comitant/adjuvant ADT has been shown to prolong overall survival. For patients with clinically localized disease, 6 months of hormonal therapy starting 2 months preradiation has been shown to prolong overall survival, but the long-term outcomes of the 6-month ADT trials are still relatively immature. Comparisons of 6 months versus 3 years of ADT have yet to be published in the peer reviewed literature, but the recently reported EORTC trial (22961) suggests that for many patients, especially those with extra-glandular spread, three years of ADT may be the preferred duration.

References


The Role of Chemotherapy in Multimodality Treatment of Locally Advanced Prostate Cancer

Daniel J. George, MD, and Phillip G. Febbo, MD

Neoadjuvant Chemotherapy

Existing nomograms and other risk-stratification schemes can identify men with high-risk prostate cancer who are likely to have micrometastatic disease at time of diagnosis (1). Although this represents a minority of patients diagnosed with prostate cancer, there are still approximately 39,000 men diagnosed annually with aggressive disease with a relatively high risk of dying from prostate cancer despite definitive therapy. To decrease recurrence after definitive local therapy, a significant investigative effort has been expended in determining if and when systemic therapies can be combined with local therapy to improve outcome.

The obvious therapy to test first was androgen ablation. For radiation therapy (RT), multiple trials have now demonstrated a clear benefit of combining androgen withdrawal with external beam radiation for men with high-risk, locally advanced prostate cancer (T3) (2). More recently, short-term androgen ablation (6 months) has been found to have a role in patients with intermediate-risk prostate cancer treated to a total dose of 70 Gy (3). Although the optimal combinations of total radiation dose, duration of androgen ablation, and disease risk level have yet to be fully established, androgen ablation is of proven value when combined with external beam RT in multiple situations.

A similar improvement in disease-free recurrence and survival has not been found in the large number of trials looking at neoadjuvant or adjuvant androgen ablation therapy when men are treated with radical prostatectomy (RP). In more than 25 published stud-
ies evaluating neoadjuvant androgen deprivation in patients with clinical stage T3 prostate cancer undergoing RP (4), there have been a consistent decrease in prostate-specific antigen (PSA) and shrinkage of the prostate but no demonstrated benefit in disease-free or overall survival. No survival benefit from neoadjuvant androgen ablation was observed in men with intermediate-risk disease either. Thus, neoadjuvant androgen ablation before definitive surgery does not appear to improve survival compared to surgery alone.

The role of neoadjuvant chemotherapy for men with high-risk prostate cancer has more recently been the focus of early- and late-phase clinical trials. As chemotherapy trials have now demonstrated chemotherapy to improve symptoms and survival for men with metastatic prostate cancer (5,6), there is renewed enthusiasm to understand the role of chemotherapy for men with high-risk localized disease.

The feasibility and safety of cytotoxic chemotherapy before RP have been demonstrated in multiple phase II trials. Cytotoxicity regimens including paclitaxel, estramustine, and carboplatin (TEC) (7); estramustine and etoposide (8); ketoconazole and doxorubicin alternating with vinblastine and estramustine (KAVE) (9); docetaxel and estramustine (10); single-agent docetaxel (11,12); docetaxel and mitoxantrone (13); and the combination of docetaxel with androgen deprivation (14) have been found to be feasible and safe before RP, with encouraging preliminary signs of efficacy.

Toxicity for most chemotherapy regimens was no greater than expected and generally well tolerated. Patients experienced preoperative grade 3–4 toxicity at rates of 12% (4/33) for KAVE (9), 15% (3/19) for docetaxel alone (12), 34% (5/16) for estramustine and etoposide (8), and 42% (9/21) for docetaxel and estramustine (10). Regimens including estramustine had significant rates of deep venous thrombosis (7,8,10). In general, chemotherapy-related toxicity does not preclude patients from RP.

Neoadjuvant therapy did not increase the duration of surgery, amount of blood loss, length of hospitalization, or rate of surgical complications. For example, based on three trials (7–9), median operative time ranged between 125 and 300 minutes for open RP, median estimated blood loss ranged between 665 and 1,250 mL, and perioperative complications occurred in between 17% and 33% of patients (most of which were minor). These surgical characteristics are roughly similar to that ordinarily seen for men with high-risk, aggressive prostate cancer.

The efficacy measures for most of these early trials were focused on serum PSA and pathologic end points and not recurrence or survival. In general, serum PSA levels consistently decreased during therapy. For regimens that did not include estramustine or androgen deprivation, the decrease in PSA occurred while testosterone levels were non-castrate (12,13), suggesting the observed effects were due to chemotherapy and not confounding hormonal changes. Magnetic resonance imaging performed with an endorectal coil before and after treatment with single-agent docetaxel demonstrated a median decrease in maximum tumor volume of 48% at 6 months (3.1 cm$^2$ to 1.6 cm$^2$), although no impact on prostate size was seen (12). Thus, neoadjuvant chemotherapy has had encouraging effects on serum PSA and evaluation of tumor size.
The impact of neoadjuvant cytotoxic therapy on histologic grade and pathologic stage was largely equivocal. Cytotoxic therapy, especially combinations including estramustine, can result in “treatment effect” that obscures traditional characteristics used to define Gleason pattern growth. After neoadjuvant paclitaxel, estramustine, and carboplatin (TEC), 63% (21/33) of the prostatectomy specimens were “ungradeable” due to “pathologic treatment effect” (7). With single-agent docetaxel, only modest treatment effect was noted in specimens, similar to that seen with androgen ablation, and Gleason score was not changed significantly (12). Approximately 65% of patients had extraprostatic extension after neoadjuvant therapy and no consistent change between the Gleason score of the diagnostic biopsy and the RP specimen. Importantly, only one trial testing the combination of docetaxel with androgen ablation resulted in men having a pathologic complete response (pT0 in 2.7% [2/72] men enrolled) (14). Although no definitive analysis is possible with respect to disease recurrence and patient survival, the general consensus from these trials is that neoadjuvant cytotoxic therapy is relatively well tolerated, does not complicate surgery, and may be effective in decreasing recurrence.

Neoadjuvant chemotherapy trials in prostate cancer to date have not demonstrated a consistent impact on pathologic stage. Organ-confined disease was found in approximately 30%–40% of patients after neoadjuvant therapy, and negative surgical margins were observed in 78%–87% (7–9,12). Importantly, only one study combining androgen ablation with docetaxel has reported pathologic complete response and pT0 disease at the time of RP (14). The authors reported that 2 of 64 patients completing treatment had no residual tumor within the prostate and an additional 10 of 64 had only residual “microfoci of cancer.” As complete pathologic response to neoadjuvant therapy has been associated with good clinical outcome in patients with various cancer types, including breast, rectal, and head and neck cancer, these findings, although preliminary, are of great interest.

None of the studies published to date was powered to determine if neoadjuvant cytotoxic therapy impacts progression-free survival (PFS) or overall survival. Definitive phase III trials testing cytotoxic chemotherapy in the neoadjuvant setting for prostate cancer are now under way (Table 1). For instance, the Cancer and Leukemia Group B (CALGB) has recently launched a phase III study that randomizes men with high-risk prostate cancer (Kattan nomogram probability of being disease-free at 5 years ≤60%) to either immediate surgery or neoadjuvant docetaxel (every 21-day treatment cycle), prednisone, and androgen deprivation for six cycles before surgery (CALGB 90203) (15). This trial, with an accrual goal of 750 patients, will have the ability to determine if neoadjuvant therapy decreases the 3-year biochemical PFS rate (bPFS) by 12% (from 57.7% in the standard arm to 69.1% in the neoadjuvant chemotherapy arm). In addition, the secondary end points include 5-year bPFS, time to clinical local recurrence, time to metastatic disease progression, prostate cancer–specific free survival, and overall survival. CALGB 90203 opened Dec. 15, 2006, and is expected to accrue over a 60-month period. A data safety monitoring board will evaluate data on a semiannual basis, with the first meaningful evaluation likely to occur around April 2011.
### Table 1. Current neoadjuvant chemotherapy trials in prostate cancer

<table>
<thead>
<tr>
<th>Trial (primary investigator)</th>
<th>Prostate cancer setting</th>
<th>Local treatment</th>
<th>Number</th>
<th>Phase</th>
<th>Regimen</th>
<th>Locations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dubray</td>
<td>Stage II and III</td>
<td>RT</td>
<td>450</td>
<td>III</td>
<td>Flutamide + triptorelin + RT vs. RT alone</td>
<td>France</td>
</tr>
<tr>
<td>Kim</td>
<td>Stage II</td>
<td>RP</td>
<td>200</td>
<td>RP II</td>
<td>Flutamide vs. placebo</td>
<td>MDACC</td>
</tr>
<tr>
<td>Sokoloff</td>
<td>Locally advanced</td>
<td>RP</td>
<td>132</td>
<td>RP II</td>
<td>Leuprolide acetate, bicalutamide, and squalamine lactate</td>
<td>OHSU</td>
</tr>
<tr>
<td>Logothetis</td>
<td>High-risk</td>
<td>RP</td>
<td>36</td>
<td>II</td>
<td>LHRH agonist + sunitinib</td>
<td>MDACC</td>
</tr>
<tr>
<td>90203 (Eastham)</td>
<td>High-risk</td>
<td>RP</td>
<td>750</td>
<td>III</td>
<td>LHRH agonist + docetaxel vs. immediate surgery</td>
<td>CALGB/NCIC/ECOG</td>
</tr>
<tr>
<td>GETUG-12 (Fizazi)</td>
<td>High-risk</td>
<td>RP/RT</td>
<td>250</td>
<td>III</td>
<td>CAB + docetaxel + estramustine vs. CAB before RT or RP</td>
<td>France</td>
</tr>
<tr>
<td>Oh</td>
<td>High-risk</td>
<td>RP</td>
<td>42</td>
<td>II</td>
<td>Bevacizumab + docetaxel</td>
<td>DFIC/BIDMC/Duke</td>
</tr>
<tr>
<td>Garzotto</td>
<td>High-risk</td>
<td>RP</td>
<td>42</td>
<td>I/II</td>
<td>Docetaxel + KT</td>
<td>OHSU</td>
</tr>
<tr>
<td>Chaudhary</td>
<td>Locally advanced</td>
<td>RT</td>
<td>36</td>
<td>I</td>
<td>Docetaxel + LHRH + biclutamide</td>
<td>MUSC</td>
</tr>
</tbody>
</table>
## Novel Therapies

<table>
<thead>
<tr>
<th>Team</th>
<th>Disease Stage</th>
<th>Treatment</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amato</td>
<td>Intermediate to high-risk</td>
<td>RP 40 RP II</td>
<td>Cetuximab + docetaxel vs. cetuximab</td>
</tr>
<tr>
<td>Chi</td>
<td>Localized</td>
<td>RP 45 II</td>
<td>OGX-011</td>
</tr>
<tr>
<td>Trump</td>
<td>Localized</td>
<td>RP 80 II</td>
<td>Calcitriol + dexamethasone</td>
</tr>
<tr>
<td>Bergen</td>
<td>Localized</td>
<td>RP 88 I/II</td>
<td>Genistein</td>
</tr>
<tr>
<td>Kadmon</td>
<td>Localized</td>
<td>RP 36 I</td>
<td>RTVP-1 gene therapy</td>
</tr>
<tr>
<td>Carducci</td>
<td>Intermediate-risk</td>
<td>RP 60 PD</td>
<td>Sirolimus</td>
</tr>
<tr>
<td>Fong</td>
<td>Any localized</td>
<td>RP 28 Pilot</td>
<td>GM-CSF</td>
</tr>
</tbody>
</table>

BIDMC = Beth Israel Deaconess Medical Center, Boston; CAB = complete androgen blockade; CALGB = Cancer and Leukemia Group B; DFCI = Dana-Farber Cancer Institute; ECOG = Eastern Cooperative Oncology Group; GETUG = Groupe d’Etudes des Tumeurs Uro-Génitales; GM-CSF = granulocyte-macrophage colony-stimulating factor; JHMI = Johns Hopkins Medical Institute; LHRH = luteinizing hormone–releasing hormone; MDACC = M D Anderson Cancer Center; MHS = Methodist Hospital System; MUSC = Medical University of South Carolina; NCIC = National Cancer Institute Canada; OHSU = Oregon Health Services University; PD = pharmacodynamic; RLCC = Robert H. Lurie Cancer Center (Northwestern); RP = radical prostatectomy; RPCI = Roswell Park Cancer Institute; RP II = randomized phase II; RT = radiation therapy; UBC = University of British Columbia; UCSF = University of California, San Francisco; UM = University of Michigan.
As mentioned previously, androgen ablation combined with local RT has demonstrated improved efficacy over radiation alone, but whether chemotherapy can improve further on these results is unknown. Phase I/II studies above have demonstrated that docetaxel-based chemotherapy can be given safely in the neoadjuvant setting. In addition, a recently reported phase I study demonstrated that weekly docetaxel can be given safely with concurrent conformal beam radiotherapy (16). Based on these results, a phase III study is ongoing, looking at the use of androgen ablation with both neoadjuvant followed by concurrent weekly docetaxel chemotherapy and definitive RT versus standard androgen ablation and RT alone. In this study, chaired by Anthony D’Amico and Philip Kantoff from the Dana-Farber Cancer Institute, intermediate- and high-risk localized prostate cancer patients are randomized to 6 months of combined androgen blockade and 70 Gy of RT with or without three cycles of every-3-week neoadjuvant docetaxel chemotherapy (60 mg/m\(^2\)) followed by weekly docetaxel (20 mg/m\(^2\)) concomitant with radiation. This multicenter study opened in June 2005 is actively accruing and has an accrual goal of 350 patients. The primary end point is overall survival.

In summary, neoadjuvant chemotherapy trials have clearly demonstrated that systemic chemotherapy can be given safely with good tolerance in patients with high-risk prostate cancer before prostatectomy. Ongoing studies will test if the clinical responses seen to date translate into survival benefit. By design, neoadjuvant systemic therapy aims to reduce or eliminate microscopic extraprostatic disease (microscopic metastases) and offers the advantage over adjuvant trials as having a potential surrogate for clinical benefit in pathologic response. As such, although the observation of pathologic complete response in a small percentage of patients treated with a combination of docetaxel and androgen ablation is promising, the true usefulness of neoadjuvant therapy will not be known until definitive studies are completed that look at bPFS and patient survival.

### Adjuvant Chemotherapy in Cancer

The rationale for the addition of chemotherapy after local treatment of cancer is well established. Although the exact biologic mechanisms of tumor cell extirpation are not fully understood, the basic tenet is that microscopically spread malignant cells after local treatment may be particularly vulnerable to cytotoxic chemotherapy or hormonal therapy using regimens that have demonstrated antitumor effect in the grossly metastatic disease. Over the past 30 years, this theory has been validated numerous times in randomized controlled trials involving many different tumor types.

The most well-studied and validated data on adjuvant chemotherapy in solid tumors come from breast cancer studies. A recent metaanalysis reviewed 194 randomized adjuvant chemotherapy trials conducted between 1985 and 2000. Ten- and 15-year survival data continue to validate the early findings of a substantial survival advantage for patients with node-positive breast cancer treated with chemotherapy (17). Similarly, endocrine therapy first with tamoxifen but more recently with aromatase inhibitors has
also demonstrated significant disease-free survival benefits in women with estrogen receptor–positive breast cancer (18).

Another important example of the benefits of adjuvant chemotherapy comes from studies in patients with locally advanced colon cancer. Numerous clinical studies have established 5-fluorouracil (5-FU) and leucovorin as the standard of care for patients with stage III colon cancer after resection (19). More recently, an oxaliplatin and capecitabine (XELOX) chemotherapy regimen has shown promise in the adjuvant setting, and a large phase III trial randomizing 1,886 patients to either XELOX or 5-FU and leucovorin was recently completed, demonstrating the robust accrual still capable today for adjuvant trials in colon cancer (20).

In addition to breast and colorectal cancer patients, adjuvant chemotherapy and/or hormonal therapy has demonstrated clinical benefit in at least ten other solid tumor types, ranging from rectal cancer to head and neck tumors. Review of the pivotal studies leading to these indications reveals a wide range of treatments, including single-agent and combination chemotherapy, hormonal therapy, targeted agents, and immune-based strategies. These agents vary widely in both their mechanisms of action and their clinical activity in the metastatic setting. For instance, bleomycin, etoposide, cisplatin (BEP) chemotherapy is curative in many patients with metastatic testicular cancer, whereas interferon-α demonstrates only a modest response rate and no survival advantage in patients with metastatic melanoma (21,22).

**Adjuvant Chemotherapy in Prostate Cancer: Past Experience**

In prostate cancer, adjuvant androgen-deprivation therapy (ADT) has demonstrated a survival advantage following RT or surgery in several studies (2,3,23). However, few clinical trials of adjuvant chemotherapy have been completed, and none has established a clinical benefit in patients with clinically localized and/or locally advanced prostate cancer. Table 2 highlights several of the adjuvant chemotherapy clinical trials completed to date in prostate cancer patients. The first trial was completed in the 1980 by Schmidt et al. from the National Prostate Cancer Group. Patients with locally advanced prostate cancer treated with radical prostatectomy (RP) were randomized to either oral cyclophosphamide or estramustine phosphate for 2 years or observation (24). With mature follow-up, this study revealed an improvement in disease-free survival for the patients treated on the estramustine arm versus observation; however, there was no overall survival advantage due to the small number of patients (187 total). In another smaller exploratory study, Wang et al. reported on 96 patients with either newly diagnosed metastatic prostate cancer or locally advanced T3 or T4 cancer who were randomized to mitoxantrone plus combined androgen blockade versus combined androgen blockade alone (25). In the patients with locally advanced disease, median survival was improved with mitoxantrone and ADT with antiandrogen versus ADT and antiandrogen alone (80 vs. 36 months; \( P = .04 \)). Although these results are interesting, the sample size is too small to confirm any clinical benefit from the mitoxantrone therapy.
### Table 2. Randomized adjuvant chemotherapy trials in prostate cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Local treatment</th>
<th>Regimen</th>
<th>Outcome/end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPCP 900</td>
<td>Locally advanced</td>
<td>RP</td>
<td>Cyclophosphamide vs. estramustine phosphate vs. observation</td>
<td>Improved disease-free survival; no difference in overall survival</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>T3–T4, metastatic</td>
<td>RP</td>
<td>Mitoxantrone + CAB vs. CAB</td>
<td>Improved overall survival (84 vs. 36 mos, ( P = .04 ) in T3,4)</td>
</tr>
<tr>
<td>SWOG 9921</td>
<td>High-risk</td>
<td>RP</td>
<td>Mitoxantrone + prednisone + CAB vs. CAB</td>
<td>Closed prematurely due to increased incidence of leukemia</td>
</tr>
<tr>
<td>RTOG 9902</td>
<td>High-risk</td>
<td>RT</td>
<td>Paclitaxel + estramustine phosphate + etoposide + CAB vs. CAB</td>
<td>Closed due to increased toxicity</td>
</tr>
<tr>
<td>TAX 3501</td>
<td>High-risk</td>
<td>RP</td>
<td>ADT (18 mos) +/- docetaxel + prednisone for six cycles (immediate vs. delayed treatment)</td>
<td>Progression-free survival 2 × 2 factorial design</td>
</tr>
<tr>
<td>VA #553</td>
<td>High-risk</td>
<td>RP</td>
<td>Docetaxel + prednisone for six cycles vs. observation</td>
<td>Progression-free survival at 5 yrs</td>
</tr>
<tr>
<td>RTOG 0521</td>
<td>High-risk</td>
<td>RT</td>
<td>ADT (2 yrs) +/- AA +/– docetaxel + prednisone for six cycles</td>
<td>Overall survival; progression-free survival; biochemical, local relapse; distant failure</td>
</tr>
</tbody>
</table>

AA = antiandrogen; ADT = androgen deprivation therapy; CAB = combined androgen blockade; RP = radical prostatectomy; NPCP = National Prostate Cancer Project; RT = radiation therapy; RTOG = Radiation Therapy Oncology Group; SWOG = Southwest Oncology Group; TAX = Taxotere; VA = Veterans Affairs.
In 1996, mitoxantrone and prednisone (M+P) chemotherapy was approved for the palliation of metastatic hormone-refractory prostate cancer patients, legitimizing the rationale for cytotoxic chemotherapy for prostate cancer and supporting the rationale for adjuvant treatment in patients with high-risk, localized prostate cancer (26,27). In 1999, the Southwest Oncology Group (SWOG) opened the first trial adequately powered study to investigate the potential benefit of chemotherapy in addition to ADT in this setting. SWOG 9921 randomly assigns patients with high-risk features after RP to 2 years of combined androgen ablation with or without six cycles of every-3-week mitoxantrone and daily prednisone therapy. This trial has an accrual goal of 1,360 patients to be completed over 9.5 years. As of this publication, the trial is currently on hold due to the incidence of possible leukemia secondary to mitoxantrone as well as to slow accrual.

In 2000, the Radiation Therapy Oncology Group (RTOG) attempted a large randomized phase III trial of RT and ADT versus RT and ADT followed by four cycles of paclitaxel, estramustine, etoposide (TEE) chemotherapy for patients with locally advanced high-risk prostate cancer (RTOG 9902). Patients were stratified by PSA, Gleason sum, tumor stage, and whether or not they had received prior hormonal therapy. All patients were then randomized to either ADT for 2 years with 70.2 Gy of RT versus ADT for 2 years; 70.2 Gy of RT; and four cycles of paclitaxel 135 mg/m², oral estramustine 280 mg tid for 14 days, and oral etoposide 50 mg/m² daily in divided doses for 14 days, every 3 weeks. This study was discontinued before it met its accrual goal because of both toxicity (e.g., venoocclusive disease requiring the addition of prophylactic warfarin anticoagulation) and slow accrual.

The premature closure of two large adjuvant clinical trials in patients with high-risk prostate cancer raises a legitimate concern that such trials may not be feasible in this population. There are several specific concerns. First, multidisciplinary clinical care is evolving in urologic cancers but currently is not a standard in most community settings. Second, the natural history of this disease requires longer follow-up than in most other disease settings, so any trial will take years of follow-up before results are known. Finally, and most important, there has been only modest activity of chemotherapy in patients with metastatic prostate cancer, making the rationale and robustness for adjuvant chemotherapy unlikely to result in clinical benefit.

In 2004, docetaxel chemotherapy was approved by the U.S. Food and Drug Administration for the treatment of patients with metastatic hormone-refractory prostate cancer, based on survival data from the Taxotere (TAX) 327 study, a multinational phase III study comparing mitoxantrone and prednisone to every-3-week docetaxel and prednisone and weekly docetaxel and prednisone (6). Results of this study revealed a 24% reduction in the risk of death from prostate cancer (hazard ratio, 0.76; 95% confidence interval, 0.62–0.94; \( P = .009 \)). Updated follow-up reveals a greater median survival for the every-3-week docetaxel arm (19.6 months) compared with the mitoxantrone arm (16.6 months) (28). Importantly, safety was acceptable in all three arms, with only 11% of patients discontinuing treatment due to adverse events in the every-3-week docetaxel arm. Based on these results, the U.S.
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Food and Drug Administration approved every-3-week docetaxel with daily prednisone for first-line treatment of patients with metastatic hormone-refractory prostate cancer. Earlier this year, post hoc analyses of the TAX 327 data were reported that revealed much greater clinical benefits among patients demonstrating a response to chemotherapy. For instance, 67% of patients treated with docetaxel chemotherapy demonstrated at least a 30% decline in PSA from baseline at 3 months, with a median survival of 23 months, compared with 14 months for the population that did not achieve a 30% decline by 3 months (hazard ratio, 0.50; 95% confidence interval, 0.43–0.57) (29). Twelve percent of patients treated achieved normalization in their PSA level, defined as a drop to 4 ng/mL or less. In this population, median survival was nearly 3 years. These results underscore the robust cytotoxic effect of this regimen and justify an evaluation of docetaxel-based chemotherapy in the adjuvant setting.

Adjuvant Chemotherapy in Prostate Cancer: Current Trials

With the approval of docetaxel prednisone for treatment of patients with metastatic hormone-refractory prostate cancer, investigations were initiated to determine if this regimen could also demonstrate clinical benefit in earlier disease settings. In patients with metastatic hormone-naive prostate cancer, two phase III randomized studies are evaluating the addition of docetaxel and prednisone to ADT versus ADT alone (Eastern Cooperative Oncology Group [ECOG] 3805 or ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer [CHAARTED] and a French study Groupe d’Études des Tumeurs Uro-Génitales [GETUG]-15/0403). In the United Kingdom, a large phase III, six-arm, 3,300-patient randomized trial is under way in patients with locally advanced or recurrent prostate cancer to compare ADT alone versus combinations with docetaxel and prednisone; zoledronic acid; celecoxib; docetaxel, prednisone, and zoledronic acid; and zoledronic acid and celecoxib (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy [STAMPEDE] study). Finally, a U.S. trial in patients with rising PSA will compare ADT alone with ADT and docetaxel and prednisone for six cycles.

The adjuvant setting is also being investigated using docetaxel and prednisone chemotherapy. The TAX 3501 study is a potentially seminal study to evaluate the clinical benefit of adjuvant hormonal therapy and chemotherapy in patients with pathologically defined high-risk disease after RP. The primary end points are to compare PFS benefits of immediate versus delayed treatment and ADT versus ADT and docetaxel and prednisone combined using a 2 × 2 factorial design. In this study, patients with pathologic findings of high-risk disease (defined as a 40% chance of relapse at 5 years by the Kattan nomogram) are randomized to immediate (adjuvant) versus delayed treatment (at the time of PSA relapse). In a second randomization, patients are treated with either ADT for 18 months or ADT and six cycles of every-3-week docetaxel and prednisone, either adjuvantly or at the time of PSA relapse (see Table 2 and Figure 1A).
Figure 1. Schematics for three ongoing phase III trials of adjuvant chemotherapy in prostate cancer patients. (A) Schematic for Taxotere (TAX) 3501. Patients are classified by age, country, and 5-year disease-free survival probability and then randomized to immediate versus delayed treatment and either androgen-deprivation therapy (ADT) alone for 18 months or ADT plus docetaxel and prednisone for six cycles. Patients are followed for progression-free survival (PFS). (B) Schematic for VA Cooperative Study #553. A two-arm phase III trial, patients are stratified by prostate-specific antigen (PSA), T stage, Gleason score, positive margins, and planned radiation therapy (RT). Patients are then randomized to observation versus docetaxel and prednisone for six cycles. PFS at 5 years is the primary end point. (C) Schematic for Radiation Therapy Oncology Group (RTOG) 0521. A two-arm phase III study in which all patients receive upfront ADT plus antiandrogen (AA) for 2 months followed by RT and are then randomized to ADT alone versus ADT + docetaxel and prednisone chemotherapy for six cycles. Patients are stratified by high-risk features and followed for survival. FRP = free of relapsed prostate cancer; XRT = external beam radiation therapy.
TAX 3501 is powered for an enrollment of 1,696 patients; however, accrual to date has been slow, with only 82 patients accrued in the first year. Although some sites have been slow to open, this trial may be at risk to close prematurely, like others before it, if accrual does not improve. Confounding issues include a required postoperative PSA level of 0.1 or less and inhibition of any adjuvant RT. With a recently reported phase III European Organisation for Research and Treatment of Cancer (EORTC) trial demonstrating an PFS benefit to adjuvant RT in pT3 patients, some physicians are opting to treat patients with adjuvant RT rather than this randomized trial (30). Although the data for PFS are intriguing, no overall survival benefit has been established. In addition, salvage RT may be used in the TAX 3501 study before starting delayed treatment. For these reasons, practitioners are encouraged to enroll patients into this critical trial.

The TAX 3501 study evaluates the role of docetaxel and prednisone in combination with ADT, as either immediate or delayed therapy after RP; however, there is no arm that assesses the effect of chemotherapy alone in hormone-naïve patients. For this assessment, a separate study being supported by the Veterans Affairs Cooperative Studies Program will investigate the clinical benefit of docetaxel and prednisone chemotherapy after RP in patients with either preoperative or postoperative high-risk features (VA #553). Eligibility includes preoperative criteria for high-risk disease (preoperative PSA level >20 ng/mL) or postoperative pathologic findings (pT3b, pT3a with Gleason sum ≥ 7). The study then randomizes patients to either six cycles of docetaxel and prednisone or the standard of care (observation) (see Table 2 and Figure 1B). Patients are followed for PSA recurrence. Six hundred thirty-six patients are planned for enrollment, and the study is powered to detect a reduction in the 5-year progression rate from 60% to 45% (15% absolute difference, 25% relative difference).

In the setting of primary RT and ADT for patients with high-risk prostate cancer, the role of docetaxel and prednisone chemotherapy is also being investigated. RTOG has initiated a replacement study for RTOG 9902. In the current study, RTOG 0521 will enroll 600 patients with high-risk prostate cancer, defined by Gleason score 9–10, PSA of less than 150 ng/mL; Gleason score 8, PSA of less than 20 ng/mL, and T2 or greater disease; or Gleason score 7–8, PSA of more than 20 and less than 150 ng/mL. All patients must have clinically negative nodes 1.5 cm or less in size. All patients receive ADT and an antiandrogen for 2 months, followed by RT (either three-dimensional conformal beam or intensity-modulated RT). Patients are then randomized to 24 months of ADT alone beginning 2 months before RT (with antiandrogen before and during RT) or ADT with six cycles of every-3-week docetaxel and prednisone following completion of RT (see Table 2 and Figure 1C). The primary end point is overall survival, with secondary end points including PFS, biochemical control, local control and freedom from metastases, to validate PSA as a surrogate for survival, and to correlate testosterone levels with time from PSA relapse to metastases. The trial opened in December 2005 and is actively enrolling patients.
Conclusion

Neoadjuvant and adjuvant chemotherapy trials are actively being investigated in phase I–III clinical trials in the United States and worldwide. Although past experiences have been disappointing, the validation of a clinically beneficial and robustly active regimen in the metastatic disease setting has resulted in renewed enthusiasm for neoadjuvant and adjuvant chemotherapy. Integration with other standard modalities (surgery, radiation and hormonal therapy) is critical to the success of these trials. Thousands of patients are needed to complete these studies, requiring substantial accrual from both the academic and community setting. In addition, unprecedented multidisciplinary cooperation among urologists, medical oncologists, and radiation oncologists is needed to facilitate these studies. If unsuccessful, prostate cancer patients will continue to be treated in a sequential manner, with little data to support treatment otherwise.

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Future Directions

Philip Kantoff, MD

Prostate cancer remains a remarkably heterogeneous disease and thus presents a real challenge for clinicians. Prostate-specific antigen (PSA)-based screening uncovers both clinically important and clinically insignificant disease. As such, it is clear that many patients with newly diagnosed disease do not require treatment, but the ascertainment of those who do not require treatment remains challenging. Providing a rational basis for selection of patients based on both clinical parameters and molecular markers is an important goal. For those who require treatment, a greater emphasis is being placed on decreasing the morbidity of treatment. Notwithstanding the impressive advances in surgical as well as the radiation management of this stage of disease, efforts for focal ablation remain a goal. The ability to ablate small foci of cancer is feasible using a variety of technologies, but the precise imaging and localization of disease remain the bigger challenge.

The appropriate integration of existing therapies such as hormonal therapy and chemotherapy into the management of high-risk localized disease appears to be an important strategy, although many questions remain regarding the duration and timing of these therapies. Moreover, as critical molecular targets are identified such as the TRMPRSS2/ERG fusion protein, a relatively early event in the pathogenesis of the disease, strategies at targeting these molecular abnormalities will expand our therapeutic armamentarium, and, as systemic therapies improve, the relative value of localized therapies will need to be questioned, but this seems a bit remote at the present time.

Another critical area is assessing the need to intervene in those patients with a rising PSA level after local therapy. Although some may be cured with salvage local therapy and others ultimately succumb to their disease, most of these patients will not die of prostate cancer and require no therapy. Better stratification of such patients is important, particularly in light of the increasing awareness of the side effects of androgen-deprivation therapy. Nonetheless, androgen-deprivation therapy remains a critical part of the management of relapsed disease. A surprising finding is the outstanding survival of these
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patients. Nonetheless, the 27,000 men who die of prostate cancer annually develop castration-resistant disease. The mechanism of this occurring is increasingly understood, but therapy is still relatively modest.

Several lines of evidence support the contention that persistent androgen signaling occurs in hormone-refractory prostate cancer (HRCaP), making this pathway a key pathway for drug treatment. The lines of evidence include work by Chen et al., who demonstrated cell lines grown in the absence of androgens continued to produce androgen receptor (AR) message and that the AR was the single most overexpressed transcript, suggesting its importance in this state (1). Stanbrough et al. demonstrated in human samples from patients with castration-resistant prostate cancer that androgen-regulated transcripts in these samples continued to be expressed, indicating that there was partial reactivation of AR transcriptional activity (2). This was associated with increased expression of AR (5.8-fold) and multiple genes mediating androgen metabolism. Similarly, Tomlins et al. demonstrated the persistence of expression of androgen-regulated genes. Finally, Mohler et al. showed (a) that tissue levels of testosterone were similar in recurrent prostate cancer and benign prostate; (b) that tissue levels of dihydrotestosterone, dehydroepiandrosterone, and androstenedione were lower in recurrent prostate cancer than in benign prostate; (c) and that mean dihydrotestosterone levels, although reduced, remained adequate to activate the AR (3).

A number of strategies are under investigation to test the clinical usefulness of interference with this pathway either by reduction of ligand or inhibition of signaling molecules relevant to this. The first approach might include the development of strategies that interfere with the persistent production of ligand. Ligand may be produced by the adrenal gland or alternatively by upregulation of enzymes in tumor cells capable of producing precursors to testosterone. Such approaches include the development of better antiandrogen—that is, drugs that bind the androgen receptor. The currently available antiandrogens, flutamide, bicalutimide, and nilutimide, although active, have relatively weak AR-binding properties. Such antiandrogens (e.g., BMS) are currently being tested in the clinic. An alternative strategy to interfere with ligand is to develop more robust lyase/hydroxylase inhibitors, which decrease the amount of adrenal androgen production. Similarly, such drugs are currently in clinical testing. The alternative approach would be to interfere with the androgen receptor. Such approaches include heat shock protein 90 (Hsp90) inhibitors or histone deacetylase (HDAC) inhibitors. Hsp90 is a molecular chaperone whose association is required for the stability and function of multiple mutated, chimeric, and overexpressed signaling proteins that promote the growth and/or survival of cancer cells. Hsp90 client proteins include mutated p53, Bcr-Abl, Raf-1, Akt, ErbB2, and hypoxia-inducible factor 1 alpha (HIF-1 alpha). There is strong evidence, at least in vitro, that AR is a client protein for Hsp90. One Hsp90 inhibitor, 17-allylamino-17-demethoxygeldanamycin (17-AAG), is currently in phase I clinical trial. A variety of other HSP-90 inhibitors are in clinical development, including tanespimycin and alvespimycin (Kosan Pharmaceuticals). IPI-504 (Infinity Pharmaceuticals) represents an important therapeutic advance over 17-AAG because of its improved solubility. Acetylation and deacetylation of the AR are an important mechanism for regulating its transcriptional activity. HDAC inhibitors may indirectly diminish AR
activity. A variety of HDAC inhibitors are in clinical trials; some of these are focused on prostate cancer.

Another important pathway is the IGF-1/PTEN signaling pathway. The centrality of this pathway in prostate cancer is illustrated by the finding that higher insulin-like growth factor-I levels in men years before diagnosis are associated with a higher likelihood of developing prostate cancer. Further, mutations of PTEN, the tumor suppressor gene that normally functions as a dual-specificity protein tyrosine phosphatase, occur in early prostate cancer and occur more frequently in men with advanced disease. This mutational event in turn results in activation of AKT, the serine/threonine protein kinase that is the cellular homologue of the viral oncogene v-Akt. One of the downstream targets of AKT is mTOR, another serine/threonine protein kinase in the regulation of cell growth. Mouse models that genetically activate AKT result in prostatic epithelial neoplasia (PIN), whereas those that involve loss of PTEN plus another genetic insult usually result in invasive prostate cancer. Many drugs, either alone or in combination, that affect this pathway are under investigation for prostate cancer, including IGF-1R antibodies, PI3K, AKT, and mTOR inhibitors. Whether these drugs if used alone will be effective or require combination approaches (either with other inhibitors of this pathway or with proapoptotic stimuli such as chemotherapy) has yet to be determined.

Other growth factor pathways may be important. Interest in platelet-derived growth factor (PDGF) inhibition has stemmed from a number of lines of evidence, including its overexpression of receptor (PDGFR) in advanced disease. Imatinib, an inhibitor of PDGFR, has been tested. A prospective randomized trial of docetaxel with or without imatinib has been completed. No apparent benefit was seen with the addition of imatinib, however. Inhibition of vascular endothelial growth factor signaling has been of interest. In two studies, higher serum and urine levels of vascular endothelial growth factor were associated with a poorer prognosis. Further, a study of bevacizumab in combination with docetaxel and estramustine generated high responses in a Cancer and Leukemia Group B phase II study. This prompted a large randomized phase III study of docetaxel with or without bevacizumab in men with advanced prostate cancer. This trial is currently accruing. Other inhibitors of this pathway are under investigation. Both sorafenib and sunitinib are small molecule inhibitors of the vascular endothelial growth factor receptor KDR. Two clinical trials have tested the efficacy of these agents used alone in men with advanced disease. The National Cancer Institute reported paradoxical effects of the drug, wherein some patients had improvement in bone scans but no salutary effect on PSA. The question as to the usefulness of PSA as a marker in this context has been raised. The results of the sunitinib trial have yet to be reported. Trials involving combinations of these drugs with docetaxel are under way.

Other interesting drugs in advanced disease include thalidomide. The mechanism of its proposed anticancer activity is uncertain, but many have invoked an antiangiogenic mechanism. Although the drug itself has minimal activity, in a small randomized phase II study comparing docetaxel with docetaxel plus thalidomide, an effect was seen, with a longer time to progression and survival noted with the combination, although these did not reach statistical significance. Another study at the National Cancer Institute
explored the combination of docetaxel, thalidomide, and bevacizumab, with apparent excellent response rates. Further studies with thalidomide have not occurred. The drug revlimid, a derivative of thalidomide approved for use in multiple myeloma and myelodysplastic syndrome, is now under investigation for prostate cancer.

Vitamin D or its active derivative, calcitriol, has been under investigation. Vitamin D binds the vitamin D receptor, which is part of the nuclear receptor family of transcription factors. Its effect as monotherapy in prostate cancer has been studied for years, but its effects appear to be modest. Interestingly, when combined with docetaxel in a phase II study, the response rates were remarkably higher than seen with docetaxel alone. This was subjected to a randomized phase II study (ASCENT I) in which 250 men with metastatic HRCaP were randomized to DN-101 plus weekly docetaxel or placebo plus weekly docetaxel. At an interim analysis, a trend toward improvement in PSA response rate and overall survival (23.5 vs. 16.4 months, \(P = .07\)) was seen. Interestingly, substantial reductions in serious adverse events and any grade 3 or 4 adverse event were seen in the DN-101 arm (27% vs. 41% for serious adverse events and 58% vs. 70% for any grade 3 or 4 event). This concept is now being validated in a larger randomized phase III study (Androgen-Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere II).

Finally, immunotherapeutic approaches have shown some promise in prostate cancer. The most advanced approach is the sipuleucel-T (APC8015, Provenge) vaccine. This vaccine consists of the patient’s own dendritic cells (antigen presenting cells), which are collected, exposed ex vivo to human prostatic acid phosphatase and granulocyte-macrophage colony-stimulating factor, then reintroduced. In a placebo-controlled phase III trial in 127 men with asymptomatic metastatic HRCaP, patients received sipuleucel-T or placebo every 2 weeks for three doses. Those in the placebo group received a frozen version of sipuleucel-T at progression. Interestingly, although the time to progression in this relatively small trial was not different between the two arms (11.7 vs. 10.0 weeks for treatment vs. control, respectively), there was a significant survival difference favoring the treatment arm (25.9 vs. 21.4 months, \(P = .01\)). A confirmatory phase III trial is under way to attempt to validate this exciting result. Other vaccine approaches, including GVAX (a granulocyte-macrophage colony-stimulating factor gene transduced allogeneic vaccine) and Prostvac (a poxvirus-based vaccine containing PSA) are being tested in clinical trials. Finally, antibody targeting of prostate-specific membrane antigen (PSMA) and prostate stem cell antigen are promising approaches as well.

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