PROSTATE CANCER is the most common cancer in men, with 233,000 new cases diagnosed per year. Although prostate cancer remains the second leading cause of cancer death in men, mortality rates have declined by nearly half since the early 1990’s. The reduction in mortality is attributed to both early detection and advances in multidisciplinary treatment. In this publication, prostate cancer specialists at Good Samaritan Hospital Medical Center review recent topics in the diagnosis and management of prostate cancer.

SCREENING
Prior to the development of prostate specific antigen (PSA) testing, prostate cancer was typically diagnosed based on abnormal digital rectal examination or with a history of increasing urinary symptoms. Since neither approach is sensitive or specific, the majority of prostate cancers presented at locally advanced or metastatic stage. PSA, a convenient blood test, emerged as a more sensitive and specific prostate screening tool. Benign causes of PSA elevation include benign prostatic hyperplasia, prostatitis, recent ejaculation or pelvic trauma, including recent digital rectal examination. A PSA cutoff level of ≥4.0 ng/ml is associated with a sensitivity of 21%, specificity of 91% and a positive predictive value of 30%. For PSA values ≥10 ng/ml, the positive predictive value exceeds 50%.

HIGHLIGHTS
• The lifetime risk of developing prostate cancer is 1 in 6.
• Prostate cancer mortality in the U.S. has decreased by 46% since 1992.
• Although controversial, PSA screening in men aged 55 to 74 with an estimated life expectancy of >10 years reduces the risk of prostate cancer death by approximately 20%.
• Appropriate selection of patients for either active surveillance or immediate treatment is necessary to reduce the risk of treatment morbidity in favorable risk patients.
• For intermediate to high risk patients, immediate treatment with either surgery or radiation therapy reduces the risk of distant metastasis and prostate cancer death.
• Recent technological advances, including daVinci® Robotic-assisted prostatectomy and Varian TrueBeam™ image-guided radiation therapy offer promise of reduced toxicity in patients requiring treatment.
• For patients with locally advanced or metastatic cancer, significant improvements in systemic therapy have further improved overall survival.
The best evidence supporting use of PSA screening comes from the European Randomized Study of Screening for Prostate Cancer. The European study randomized 182,160 men age 50 to 74 to PSA screening every two to four years vs. usual care. PSA screening was associated with a 26% increase in the diagnosis of prostate cancer (8% with screening vs. 4.8% with usual care) and a 21% reduction in prostate cancer death. Since prostate cancer death was relatively uncommon, there was no improvement in overall survival and 1,055 men would need to be screened and 37 prostate cancers would need to be diagnosed to prevent one death from prostate cancer. Importantly, PSA screening reduced the incidence of advanced stage tumors (T3 to T4) by 35%, incidence of high grade tumors (Gleason 8 to 10) by 27% and metastatic disease by 51%. Despite concerns of increased toxicity associated with increased biopsy rates and potential overtreatment of prostate cancers with an indolent natural history, screening for prostate cancer was associated with a net gain in quality adjusted life years.

Adding to the controversy are the negative results from the Randomized Prostate, Colorectal and Ovarian Cancer Screening Trial. The US trial randomized 76,685 men age 55 to 74 to annual PSA screening for six years vs. usual care. The validity of these results was compromised because 85% of the usual care group received at least one PSA test. Although there was no evidence of benefit for screening for the overall population, there were fewer prostate cancer deaths among patients with no or minimal comorbidity.

The American Urological Association recommends shared decision-making for men aged 55 to 69 who are considering PSA screening and proceeding based on the patient’s values and preferences. PSA screening can be performed every two years. Selected men over the age of 70 in excellent health are also potential candidates for screening due to life expectancy of >15 years. Despite the limitations of PSA screening that are now well documented, screening remains the most effective strategy to reduce the risk of prostate cancer mortality.

**PREVENTION**

The lifetime risk of prostate cancer in the US is one in six men. Finasteride, which is a 5α-reductase inhibitor that is used to treat benign prostatic hypertrophy and to prevent male pattern baldness, has been shown to reduce the incidence of low risk prostate cancer (Gleason ≤6). However, finasteride slightly increased the risk of Gleason 7 to 10 prostate cancer and failed to improve overall survival. Prior randomized studies showed that dietary supplementation with selenium failed to reduce the risk of prostate cancer and vitamin E (400 IU/day) actually increased the risk of prostate cancer.

Family history and an African American genetic background are associated with an increased risk of prostate cancer. Patients diagnosed with prostatic intraepithelial neoplasia have a 35% risk of subsequently developing prostate cancer. Strong consideration of PSA screening is recommended for patients at increased risk of prostate cancer. Recently, BRCA mutation has been shown to increase the risk of high-grade prostate cancer.

**DIAGNOSIS AND STAGING**

Patients with suspicion of prostate cancer based on elevated PSA, abnormal digital rectal examination and/or rising PSA undergo

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**TABLE 2**  Estimated Life Expectancy for Men Based on Age and Health Status

<table>
<thead>
<tr>
<th>Age</th>
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transrectal ultrasound-guided biopsy. Typically 12 cores are taken for analysis. Clinical tumor staging is based on digital rectal examination. Patients with no palpable prostate tumor are T1. Patients with a tumor limited to the prostate are T2. Patients with extension beyond the prostatic capsule or seminal vesicles are T3 and invasion or fixation of the bladder, levator muscles or pelvic wall are T4.

For patients with prostate cancer, pre-treatment PSA, Gleason score and tumor stage are the primary factors analyzed. Additionally, PSA velocity and percentage of positive cores are factors that further inform the clinician regarding the natural history of the patient’s tumor and disease burden. Bone scan and pelvic CT or MRI are indicated only for patients with a high risk disease. Multiparametric MRI, consisting of fused T2, diffusion weighted imaging and dynamic contrast enhancement, has recently emerged as a specific test to identify clinically significant dominant lesions in the prostate. Additionally, MRI offers superior visualization of the prostate allowing for more accurate target delineation for radiation therapy planning.

### active surveillance

An estimated 20 to 40% of patients diagnosed with prostate cancer have an indolent form of the disease. Unnecessary treatment in this population results in a risk of treatment-related morbidity that can negatively impact quality of life. The challenge for the astute clinician is to identify cohorts of patients that are suitable candidates for active surveillance, which is the standard of care for very favorable risk prostate cancer. Patients with favorable risk disease are excellent candidates for active surveillance if they have low volume disease on biopsy (<1/3 positive cores) and slow PSA velocity (PSA increasing < 2.0 ng/ml per year). Selected patients with intermediate risk disease are candidates for active surveillance, particularly if the pretreatment PSA is less than 10 ng/ml, rectal examination is normal and multiparametric MRI demonstrates no dominant lesions. The primary advantage of active surveillance is the ability to avoid or delay toxicity associated with treatment in patients at low risk of progression and metastasis. However, 40 to 60% of patients managed with active surveillance eventually require treatment. A patient may continue on active surveillance unless PSA doubling time is < 3 years, PSA remains less than 10 ng/ml, rectal examination remains normal and there continues to be low volume Gleason 3+3 or Gleason 3+4 disease.

Two randomized trials inform the clinician on specific subgroups of patients that benefit from immediate treatment instead of active surveillance. The Swedish SPCG-4 trial compared watchful waiting to immediate treatment with radical prostatectomy for men predominantly diagnosed with an abnormal rectal examination. Immediate treatment significantly reduced the risk of death from metastatic prostate cancer at 15 years from 21% to 15%, which translated into improved overall survival. However, the benefit was predominantly seen in patients who were younger than 65 years of age. A more recent PIVOT study compared watchful waiting to immediate treatment with radical prostatectomy in men who underwent PSA screening and were treated in Veterans Administration Hospitals that underwent PSA screening. Although there was no significant difference in death from prostate cancer in the overall population, subgroup analysis demonstrated a ≥50% reduction in prostate cancer...
deaths in patients with a pretreatment PSA > 10 ng/ml and for patients with high risk disease. Therefore, unless life expectancy is <10 years, immediate treatment is recommended for most patients with an abnormal digital rectal examination, PSA >10 ng/ml, Gleason 4+3=7 or Gleason 8 to 10 disease.

TREATMENT OF PROSTATE CANCER

There is no available high quality data from randomized trials comparing surgery, radioactive seed implantation or intensity modulated radiation therapy (IMRT). However, the consensus from comparative retrospective series is that all three modalities are equally effective at achieving biochemical control and prostate cancer specific survival. The five-year biochemical control is 95% for low risk patients, 85% for intermediate risk patients and 50 to 70% for high risk patients. Based on patient-reported comparative series, surgery, seed implant and IMRT have different toxicity profiles, which often drives clinical decision making. In general, radical prostatectomy results in a higher rate of urinary incontinence and erectile dysfunction while seed implantation and IMRT are associated with higher rates of rectal bleeding and bowel urgency. At Good Samaritan Hospital Medical Center, treatment decisions are based on published evidence and national guidelines.

RADICAL PROSTATECTOMY

Minimally invasive or robotic-assisted radical prostatectomy has supplanted open radical prostatectomy as the standard surgical option for prostate cancer. Compared to open prostatectomy, minimally invasive or robotic-assisted surgery decreases the perioperative complication rate and length of stay. High volume minimally invasive or robotic-assisted surgery programs, such as Good Samaritan Hospital Medical Center, are associated with lower rates of surgical complications and treatment failure compared to less experienced programs. Men younger than age 70, especially men younger than 60, are typically selected for surgery. When technically feasible, nerve-sparing prostatectomy is performed to reduce the risk of erectile dysfunction. Recent technical advances, such as urethral sphincter and bladder neck preservation offer promise of reduced risks of anastomotic stricture and long-term urinary incontinence.

Risks of surgery include intraoperative bleeding and recovery following surgery. With respect to complications, patients undergoing prostatectomy typically have significant urinary incontinence for the first two months after surgery. Although most men recover urinary continence, 10 to 16% of men report frequent urinary leakage at two years. Men treated with surgery have improvement in long term of symptoms or urinary irritation or

![Figure 1. IMRT prostate plan and dose volume histogram demonstrates excellent coverage of the prostate (star) and proximal seminal vesicles with selective sparing of rectum, bladder, femoral heads and penile bulb on axial and sagittal views.](Image)

![Figure 2. Cone beam CT performed immediately before treatment (right) corrects for daily changes in rectal and bladder filling compared to during simulation (left).](Image)
obstruction compared to baseline. At two years, 51 to 79% of patients report erections insufficient for intercourse. Patients treated with prostatectomy have no significant bowel toxicity with only 2 to 14% of patients reporting bowel urgency.

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**INTENSITY MODULATED RADIATION THERAPY**

Image-guided intensity modulated radiation therapy (IMRT) has replaced three-dimensional conformal radiotherapy as the standard approach to external beam radiotherapy for prostate cancer. Recent randomized trials demonstrated significantly improved biochemical control for high dose radiotherapy (78 to 79.2 Gy) vs. low dose radiotherapy (68 to 70.2 Gy). Intensity modulated radiation therapy allows for safe dose escalation by reducing radiation dose to the rectum, bladder and penile bulb. IMRT has been shown to reduce the risk of rectal bleeding and late urinary toxicity. Good Samaritan physicians published the first study using IMRT to spare the penile bulb to reduce the risk of erectile dysfunction, which is currently a standard approach. For patients with high risk disease, combined prostate radiotherapy and long-term androgen ablation improves 10-year biochemical control (75% vs 26%, p<0.001) and overall survival (70 vs 61%, p<0.05) compared to androgen ablation alone. Finally, in patients undergoing prostatectomy with positive margins, prostate capsule invasion or seminal vesicle involvement, adjuvant radiotherapy improves biochemical control and survival. For patients undergoing prostatectomy who present with a PSA >0.2 ng/ml, salvage radiotherapy should also be considered.

The primary disadvantages of IMRT are length of treatment (eight to nine weeks) and cost. Another potential disadvantage of radiotherapy for men younger than 60 is the small risk of second malignancies in the rectum and bladder. However, IMRT is non-invasive thus avoiding the risks of surgery and anesthesia. In terms of complications, 51 to 60% of patients report erections insufficient for intercourse at two years. The rate of frequent urinary leakage at two years is two to seven percent. However, the rate of bowel urgency at two years is 16 to 34% with 5% of patients reporting rectal bleeding. Radiotherapy resulted in temporary obstructive and irritative urinary symptoms that improved to baseline by six months. At two years, patients had less urinary symptoms compared to baseline.

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**IMAGE-GUIDED IMRT USING TRUEBEAM™**

As part of the hospital’s ongoing commitment to clinical excellence, the Cancer Center at Good Samaritan proudly announces the installation of a new state-of-the-art Varian TrueBeam™ linear accelerator. As the first hospital in Suffolk County with TrueBeam radiotherapy capability, cancer patients benefit from faster, shorter and more precise treatments resulting in superior efficacy and better quality of life. The TrueBeam™ system allows Good Samaritan’s radiation oncologists to offer all key radiation treatment modalities including image-guided radiotherapy, stereotactic body radiotherapy, intracranial stereotactic radiosurgery, intensity modulated radiation therapy and respiratory gating.

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FIGURE 3. Multiparametric imaging of prostate cancer. Please note dominant mass in the left base that is appreciated on T2, dynamic contrast enhanced and diffusion weighted imaging (arrowhead) corresponding to the positive biopsy.
For prostate cancer patients, Good Samaritan’s radiation oncologists can now correct for daily changes in rectal and bladder filling to target the prostate tumor with unprecedented precision. In contrast to Cyberknife, which requires a 30 to 60 minute daily session, the Varian TrueBeam™ can safely and accurately treat the prostate in as little as two minutes.

**RADIOACTIVE SEED IMPLANTATION**

Since there have been no recent technical advances in prostate brachytherapy, the number of patients receiving seed implants have been declining relative to more heavily marketed alternative modalities. However, radioactive seed implant with Iodine-125 seeds to a dose of 145 Gy to 90% of the prostate remains a convenient, effective and relatively low cost approach to treating prostate cancer. As a minor surgical procedure, surgical experience is a major factor in determining successful outcomes. Good Samaritan Hospital physicians have published extensively in the field of prostate cancer and prostate brachytherapy.

The primary disadvantage of seed implant is that only low risk and highly selective intermediate risk prostate cancers are candidates for this procedure alone. Seed implantation is a minimally invasive, same-day procedure requiring general or spinal anesthesia. Intermediate risk and high risk patients often require combined seed implant and IMRT. With respect to complications, 56% of patients report erections insufficient for intercourse at two years. The rate of frequent urinary leakage at two years is 10%. Importantly, seed implant results in higher rates of obstructive and irritative urinary symptoms than other modalities that persist for up to two years. At two years, 9% of patients report rectal urgency and 3% of patients report rectal bleeding.

**LESS COMMON MODALITIES**

**STEREOTACTIC BODY RADIOTHERAPY**

Stereotactic body radiotherapy (SBRT) is heavily marketed by Cyberknife centers for patients as a convenient and non-invasive alternative to seed implantation or IMRT. SBRT is a form of IMRT that completes treatment in five days instead of eight to nine weeks. Although SBRT is relatively new with only five years of clinical follow-up, SBRT is likely as effective as IMRT or seed implant for low risk and selected intermediate risk patients who are also candidates for active surveillance or seed implantation. At Good Samaritan, our new TrueBeam™ linear accelerator can deliver SBRT faster and more precisely than the Cyberknife. Careful patient selection is important because a recent randomized study demonstrated higher risk of urinary symptoms in patients receiving shortened courses of radiation. Good Samaritan’s radiation oncologists believe that the aggressive marketing programs for SBRT for prostate cancer are misleading to patients. The hospital offers SBRT or a shortened five week course of IMRT for highly selected patients requesting a more convenient treatment regimen. However, the Cancer Center will review all appropriate options with the patient including active surveillance, surgery, seed implant and IMRT.

**PROTON BEAM THERAPY**

There are currently no proton beam facilities in New York State with the closest location in Somerset, N.J. Since a proton facility costs over $100M to build, proton beam radiotherapy is heavily marketed. Although more costly to patients and insurers, proton beam radiation achieves dose distributions that may reduce the risk of complications for pediatric tumors and skull base tumors. In contrast, there is no data suggesting superiority efficacy or reduced toxicity of protons to IMRT for prostate cancer. A recent study suggested that protons result in a higher rate of gastrointestinal toxicity than IMRT and a second study demonstrated erectile dysfunction in 72% of treated patients. As part of the Choosing Wisely campaign, the American Society for Radiation Oncology does not recommend proton beam radiotherapy for prostate cancer outside of a clinical trial.

**OTHER ABLATIVE THERAPIES (CRYOTHERAPY, HIGH INTENSITY FOCUSED ULTRASOUND)**

Cryotherapy uses freezing to ablate the prostate. Published results suggest a higher complication rate, particularly erectile dysfunction, associated cryotherapy as compared to radiotherapy. High intensity focused ultrasound has also been developed but the clinical experience has been limited. Neither treatment is recommended outside of a clinical trial.
Systemic Therapy

Androgen Ablation

The mainstay of systemic therapy is androgen ablation, most commonly via the luteinizing hormone-releasing hormone Lupron. For most patients with intermediate risk disease, a six month course of Lupron combined with radiotherapy improves biochemical control and overall survival compared to radiation alone. For patients with high risk disease, a two to three year course of Lupron combined with radiotherapy improves biochemical control and overall survival compared to radiation alone. In contrast, there is no evidence that adjuvant androgen ablation improves outcome for patients undergoing surgery, save for patients with positive lymph nodes. Common side effects from androgen ablation include hot flashes, weight gain, fatigue and osteoporosis. Recent data suggests a higher risk of diabetes and cardiovascular disease during androgen ablation.

For patients with a biochemical failure after surgery or radiotherapy or newly diagnosed metastatic disease, androgen ablation is considered. Recent data suggests that intermittent hormonal blockage can reduce toxicity compared to continuous hormonal blockage for patients with biochemical failure after local therapy. For patients with metastatic disease, combining oral antiandrogen (Casodex) with Lupron may slightly improve survival compared to Lupron alone. However, patients with metastatic prostate cancer eventually become resistant to hormonal therapy. Two new antiandrogen agents include abiraterone acetate, an androgen synthesis inhibitor, and enzalutamide, an androgen receptor inhibitor. Both agents significantly improved median survival in patients who were resistant to conventional androgen ablation and who failed docetaxel chemotherapy from 11 to 14 months with placebo to 16 to 18 months (p<0.001) with abiraterone or enzalutamide.

Newer Agents

Treatment of hormone refractory metastatic prostate cancer has historically been limited with metastatic prostate cancer patients typically suffering significant bone pain that is often refractory to treatment. In addition to abiraterone and enzalutamide, four drugs recently received FDA approval for hormone refractory metastatic prostate cancer. While not a cure, these new agents offer patients extended survival and an improved quality of life. Both docetaxel and cabazitaxel improved median survival for patients with hormone-refractory prostate cancer by two months (p<0.001). Sipuleucel-T is an agent that involves collection of dendritic cells harvested from patients that subsequently exposed to prostatic acid phosphatase and reinfused to the patient. Median survival in asymptomatic hormone-refractory patients with was 26 months with sipuleucel-T vs. 22 months. Finally, intravenous Radium-223 (Xofigo) improved median survival in patients with symptomatic hormone refractory prostate cancer (15 months vs. 11 months, p<0.001) with a favorable toxicity profile.

Finally, patients with bone metastases benefit from agents such as zoledronic acid (Zometa) or denosumab (Xgeva) to reduce the risk of pathologic fracture, spinal cord compression or intractable bone pain.

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Further Reading

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