

Prostate Cancer 2005
Shandra S. Wilson, MD
Assistant Professor, University of Colorado

**Terms, Definitions, and Additional Information About
Prostate Cancer**

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Terms and Definitions

Adjuvant: Concurrent or additive, generally a reference to treatments given at the same time

Age-Specific PSA: The adjustment for PSA for age in the hopes to improve its sensitivity and specificity. By lowering the threshold of PSA for younger men, it is hoped that fewer prostate cancers will be missed, while increasing the threshold for older men, it is hoped that fewer unnecessary biopsies for enlarged prostate conditions without cancer will be performed

Androgen: A term for the male hormone testosterone

Androgen Deprivation: The act of removing or decreasing circulating testosterone (which stimulates prostate cancer growth) with medications or surgery in the hopes of slowing the growth of prostate cancer

Androgen Independent Prostate Cancer: Prostate cancer that appears to be progressing despite treatment with androgen deprivation

Anti-Androgen: A medication, usually given in tablet form, which blocks the effect of circulating testosterone. Examples of this medication include Flutamide and Bicalutamide (or Cassodex)

Benign: Non-cancerous

Benign Prostatic Hypertrophy: The non-cancerous growth seen in most men's prostate over time. This growth typically occurs in the central zone of the prostate (where the urine flows during elimination) and may result in urinary symptoms such as a slow stream, voiding frequently, incomplete emptying, and difficulty initiating the urinary stream

Bicalutamide (Cassodex): An anti-androgen given in combination with Leutinizing Hormone Releasing Hormone (LHRH) agonists at the initiation of treatment of advanced prostate cancer. Some practitioners continue this medication even after the first two weeks. Rarely, the medication is used without the injectable LHRH agonist

Biopsy: The sampling of tissue, usually performed to evaluate for cancer

Bisphosphonates: Medications given orally or intravenously that have been shown to stop the destruction of bone. These are generally given for patients with osteoporosis and have been found to decrease fracture rates in patients with bone metastases

Bladder: A hollow muscular pelvic organ which stores and expels urine

Bone Scan: A radionucleotide scan whereby antibodies that detect rapid calcium turn over are linked to radioactive signals so that areas of possible bone metastases can be identified

Brachytherapy: A treatment for low-risk prostate cancer that involves the surgical placement of small radioactive seeds which slowly release radiation to the surrounding prostate tissue. The two main types of seeds used to treat prostate cancer are those made of radioactive Iodine and or Paladium.

Capsule: A very thin layer of tissue surrounding an organ

Carotenoid: Antioxidant substance found in tomatoes, guava, rosehip, watermelon and pink grapefruit. This substance helps give a red color to these fruits and vegetables and may be useful in prostate cancer prevention and treatment

Catheter: Latex or silastic tube allowing for the passage of a fluid, generally referring to a narrow tube which facilitates urinary drainage via the urethra

Clinical Trial: An investigation into a novel surgical, medical, or other disease treatment that involves treatments that are at least as good as the standard-of-care for that disease. The most meaningful clinical trials are randomized, wherein patients are randomly assigned to treatment options. Some clinical trials are also “blinded” (where the patient and/or the physician are not notified of which treatment arm the patient is involved in)

Complexed PSA: PSA protein that is bound to specific proteins that circulate in the blood. The percentage of complexed PSA compared to total PSA may be a more specific indicator of prostate cancer than total PSA

Computerized Tomography (CT): A two-dementional x-ray which shows anatomic detail of soft tissue structures and can be used to evaluate for the spread of prostate cancer

Cryotherapy: The treatment of prostate cancer accomplished by placing probes through the skin, into the prostate to freeze the

cancerous tissue. This can be used as a first-line treatment or in cases where previous radiation treatments have not been effective. This treatment is associated with a relatively high rate of erectile dysfunction

Deltanoids: Vitamin D analogs that may be useful in the prevention or treatment of prostate cancer

Definitive Treatment: A treatment recommended with an intent to cure. Definitive treatments for prostate cancer include surgery, radiation, and cryotherapy.

Digital Rectal Exam: The process of examining the prostate. A clinician's finger is inserted into the patient's rectum whereby the back side of the patient's prostate can be felt. Nodules or lumps of the prostate can be a sign of prostate cancer, prostatic stones, or areas of asymmetric prostate cancer growth. A special reagent can also be used for check for blood in the gastrointestinal tract as part of the digital rectal exam

Dihydrotestosterone (DHT): A hormone made from testosterone which performs the same functions, but is considerably more potent than testosterone itself

Distal: Further from the center of the body

Downstaging: The process by which a detected cancer is made to be less extensive over time. This is usually accomplished by either by screening or prevention

Dutasteride (Avodart): A 5-alpha-reductase inhibitor that prevents the formation of dihydrotestosterone (DHT) from testosterone. This medication can be used to shrink the prostate and a similar medication has been used in experimental studies to prevent or treat prostate cancer

Erectile Dysfunction: The inability to produce or maintain an erection suitable for sexual penetration

External Sphincter: A voluntary muscle just below the prostate that eventually provides urinary control in men who have had their prostates removed. Women rely only on the external sphincter for urinary control.

Extracapsular: Disease that has spread beyond the capsule of the primary affected organ

False Negative: A negative test result in a patient who actually harbors the condition being evaluated

False Positive: A positive test in a patient who does *not* harbor the condition evaluated for by the test

Finasteride (Proscar): A 5-alpha-reductase inhibitor that prevents the formation of dihydrotestosterone (DHT) from testosterone. This medication can be used to shrink the prostate and has been used in experimental studies to prevent or treat prostate cancer

Fistula: An abnormal connection between two organs or an organ and the skin

Flavonoid: A naturally-occurring compound found in plant-based foods which appears to act as an antioxidant. Flavonoids are found in a variety of foods and beverages, including soy, cranberries, peanuts, apples, chocolate, tea and red wine

Flutamide (Eulixin): An anti-androgen given in combination with Leutinizing Hormone Releasing Hormone (LHRH) agonists at the initiation of treatment of advanced prostate cancer. Some practitioners continue this medication even after the first two weeks. Rarely, the medication is used without the injectable LHRH agonist

Free PSA: Circulating PSA which is unbound to serum proteins. In general, the lower the percent free PSA value, the higher the risk of prostate cancer being detected

Goserelin (Zoladex): An injectable LHRH agonist used to decrease PSA and the growth of prostate cancer. Side effects of LHRH

agonists include hot flashes, fatigue, occasional mental complaints and osteoporosis over time

Grade: Gleason sum assigned to a particular tumor reflecting the pattern visualized under the microscope by the pathologist which predicts tumor behavior. Gleason sum is a compilation of two numbers. Each number (1-5 scale) represents how typical (1) or aggressive (5) a tumor looks under the microscope. The sum of the two scores suggests the overall prognosis. A Gleason's sum of 2-6 represents cancers are considered low-grade and tend to behave very well (sometimes even without treatment), Gleason's sum 7 cancers are considered to be intermediate-grade and behave in a more aggressive fashion. Gleason sum 7 cancers are more likely to recur after definitive treatment and are more likely to spread or metastasize. Gleason's sum 8-10 cancers are considered high-grade or aggressive and are likely to recur after definitive treatment and are more likely to spread or metastasize

Histology: The evaluation of tissue under a microscope

"Hormones": A shorthand form of referring to androgen deprivation or the act of significantly decreasing circulating testosterone in the hopes of slowing the growth of prostate cancer

Impotence (erectile dysfunction): The inability to produce or maintain an erection suitable for sexual penetration

Incidence: The rate of new development of a particular disease over a particular period in time

Incontinence: The leakage of urine. In 15-20% of males who have undergone prostate removal, "stress incontinence" can be identified. Stress incontinence implies leakage with increased abdominal pressure (such as when lifting a heavy object or coughing), but rarely results in significant leakage amounts after prostatectomy

Internal Sphincter: An involuntary muscle located inside the central prostate that provides excellent urinary control in men with the prostate in tact. This muscle must be removed with prostatectomy

Isoflavones: A group of compounds found in soy and other foods being evaluated in the prevention and treatment of prostate cancer

Kegel Exercises: Contractions of the external sphincter muscle to improve urinary control

Laparoscopic: An approach to surgery that involves the use of tiny instruments on long handles to minimize external scars

Leutinizing Hormone Releasing Hormone (LHRH) Agonist: A medication given as an injection which suppresses testosterone in the hopes of slowing prostate cancer growth. Examples of LHRH agonists include Luprolide (Lupron/Eligard/Viadur) and Goserelin (Zoladex). LHRH agonists should always be started with a concurrent 2-4 week treatment with an oral anti-androgen

Leutinizing Hormone Releasing Hormone (LHRH) Antagonist: A new medication also given as a slow-release injection which decreases circulating testosterone, thereby decreasing PSA and possibly prostate cancer growth. Unlike LHRH agonists, his medication does not need to be taken with an oral anti-androgen upon treatment initiation

Localized: Confined to one area of the body

Luprolide (Lupron): An injectable LHRH agonist used to decrease PSA and the growth of prostate cancer. Side effects of LHRH agonsists include hot flashes, fatigue, occasional mental complaints and osteoporosis over time

Lycopene: An anti-oxidant occurring in reaonalbe levels in processed red tomatoes that may have a role in the prevention and treatment of prostate cancer; a type of carotenoid

Maligancy: Cancer

Malignant: Cancerous

Margin: The edge of the specimen that is removed surgically. In prostate cancer, when a positive margin is identified there is a 40%

chance that a patient will have a rise in his PSA following surgery when a positive margin is detected. This rate is less in patients who have only one area of positivity

Metastases: Areas of cancer detected outside of the primary cancerous organ. Surrounding lymph nodes and bones are common areas for prostate cancer metastases

Metastasize: The act of a primary tumor spreading to other organ systems

Monotherapy: A treatment given alone such as an anti-androgen medication given alone without other pharmacologic, surgical, or radiologic combination treatments

Nadir: The lowest point; generally used when referring to the lowest PSA value detected following radiation in prostate cancer

Neo-Adjuvant (therapy): A therapy given before the primary therapy (generally in the hopes of improving outcome)

Palliative Care: Palliative treatment or care given without the hope for cure, but with the intent of improving the quality of life in a patient with incurable disease

Palpate: To feel with one's hands

Pathology: The microscopic evaluation of an abnormal tissue under a microscope

Perineum: The anatomic location between the scrotum and anus

Placebo: A treatment (generally used in a study) that has no active ingredients. Placebos are used to help produce a more accurate assessment of how well the actual treatment is working

Posterior: The back side of an object, behind

Prevalence: The rate of the development of a disease over a given period of time relative to the population at risk for development of the disease

Pro-PSA: A PSA precursor that may be a more specific indicator of prostate cancer than total PSA

Prognosis: Expected outcome from a given condition

Prospective Trial: A trial that is designed prior to initiation of the study

Prostate: A gland that is used in sexual reproduction. The prostate provides over 90% of the fluid content of male semen and assists sperm in reaching the fallopian tube and egg

Prostate Specific Antigen (PSA): A protein made by the prostate that can correlate with the presence of prostate cancer. PSA is made in the prostate and increases with prostate growth, prostate cancer, and prostate irritation

Prostatectomy: The process of removing the prostate and attached seminal vesicles from its attachments to the bladder, urethra, and vas deferens and reconnecting the bladder to the urethra

Prostatic Intraepithelial Neoplasia (PIN): Microscopic diagnosis that may be an indicator of prostate cancer elsewhere in the prostate or may be a precursor to the development of prostate cancer. Most clinicians recommend a repeat prostate biopsy when PIN is detected on initial biopsy, as the rate of finding cancer on repeat biopsy is as high as 50%

Proximal: Closer to the body's center

PSA Velocity: The change in PSA over time. A PSA velocity of less than 0.75ng/ml per year is much less concerning than a velocity of 0.75ng/ml per year or greater

Screening: The process of attempting to find a disease prior to its symptomatic manifestation in the hopes of improving disease outcomes

Selenium: A trace mineral that may be helpful in stimulating the formation of antioxidants which are helpful in prostate cancer prevention. Animals that eat grains or plants that are grown in selenium-rich soil have higher levels of selenium in their muscle. Grains are also a source of selenium and Brazil nuts are known to be an excellent source of the mineral

Semen: Ejaculatory fluid made up of prostatic secretions (90%) as well as sperm (10%)

Seminal Vesicles: Fluid-filled sacks on the back surface of the prostate that contribute additional fluid to the ejaculate. Invasion of prostate cancer into these structures suggests a higher stage of disease and may portend a worse prognosis

Sensitivity: The ability of a screening test to detect disease if it is present. Tests with high sensitivity have a low false negative rate

Serum: Liquid portion of blood

Specificity: The ability of a positive test to accurately diagnose disease. Tests with high specificities have a low false positive rate

Sperm: Very tiny cells with a propulsive tail containing genetic information. Sperm establish a full set of genetic information when combined with an egg

Sphincter: A circumferential muscle. In the urethra, the sphincter(s) control urinary flow. In the male, one sphincter is internal or inside the prostate and does not require voluntary control the other is outside the prostate and requires some voluntary signaling for control, but can get stronger over time

Spinal Cord Compression: The collapse of the vertebral bones resulting in pressure on the spinal cord. Neurological symptoms such as paralysis, inability to empty one's urine or bowel contents can be

the result of spinal cord compression. This condition is increased with vertebral metastases

Stage: A measurement of the extent of a given cancer. Generally clinical stage estimates how extensive a cancer is based on physical exam and xrays, while pathological stage evaluates the extensiveness by microscopic evaluation. In general the more advanced the stage the worse the expected prognosis

Systemic: Throughout the body

Ureter: Tubular structure used to transmit urine from the kidney to the bladder

Urethra: Tubular structure used to drain urine from the bladder. The prostate surrounds the urethra at the base of the bladder

Vas Deferens: A thin tube connecting the testicle to the prostate in order to facilitate sperm deposition into seminal fluid

Vertebra: The bones that surround and support the spinal cord and allow for support and flexibility of the back

Information About Prostate Cancer

Prostate Cancer Prevention

Many studies have been done to evaluate the possibility of preventing prostate cancer. A large United States study recently evaluated the effect of Finasteride (Proscar) on the development of prostate cancer. This study involved nearly 19,000 men and found that when this medication taken daily for 7 years, it decreased the incidence of prostate cancer from 24.4% to 18.4%. The medication studied decreases the production of dihydrotestosterone (DHT), the most potent form of testosterone. Patients on finasteride frequently experience a shrinkage of the prostate gland, which can improve urinary voiding symptoms, but also may cause sexual dysfunction in a small proportion of men as well. Additionally, in this study, prostate

cancers that developed in the men taking Finasteride appeared to be slightly more aggressive than in the men taking placebo [1].

Soy is currently being evaluated in the prevention of prostate cancer. Prostate cancer prevalence is significantly lower in Asian men, particularly those who consume a high-soy diet. Soy is thought to be a naturally-occurring 5-alpha reductase inhibitor [2].

Selenium and vitamin E have both been seen to decrease the incidence of prostate cancer in studies evaluating the effect of these supplements on lung cancer [3,4]. Prospective evaluation of the effect of selenium and vitamin E on the development of prostate cancer is currently underway.

Lycopene, an antioxidant found in processed red tomatoes (in addition to other sources) has also shown some anti-tumor activity and is actively being studied in the prevention and treatment of prostate cancer [5].

The correlation between testosterone levels, obesity, and prostate cancer is still being investigated. While traditional studies have shown testosterone stimulates the growth of prostate cancer, recent studies indicate *low* testosterone may be a risk factor for prostate cancer. Some speculate low testosterone may mask prostate cancer by keeping BPH (benign prostatic hypertrophy) to a minimum and thereby suppressing the baseline PSA [6]. Some studies even show that those cancers found in men with low testosterone levels may be more aggressive than those in men with normal testosterone [7]. There are many studies that show no link between obesity and prostate cancer, but others find that obese men who develop prostate cancer have a worse outcome [8]. This may be secondary to increased positive surgical margins (with more difficult surgery) or because of a relative decrease in circulating testosterone (heavier patients make more proteins that bind to testosterone, making it less active) [9]. Studies are ongoing evaluating the signaling cascades induced by some of the agents felt to be active in prostate cancer as well as genetic combinations that may make some individuals more prone to the development of prostate cancer [10-15].

Screening for Prostate Cancer

PSA became approved by the United States' Food and Drug Administration in 1986 to follow patients who had developed prostate cancer and in 1994 to screen for prostate cancer. The rate of mortality (or death) from prostate cancer has declined from 41,000/year in 1996 to under 32,000/year in 2000 with the use of PSA and prostate cancer screening [16]. Cancers that are detected with PSA screening are smaller, with less likelihood of spread to other organs or outside the prostate than cancers detected before PSA screening. In 1986, 2/3 newly diagnosed prostate cancers were metastatic (40%) or extracapsular (25%) [17, 18], whereas in 2003, only 2-4% of newly diagnoses prostate cancers were metastatic and only 1/3 were large, locally extensive, or of high grade [19, 20]. This effect is called downstaging. Unfortunately, however, PSA screening has not resulted in fewer low-grade cancers. Approximately 15% of cancers are found to be high grade cancers (Gleason's sum 8-10) with or without screening. This may be due to inherent genetic potential of these tumors [21].

The current recommendations by the American Urological Association are that men over 50 have a PSA test and digital rectal exam annually if a patient has no family history of prostate cancer or African-American heritage. Men who do have a family history or prostate cancer or African American heritage should begin the same screening regimen at age 40.

Although PSA is not perfect (15% of patients with a PSA in the normal range were found to have prostate cancer on biopsy in one recent study [1], advances have been made to improve the sensitivity and specificity of PSA. By lowering the threshold of PSA to 2.5 (especially in relatively younger men), the sensitivity of PSA is improved and fewer false negatives are seen [22]. Similarly, by using the percentage of free PSA (that which is unbound to other proteins in the blood), complexed PSA (that which is bound to only certain proteins in the blood), or pro-PSA (a precursor protein to PSA) the specificity of PSA can be improved thereby decreasing the amount of unnecessary biopsies are performed on men who do not have prostate cancer [23].

Although it has yet to be proven definitively that screening for prostate cancer improves an overall mortality, it has been clearly shown that over 50% of patients with low-grade, organ confined prostate cancer develop metastases at 15 years if no treatment is undertaken [24]. Additionally, it has been shown that death from prostate cancer and the development of metastases (or spread) from prostate cancer is considerably less when surgical treatment is performed for prostate cancer as opposed to watching the cancer [25].

Different laboratories use different antibodies to detect PSA levels. Some lab antibodies are more sensitive than others, so it is recommended to have the same lab monitor PSA values over time [26]. Additionally there are some studies that show PSA values may change following sexual activity so it is also recommended to abstain from sexual activity for 24 hours prior to a PSA blood draw for the most accurate results [27]. It was also previously thought that a digital rectal exam could raise the serum PSA value, although most feel this increase is probably not of statistical significance.

The recommended progression for patients with an elevated PSA is to proceed with an ultrasound-guided prostate biopsy of the prostate if the patient's life expectancy exceeds ten years.

Staging Prostate Cancer and Predicting Prognosis

One of the first factors to consider after a diagnosis of prostate cancer is established is the aggressiveness of the tumor. Aggressiveness or grade of prostate cancer is measured on a 10 point scale. This aggressiveness is determined on microscopic evaluation of the biopsy cores and is made up of two numbers, each representing the most common patterns of cancer seen microscopically. This Gleason's sum correlates well with prostate cancer prognosis. In general, a Gleason's sum of 2-6 is thought to represent a low-risk cancer, a Gleason's sum of 7 cancer represents a cancer of intermediate risk, and a cancer graded with a Gleason's sum of 8-10 represents high-risk disease.

In addition to microscopic grading, it is also important to understand the extent (or stage) of prostate cancer. Staging is generally performed by physical exam (digital rectal exam). The stages that

can be detected on physical exam are stage T1, T2 and rarely stage T3b. A stage T1 cancer is a cancer that is not evident on digital rectal exam. A T2 cancer is a cancer that can be felt on digital exam, either on one side (T2a) or both sides (T2b of the prostate). And, although rare, a T3b cancer is one that feels as though it invades the seminal vesicles, or fluid-storing sacks on the back of the prostate. In addition to local staging within the prostate, an effort is also made to stage the extent of prostate cancer outside of the prostate as well. The most frequent areas of prostate cancer spread (or metastasis) are to the surrounding lymph nodes (which are not able to be felt from outside the body) and bony skeleton. For patients with high-grade or clinically high-stage disease, a clinician may recommend a CT (computerized tomography) or bone scan to evaluate for external spread. These are generally not considered necessary in patients with low-risk disease. In patients who undergo surgery for prostate cancer (prostatectomy) the clinical stage is replaced by a more accurate pathological stage. With careful microscopic examination, the exact extent of the cancer can be identified.

PSA and percentage of biopsy cores found to harbor cancer are also important prognostic variables predicting prostate cancer outcome. In general, PSA values less than 10ng/ml indicators of lower-risk disease, PSA values between 10-20 ng/ml are indicators of intermediate-risk disease, and PSA values higher than 20 are indicators of high-risk disease. In addition, if less than a third of all biopsy tissue submitted for microscopic review harbors cancer, the cancer is predicted to be of lower risk, if between 33 and 50% of the submitted tissue harbors cancer the disease is felt to be of intermediate risk, and if greater than 50% of the tissue submitted contains cancer, the cancer is considered higher risk.

Many tables and configurations have been developed that attempt to account for these four independently predictive variables and predict prognosis (tumor stage, grade, PSA and percentage of biopsy cores positive). In general, patients with low-risk features by all four measures are candidates for all treatment options (including watchful waiting in older patients, surgery, radiation including radioactive seed placement (or brachytherapy), as well as cryotherapy (or freezing). Patients considered intermediate risk are generally counseled against watchful waiting (if a 10-15 year life expectancy is predicted) or

brachytherapy (which does not appear to work as well as a solitary treatment in intermediate- and high-risk cancer). Finally, men with high-risk disease should understand that they have significant innate risk of cancer recurrence after treatment and that multiple types of treatments may be necessary. Additionally, these men may want to consider enrollment in clinical trials investigating more effective first-line therapies for high-risk prostate cancer.

The most recent data to be added to this prognostic armamentarium for prognostication is that of the PSA doubling time. This number can be calculated using several PSA values over time and gives one an idea of how rapidly the cancer volume (reflected by PSA) is doubling. Patients with a PSA doubling time of less than 6 months are also considered high-risk and may also wish to consider systemic therapy or participation in experimental protocols [28].

In general, once prostate cancer has spread outside the prostate, it is generally felt that the cost of localized treatment does not improve survival enough to justify its risks. A recent retrospective study questions this dogma and suggests localized treatment even in patients with metastatic disease may prolong survival [29].

Surgery and Prostate Cancer

Surgery was the initial treatment described for prostate cancer and continues to be the option chosen by most men with prostate cancer [30]. Although other treatment options may have similar cure rates to surgery, no other treatment has ever proven to be superior to surgery for controlling prostate cancer.

The benefits of surgery include: complete pathological staging, with no need to administer hormones (or androgen deprivation) prior to surgery, the possibility of effective, low-risk treatments in follow-up if prostate cancer recurs after surgery, a straight-forward follow-up for cancer following treatment, a relatively low rate of erectile dysfunction with treatment, and the absence of inducing additional cancers in surrounding organs with treatment. In general, surgical treatment for low-risk prostate cancer yields a 94% 10-year disease-free survival, a 70-85% 10-year disease-free survival for intermediate-risk prostate cancer (Gleason's 3+4 cancers perform more favorably than Gleason's 4+3 cancers) and a 10-50% 10-year disease-free survival

for high-risk prostate cancer (with stage being the most significant driver of relapse in this setting) [31]. If a cancer recurs following surgical treatment for prostate cancer, radiation can be performed with cure of the recurrent disease in approximately 45% of patients. This outcome is optimized when PSA values are below 1-2 ng/ml and are not rising rapidly, and when there is no evidence of disease outside of the pelvis. Post-operative radiation appears to work better in patients with positive surgical margins, a PSA that rises slowly at least one year following surgery, and in patients who did not have evidence of cancer invading the seminal vesicles at the time of surgery [32]. In general, there appears to be no difference in the quality of life in patients who undergo radiation and those who do not following surgery for prostate cancer [33].

The nerve-sparing approach to prostatectomy has improved the rate of erectile dysfunction dramatically following surgery. The rate at one year of erectile dysfunction following surgery in one specialized study was only 16.5% in men with both neurovascular bundles spared and 37.2% in men with only one bundle spared at the time of surgery. Importantly, positive margin rates (suggesting that cancer may be left behind) is *not* more common in men undergoing the nerve sparing procedure than in those where the neurovascular bundles are removed with the prostate [34]. Additionally, the rate of total incontinence in modern series is reported to be less than 1% where the risk of stress incontinence (minor leakage with coughing or lifting) approximates 20% [35]. Patients with difficulty urinating because of a large prostate are commonly cured of this condition (BPH) as well as of their prostate cancer with surgery.

Surgery can be performed laparoscopically (with small instruments) as well as through a small incision above the pubic bone. Again, this approach has never been shown to be more effective than traditional surgery although studies with relatively short follow-up show that the results may be similar [36]. With laparoscopic surgery an incision large enough to remove the prostate (2-3 inches) is still required to remove the prostate after it has been dissected from the body. Laparoscopic surgery may be performed with or without the assistance of an operating robot.

The usual hospital stay following traditional or laparoscopic radical prostatectomy is 1-2 nights. A catheter is left in place while the connection between the bladder and the urethra heals for 7-14 days. Continence slowly improves as a patient learns to rely on his external sphincter since the internal sphincter required removal with the surgery. Most patients are dry or have a tolerable amount of leakage at 8-12. Most patients begin treatments with Viagra or another similar medication around this time to encourage erections if they have not already occurred spontaneously. Erectile function continues to improve for 6-12 months following surgery.

The most important factor to consider when evaluating surgery as an option for prostate cancer is the surgeon to perform the prostate removal. Studies have clearly shown that those surgeons more experienced with a particular operation are more likely to have positive outcomes [37].

Radiation and Prostate Cancer

Radiation is another viable treatment option with the potential for cure for patients with prostate cancer. Radiation can be given externally or internally (with the surgical placement of radioactive seeds that release radiation over time). External beam radiation is generally given daily during the weekdays over a 6-7 week treatment course. Since radiation can cause damage and cancerous changes to other organs over time, the more exact the placement of the radiation treatments, the fewer side effects a patient will experience. In general, androgen deprivation (usually accomplished with an injection with or without accompanying oral tablets) should be used in conjunction with (and usually beginning a few months before) external beam radiation. Many studies have shown an improved survival when these two treatment modalities are used in combination [38-43]. It is thought that androgen deprivation may help sensitize cancer cells to the effects of radiation. Unfortunately, androgen deprivation can cause long-lasting problems with erections in a small percentage of patients even after treatment is over [44], as can radiation (generally found to be 50% with external beam radiation).

Brachytherapy (or “seed” radiation) is recommended for patients with low-risk prostate cancer and can be used without the need for concurrent androgen deprivation. Brachytherapy studies have shown

similar cancer control rates to external beam radiation or surgery in patients with low-risk disease [45]. Brachytherapy initially appeared to have a less damaging effect on erectile function than surgery or external-beam radiation [46]. However, long-term results suggest that all three modalities may have a similar effect on erectile function [47].

Although total incontinence is not seen following treatment with radiation, patients can suffer from urinary frequency from bladder irritation or difficulty voiding secondary to the inflammation of the prostate around the urethra with treatment. It is advised that patients with extreme difficulty emptying their bladders should not undergo treatment with brachytherapy unless they are counseled that catheterization may be required (at least temporarily) [48].

The risk of incontinence in patients requiring removal of obstructing tissue after brachytherapy may be increased over those who have not had brachytherapy [*]. The risk of the development of secondary cancers from radiation is difficult to evaluate since these cancers can appear years to decades after radiation treatment. One study estimates the risk of bladder cancer in the adult population to be 3% and states that this may reach 5% in patients who have undergone pelvic irradiation [49].

There are many long-term studies reporting the results of external beam radiation (EBXRT) for prostate cancer. One study finds the 10-year disease-free recurrence rate for patients with low-risk disease is 54% following EBXRT, while this rate is 42% for patients with intermediate-risk disease, and 40% for patients with high-risk disease. Clinical studies are ongoing to find biological markers to predict who may best respond to radiation [51, 52].

A recurrence of prostate cancer in patients who have undergone radiation is sometimes difficult to detect as PSA values can fluctuate after treatment (particularly after brachytherapy). After radiation, PSA can also take a year or longer to decrease (or nadir), and values other than zero (or undetectable) may still not imply cancer. The accepted definition of radiation failure is 3 consecutive rises in PSA values separated by at least a month. Although prostate biopsies can still show false positive results within two years of treatment with

radiation therapy, the recommended evaluation for a continually increasing PSA following radiation is prostate biopsy.

Although surgery is more difficult following radiation, in patients who fail treatment with radiation, surgery can be offered with an up to 66% cure rate and up to a 66% continence rate at some centers[53]. Cryotherapy is another salvage treatment for patients who have failed radiation and appears to have similar cancer control rates to surgery – at least in the short term [54]. Androgen deprivation can also be offered in this setting although without curative intent.

Cryotherapy and Prostate Cancer

Cryotherapy has undergone significant evolution since its initial use in the 1960's. The use of transrectal ultrasound monitoring, temperature-sensing thermocouples, and a urethral warming device has significantly reduced the risk of recto-prostatic fistulae (unintended connections between the urethra and rectum), stress urinary incontinence, and urethral obstruction or sloughing. Permanent erectile dysfunction rates, however, remain in the 85-96% range [55,56].

The data remain immature regarding the long-term efficacy of cryotherapy. Short-term data, however, suggest that cryotherapy may have cure rates near that of surgery or radiation. Cryotherapy, as mentioned above can also be used in cases where cancer has recurred following radiation [57].

Cryotherapy is performed in the operating room but patients are discharged home following the procedure. A tube is generally placed into the bladder at the time of surgery to allow urine to pass while the swelling of the prostate from treatment resolves. This tube is generally in place for 10-14 days. Stress incontinence is seen in 1-6% of patients, rectal pain is experienced by 10-30% of patients. Cancer recurrences have been seen in 30% of patients at nine months (when patients with all grades of cancer, PSA and Gleason scores are considered, as well as those who are treated following radiation failure) [56]. In general, PSA values that fall below 0.1ng/ml following cryotherapy are more likely to predict a disease-free status.

Hormones (Androgen Deprivation), Bisphosphonates, and Prostate Cancer

Androgen deprivation is generally used for palliative care in patients with prostate cancer. Testosterone excels the growth of prostate cancer and very low levels of testosterone can slow the growth and drop a patient's PSA. Traditionally this was accomplished by orchiectomy (a surgical procedure whereby the testicles are removed) however, the same effect can now be accomplished by injections and/or oral tablets.

Injectable agents, in general, are classified as leutinizing-hormone releasing hormone (LHRH) agonists. These alter the signal that causes testosterone to be produced and are available in intramuscular injectable, subcutaneous pellet, and subcutaneous depot form and are given at monthly, quarterly, or triannual intervals. The main side effects of LHRH agonists include hot flashes and erectile dysfunction. Additional complaints include fatigue, mental status changes, decreased muscle mass and increased body fat, as well as osteoporosis with extended usage. Despite these drawbacks, many patients tolerate LHRH agonist therapies for many years without difficulty.

Oral medications called anti-androgens block any testosterone that is circulating in the bloodstream. And can be taken with injectable LHRH agonists, at the initiation of LHRH agonist treatment, or alone. The advantage of the combination with LHRH agonists is real, but small and can be costly in terms of side effects and financial cost [58]. Anti-androgens should always be used at the initiation of LHRH injections as LHRH agonists can cause a flare in the serum testosterone which can have significant negative effects. Some studies have evaluated anti-androgens alone, as this regimen has no complications of osteoporosis, no complications of mental status changes or increased body fat composition, and a significant less proportion of erectile dysfunction. However, this medication, when used alone, can cause significant irreversible breast growth and tenderness. Most doctors prescribe a short-course of pre-treatment breast radiation before beginning anti-androgen monotherapy to attempt to avoid this complication, which has been documented to be helpful in this arena [59]. Although some studies show promising

results with anti-androgen monotherapy [60], most data suggest it is not as beneficial as LHRH agonist therapy [61].

A new medication was introduced in 2004 which is considered an LHRH antagonist. This is also an injectable agent and does not require the initial concomitant 2-week treatment with anti-androgen medication. The side effects are similar to those of LHRH agonists.

Current international prospective trials are currently evaluating androgen deprivation given on an intermittent schedule in the hopes to improve outcome and decrease side effects. Although side effects do appear to be lessened with intermittent androgen deprivation, no studies have shown an improved outcome from a cancer standpoint [62].

A form of androgen deprivation (usually LHRH agonist treatment alone) should always be used with external beam radiation. Several studies have shown this to improve outcomes significantly [63,64,65,66]. On the other hand, androgen deprivation prior to surgery does not appear to improve the ultimate outcome and is generally not recommended [67,68]. Most agree that androgen deprivation is also not required with brachytherapy or seed placement for low-grade disease of the prostate. Data is still being evaluated for the benefit of androgen deprivation and cryotherapy.

There has been no proven survival advantage for beginning androgen deprivation earlier rather than later if a patient's PSA begins to rise following definitive treatment for prostate cancer [69]. However, studies do show that for those men diagnosed with prostate cancer in the lymph nodes at the time of surgery, immediate and continuous androgen deprivation improves survival. Additionally it has been shown that earlier androgen deprivation may improve urinary symptoms and decrease rare complications of prostate cancer such as kidney failure from blocked ureters or spinal cord compression from vertebral fractures [70].

Bisphosphonates are inhibitors of the cells which break down bones and are frequently used to treat osteoporosis. A potent new intravenous bisphosphonate has been studied in men with metastatic prostate cancer to the bones and these studies show that clearly,

intravenous bisphosphonates (zoledronic acid or zometa) given regularly can decrease the risk of bony fractures from these metastases [71,72]. Bisphosphonates should be considered in men with evidence of osteoporosis or metastatic disease. The diagnosis of osteoporosis should be investigated in men maintained on androgen deprivation for over 2-3 years.

Androgen Independent Prostate Cancer and Clinical Trials

Once a patient has been on androgen deprivation treatment for an extended period of time, prostate cancer tends to progress in spite of androgen deprivation. In this scenario, blood levels of testosterone are verified to be low and anti-androgen tablets are added if they have not been used in the past. If a patient has been taking anti-androgen tablets, these are discontinued, as rarely anti-androgen tablets can serve to increase the activity of an androgen receptor. Once these conservative measures have been tried, a patient is considered to have “androgen independent or insensitive prostate cancer.” This condition is also referred to as hormone refractory prostate cancer. Certain chemotherapeutic combinations have been shown to improve survival in androgen independent prostate cancer, such as docetaxol and estramustine [73]. Mitoxantrone and prednisone has also been used in this setting and has been shown to improve the quality of life in patients with this condition. A large multinational trial is evaluating this combination given prior to the development of androgen independent disease in patients with high risk features in the hope to improve overall survival from prostate cancer.

Estrogen can also be tried in patients with prostate cancer which is progressing despite the use of traditional androgen deprivation, or can even be used prior to the development of androgen independence, but should be used carefully due to the increased risk of blood clots if given alone and/or in high doses [74]. Since none of these options provide a dramatic improvement in outcome and since many are difficult treatments to tolerate, many clinical trials continue to investigate the best treatment option for patients with this condition. Since no clinical trial includes any therapy that is thought to be worse than the standard of care, clinical trial participation is encouraged to provide for possible improved outcomes in patients

with a given condition as well as future patients who may develop the condition.

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