Treatment of Localized Prostate Cancer

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This article provides an overview of treatment of localized prostate cancer, which was discussed in detail in the second scientific session of the 16th International Prostate Cancer Update. The role of radical prostatectomy in localized disease was presented by Bob Djavan, MD. Benefits and risks of radical prostatectomy were addressed by Gerald Chodak, MD. Robert E. Donohue, MD, presented the role of radical prostatectomy in Gleason grade 8, 9, and 10 tumors. Impact of positive margins on outcomes after radical prostatectomy was presented by James A. Eastham, MD. E. David Crawford, MD, provided an overview of the role of targeted therapy. Indications and results of brachytherapy were presented by Mack Roach, III, MD. Finally, Michael J. Manyak, MD, described the evolution of radioimmunoscintigraphy and clinical outcomes data.

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Localized prostate cancer is prostate cancer in which there is no extension of tumor beyond the capsule of the prostate. The clinical course of newly diagnosed clinically localized prostate cancer can vary. It is important to identify the subset of men with aggressive localized prostate cancer, so that the natural course of their disease can be altered by definitive local therapy, while sparing the remaining patients the morbidity of unnecessary treatment. The main goals of the

second session of the 16th International Prostate Cancer Update, held in Beaver Creek, Colorado, January 18-22, 2006, were to review recent developments for assessing risk in patients with newly diagnosed, clinically localized prostate cancer; to describe factors affecting disease prognosis; and to evaluate newer treatment strategies for localized disease, including active surveillance and focal therapy.

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The Role of Radical Prostatectomy in Localized Disease

The goals of patients undergoing radical prostatectomy are to be cancer free and to recover preoperative urinary and erectile function as soon as possible after surgery. In addition, functional results, catheterization time, and cost of the procedure should be considered in the treatment decision. Although radical prostatectomy provides superior oncological outcomes compared to alternative treatment modalities, it can be a significant source of long-term incontinence and erectile dysfunction.

Stage migration of prostate cancer has been observed during the last decade. The rates of clinical stage T1c and organ-confined prostate cancer have increased, whereas positive surgical margin rates have decreased during the last decade.[1] Biochemical recurrence rate at 3 years after radical prostatectomy for patients with organ-confined disease was reported as 4% to 11%. Results for the United States and Europe were comparable.

The definition of incontinence differs in various studies. Although a group of studies defined urinary continence as total dryness, most of them defined it as urinary leakage of less than 1 or 2 pads per day. It is also interesting that the rate of urinary incontinence is higher when reported by patients themselves than when it is reported by physicians.[2] To obtain more reliable data, questionnaires regarding urinary incontinence should be filled out by patients. Urinary continence rate increases with time after surgery. Although continence rate was reported as 51% to 63% at 3 months after surgery, it was reported as 91% to 96% at 12 months after surgery. These rates can increase slightly at the second year after surgery. Consequently, before planning any type of surgical intervention for urinary incontinence after radical prostatectomy, one should wait at least 1 year to observe its natural recovery. In the meantime, Kegel exercises or other behavioral therapies to decrease the recovery period can be tried.

Potency rates also increase with time after surgery. Spontaneous erection is seen in 23% of patients at 3 months after bilateral nerve-sparing radical prostatectomy. At 1 year after surgery, this rate rises to 55%. With the addition of sildenafil or tadalafil, potency rates are 32% at 3 months and 65% at 12 months. It has been reported that early use of intracavernosal agents and phosphodiesterase-5 inhibitors improves long-term recovery of erectile dysfunction.[3,4] It is hypothesized that these agents improve cavernosal oxygenation, thereby limiting hypoxia-induced tissue damage. These data support the concept of early rehabilitation in the management of erectile dysfunction following radical prostatectomy.

Open Versus Laparoscopic Radical Prostatectomy

After the first laparoscopic radical prostatectomy was performed by Schuessler in 1991, Guillonneau defined the Montsouris Technique in 1999, Bollens described extraperitoneal laparoscopic radical prostatectomy in 2001, and the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA) was first used in 2000. During this period of development of laparoscopic radical prostatectomy, more than 9000 operations in Europe were performed using this method. Controversy still exists regarding the advantages and disadvantages of laparoscopic prostatectomy compared with open surgery. To be accepted as the gold standard in the management of localized prostate cancer, laparoscopic surgery should have better results in terms of oncologic, functional, morbidity, and cost factors than open surgery. Positive surgical margin and biochemical recurrence-free survival rates at 3 years, continence and potency rates at 1 year, incision length, learning curve, operation time, and relative costs for laparoscopic and open surgery are shown in Table 1. Laparoscopic radical prostatectomy provides comparable oncologic and functional results with similar morbidity rates. Incision length, hospital stay, and catheterization times favor laparoscopic prostatectomy, whereas operating time, learning curve, and

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Table 1
Comparison of Laparoscopic and Open Radical Prostatectomy

	Laparoscopic Surgery	Open Surgery
Positive margin for pT2 tumors	7.4%-21.9%	2.1%-16.4%
Prostate-specific antigen recurrence at 3 years for pT2 tumors	4.1%-11.0%	3.7%-6.9%
Continence at 1 year	79%-94%	80%-95%
Potency at 1 year	59%-67%	56%-86%
Incision length	7.9 cm	8.6 cm
Learning curve	> 250 cases	> 50 cases
Operation time	290-500 min	120-185 min
Cost	1.2 times higher	–

cost favor open surgery. Overall, it can be concluded that laparoscopic surgery is not inferior to open surgery in many respects. In the long term, with increased experience with laparoscopy in the field of urology, laparoscopic prostatectomy could have a greater role in the management of localized prostate cancer than it does currently. The da Vinci System provides a shorter learning curve than laparoscopic prostatectomy but with increased cost. It is currently too early to compare the long-term oncologic results for surgery done with the da Vinci System versus open surgery.

Are the Benefits of Radical Prostatectomy Worth the Risks?

All patients diagnosed with prostate cancer must decide for themselves which treatment is best. Patients vary in their willingness to accept risks and in their need for certain benefits. The urologist's role should be to provide the data so that patients can evaluate their choices. While providing information about different treatment options, a physician should provide data on his or her own results instead of data in the literature from highly experienced centers. Factors such as patient age and health, severity of disease, and the surgeon's expertise and the number of cases performed can also affect the patient's decision.

Scandinavian data[5] comparing radical prostatectomy with watchful waiting showed that radical prostatectomy reduced mortality 4.8% in 10 years and reduced metastasis by 10%. This benefit may increase with time. In this dataset, there were more Gleason grade 7-10 tumors in the watchful waiting arm than in the radical prostatectomy arm; median prostate-specific antigen (PSA) level in the entire group was 13 ng/mL. On the other hand, when we look at the characteristics of cancers diagnosed in the United States, they are mostly Gleason grade 3+3 and T1c tumors, with a median PSA of 6 ng/mL. It could be inferred that men in the United States are less likely to benefit from radical prostatectomy than were the men in the Scandinavian trial. When the question "What odds of benefiting from radical prostatectomy would be sufficient for you?" is asked, the answer can range from "1 out of 2 avoid death" to "I would have surgery no matter how small the benefit." Also, patients' willingness to accept the risks of incontinence and impotence can vary.

In conclusion, better assessment of benefits and risks of any treatment modalities should be provided to patients. Information given to patients should be accurate and objective, and it should reflect the urologist's own results. Finally, physicians should assist patients in weighing their choices.

Radical Prostatectomy for Gleason Grade 8-10 Cancers

Robert Donohue, MD, presented the study at the Veterans Administration Medical Center, Denver, CO, of patients treated with radical prostatectomy for Gleason grade 8-10 cancers. He also discussed the factors affecting prognosis in this subgroup of patients. The study included a total of 431 patients who were treated with radical prostatectomy between 2000 and 2005. Histopathologic evaluation was performed using whole-mount study in 366 patients. Pathologic characteristics of these patients are shown in Table 2. In 26 patients, Gleason grade 8-10 pattern was detected. Forty-three percent of patients diagnosed with Gleason grade 8-10 tumors turned out to have organ-confined pT2 cancer. In a study by Mian and colleagues,[6] 1199 men underwent radical prostatectomy between 1987 and 1996. A Gleason score of 8-10 was seen in 188 men. In histopathologic evaluation of their tumors, 58 men (31%) were diagnosed with organ-confined disease, and 108 men (58%) were diagnosed with specimen-confined disease. Disease-free survival at 5 years for patients with specimen-confined disease was 84%, whereas it was 50% for patients with non–specimen-confined disease. The researchers concluded that specimen-confined disease was the most important prognostic factor, that there was a relatively low incidence of organ-

Table 2
Pathologic Characteristics of Patients Evaluated With Whole-Mount Study

	Patients (n)	Percentage
Stage p0	4	1
Stage T2	135	37
Extracapsular extension	39	11
Positive margin	138	38
Seminal vesicle involvement	42	11
Lymph node positive	8	2

confined disease in tumors with a high Gleason score, and that nerve-sparing surgery should be avoided for this group of patients.

Prognostic significance of lymphovascular invasion in prostate cancer was also reported.[7] In this study, lymphovascular invasion was defined as unequivocal presence of tumor cells in an endothelium-lined space. Lymphovascular invasion was seen in 21% of patients treated with radical prostatectomy. Fifty-eight of 94 patients (62%) diagnosed with Gleason grade 8-10 tumors had lymphovascular invasion, whereas 19% of patients with Gleason grade 7 tumors and 2% of patients with tumors of Gleason grade 6 or lower had lymphovascular invasion. The 5-year biochemical recurrence-free survival rate was 83% in patients with lymphovascular invasion compared with 34% in those without lymphovascular invasion. Again, 5-year cancer-specific survival was 90% in patients with lymphovascular invasion compared with 98% in those without lymphovascular invasion.

In the final part of his presentation, Dr. Donohue addressed the modifications of Gleason grading system. Based on these modifications, the cribriform pattern previously reported as Gleason 3 pattern is currently consistent with Gleason 4 pattern. Because small-cell carcinoma has unique histologic, immunohistochemical, and clinical features, Gleason score should not be reported for this subset of tumors. When reporting Gleason score for prostatic adenocarcinoma, physicians should report primary pattern and highest pattern and should ignore third pattern. Unless the muscularis of the seminal vesicle is invaded, the tumor should not be classified as invading into the seminal vesicle.

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Impact of a Positive Surgical Margin on Outcomes after Radical Prostatectomy

Cancer at the surgical margin has the potential for tumor recurrence. Among all known risk factors such as serum PSA level, clinical stage, extracapsular extension, seminal vesical invasion, lymph node involvement, and positive surgical margin, only the status of the surgical margins can be influenced by surgical technique. The study of 1389 consecutive patients with clinical stage T1-3 prostate cancer treated with radical prostatectomy from 1983 to 2000 at Memorial Sloan-Kettering Cancer Center in New York was presented.[8] The aim of this study was to determine the significance of a positive surgical margin on cancer control outcomes. Of the 179 patients who had a positive surgical margin, 59 were pT2 and 120 were pT3 patients. Multivariate analysis demonstrated that positive surgical margin was an independent prognostic factor of 10-year biochemical relapse-free survival ($P = .002$). The 10-year biochemical relapse-free survival was 58% and 81% for patients with and without a positive surgical margin, respectively. These data suggest that a positive surgical margin has a significant adverse impact on biochemical relapse-free survival.

A second question about positive surgical margins is whether they are inherent in the nature of the cancer, like extracapsular extension, or whether the margins can be altered by surgical technique. It is known that the rate of incidence of positive surgical margins in radical prostatectomy specimens varies widely within and among hospitals and surgeons. James Eastham, MD, presented a recent study by his group that evaluated variations in the rate of positive surgical margins among surgeons performing radical prostatectomy after controlling for severity of disease and volume of cases per surgeon.[9] In this study, a total of 4629 men were treated with radical prostatectomy by 1 of 44 surgeons at 2 large urban

centers. Among the 26 surgeons in the study who treated more than 10 patients each, the rate of positive surgical margins was between 10% and 48%. In multivariate analysis, serum PSA level, level of extracapsular extension, radical prostatectomy Gleason score, surgical volume, and surgeon were associated with surgical margin status after controlling for all other clinical and pathologic variables. It was reported that the technique used by individual surgeons is a risk factor for positive surgical margins. Lower rates of positive surgical margins for high-volume surgeons could be explained by greater experience with the procedure and by the fact that careful attention to surgical details can decrease positive surgical margin rates and improve cancer control with radical prostatectomy.

What can be done to decrease the risk of a positive surgical margin? Distal resection of the dorsal vein complex, wide dissection at the apex posteriorly, deep dissection over the rectum, dissection beneath the posterior layer of Denonvillier's fascia, and proximal resection of the bladder neck are the key steps to reduce positive margins during radical prostatectomy. The dorsal venous complex can be dissected over a stainless steel wire. It must be dissected distal to all prostatic tissue. While performing apical dissection with nerve sparing, surgeons need to take 3 important steps: 1) incision of lateral pelvic fascia above the nerve, 2) dissection of the neurovascular bundle from the apical third of the prostate, and 3) sharp division of the posterior layer of Denonvillier's fascia. The entire Denonvillier's fascia must be included to reduce the risk of a positive surgical margin. Wide dissection of the lateral pedicles around the base and transection of the bladder neck above the prostate will reduce the risk of positive margins. Bladder neck preservation is not recommended because it doesn't improve continence.

Assessing the risk posed by a positive surgical margin is a very important step. Surgical specimen should be examined with the pathologist, and the differentiation between possible artifact and extent of cancer at the margin should be done. Other pathologic features suggesting systemic recurrence should be discussed. It should be remembered that not all margins carry the same risk. Patients at risk for local progression could be managed with salvage radiotherapy.

Targeted Therapy: Is There a Role for It?

Radical prostatectomy and definitive radiotherapy are the current curative treatment options for localized prostate cancer. Surveillance, Epidemiology, and End Results data showed that 94% of men with well-differentiated prostate cancer received radical therapy in the United States in 2002. Both radical prostatectomy and definitive radiotherapy are associated with significant morbidity and can greatly affect patients' quality of life. A subset of patients with localized prostate cancer and a low Gleason score of 6 or less can be treated with targeted focal therapy, minimizing the rate of complications without compromising primary curative treatment efficacy. It is known that many prostate cancers are multifocal. A successful targeted therapy is predicated on the development of intraprostatic and highly sensitive imaging models that can detect cancer foci. Currently, focal target ablation of prostatic foci is based on saturation biopsy. For this purpose, a computerized, real-time 3-dimensional reconstruction of the prostate is used to aid in the identification of significant cancerous islands within the prostate. Ablation of prostate cancer foci can be done with cryotherapy, focal radiation, high-intensity focused ultrasound, brachytherapy, or ethanol injection.

Targeted therapy possesses some inherent advantages in the management of localized prostate cancer. A potential advantage of targeted therapy is to provide an efficacious and cost-effective curative alternative to radical prostatectomy and radiotherapy with fewer complications such as erectile dysfunction, urinary incontinence, and rectal injury. The shorter procedure and hospital stay times, patient satisfaction, and quality of life are the other benefits of targeted therapy. E. David Crawford, MD, defined the objectives of his Institutional Review Board-approved protocol primarily as determining the feasibility of using target focal therapy as a primary treatment for organ-confined prostate cancer, and secondarily as assessing the incidence of the side effects urinary incontinence, rectal and urethral injury, and erectile dysfunction.

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A potential risk of targeted therapy is incomplete treatment. Incomplete treatment may be attributed potentially to missed cancer foci and inadequate treatment of target tissue. Targeted therapy may not be suitable for patients who have periurethral and extracapsular tumor extensions. Lack of radical prostatectomy material for final histopathological evaluation and the current cost are the other

drawbacks of targeted therapy. In addition, how PSA should be monitored after targeted therapy has not been well defined.

In conclusion, there is a strong rationale for targeted therapy and it should be studied further. Currently, we should rely on saturation biopsies to detect cancer foci in the prostate. Technical advances in imaging will make targeted therapy more attractive in the near future.

Brachytherapy: Indications and Results

Patient selection for brachytherapy in the management of localized prostate cancer is very important. Absolute contraindications to prostate brachytherapy include metastatic disease, seminal vesicle involvement, and T3 disease with gross extracapsular extension. Prostate size larger than 50 mL, International Prostate Symptom Score greater than 15, prior transurethral resection of the prostate (TURP), inflammatory bowel disease, and prior radiotherapy are often accepted as relative contraindications. However, acute urinary retention after brachytherapy in patients with large gland size and high symptom score usually lasts only a few days with no long-term consequence. Patients with high pre-implant scores tend to experience less dramatic changes in scores. Although early studies suggest that the risk of post-implant incontinence is about 50% in patients with prior TURP, risk of incontinence in post-TURP patients is lower when the seeds are placed peripherally. To avoid suburethral necrosis, a rim of tissues greater than 1.0 cm left around the defect is recommended by some authors. Several investigators have reported no increased morbidity in patients with prior radiotherapy, penile prosthesis, and inflammatory bowel disease.

Young age and high-risk disease are commonly mentioned as contraindications to brachytherapy. Serum PSA level of 10 ng/mL or more, Gleason score of 7 or above, and percent-positive core biopsies of 50% or more are risk factors. The low-risk group includes patients with no adverse factor, the intermediate-risk group includes patients with 1 adverse factor, and the high-risk group includes patients with 2 or more adverse factors. The prognostic significance of Gleason score in patients treated with brachytherapy was reported by Potters and associates.[10] In patients with T1-2 disease and median PSA of 8.6 ng/mL, 5-year biochemical relapse-free survival was 85% for Gleason grade 3+3 tumors, 78% for 3+4 tumors, 55% for 4+3 tumors, and 50% for 4+4 tumors.

Main Points

- Potency rates increase with time after bilateral nerve-sparing radical prostatectomy. Spontaneous erection is seen in 23% of patients at 3 months after surgery; at 1 year after surgery, this rate rises to 55%. With the addition of sildenafil or tadalafil, potency rates are 32% at 3 months and 65% at 12 months.
- Laparoscopic radical prostatectomy provides comparable oncologic and functional results with similar morbidity rates to open procedures. Incision length, hospital stay, and catheterization times favor laparoscopic prostatectomy, whereas operating time, learning curve, and cost favor open surgery. Overall, it can be concluded that laparoscopic surgery is not inferior to open surgery in many respects.
- Prognostic significance of lymphovascular invasion in prostate cancer was reported. The 5-year biochemical recurrence-free survival rate was 83% in patients with lymphovascular invasion compared with 34% in those without lymphovascular invasion. Five-year cancer-specific survival was 90% and 98% in patients with and without lymphovascular invasion, respectively.
- Cancer at the surgical margin has the potential for tumor recurrence. A study of patients with clinical stage T1-3 prostate cancer treated with radical prostatectomy from 1983 to 2000 at Memorial Sloan-Kettering Cancer Center in New York demonstrated that the 10-year biochemical relapse-free survival was 58% and 81% for patients with and without a positive surgical margin, respectively.
- Targeted therapy possesses some inherent advantages in the management of localized prostate cancer, including providing an efficacious and cost-effective curative alternative to radical prostatectomy and radiotherapy with fewer complications such as erectile dysfunction, urinary incontinence, and rectal injury. A potential risk of targeted therapy is incomplete treatment.
- Brachytherapy provides excellent outcomes for low-risk patients, and it can be used in combination with external beam radiation or hormonal therapy with a high degree of success for intermediate- or high-risk patients.
- Capromab pendetide, a radiolabeled antibody, 7E11-C5.3, that is directed against PSMA, significantly improved sensitivity for prostate cancer detection compared with standard cross-sectional imaging based on tissue confirmation.

Low-risk patients have 12-year biochemical relapse-free survival of more than 85%, whereas for high-risk patients it is about 60%. In conclusion, brachytherapy provides excellent outcomes for low-risk patients, and it can be used in combination with external beam radiation or hormonal therapy with a high degree of success for intermediate- or high-risk patients.

The Evolution of Radioimmunoscintigraphy: Clinical Outcomes Data

Radical prostatectomy and definitive radiotherapy are reserved for localized prostate cancer patients. Standard imaging techniques such as computed tomography, magnetic resonance imaging, and positron emission tomography scan are inadequate to stage prostate cancer patients appropriately. Surgical lymph node sampling is invasive and could sample a limited area. Prostate-specific membrane antigen (PSMA), a 100 kD transmembrane glycoprotein, is upregulated in prostate cancer and its metastases. Capromab pendetide, a radiolabeled antibody, 7E11-C5.3, that is directed against PSMA, significantly improved sensitivity for prostate cancer detection compared with standard cross-sectional imaging based on tissue confirmation. However, there were limitations due to early imaging technology. Findings were difficult to interpret without training, and positive predictive value was modest. Image acquisition has significantly improved over the past 5 years due to major advances in gamma scanner technology and to the use of coregistration to fuse images. Tissue confirmation of fused scan results shows an 83% accuracy for detection of prostate cancer. Seven-year outcomes data from a cohort of brachytherapy patients who had alteration of the treatment plan based on radioimmunoscintigraphy show a significant difference in biochemical disease-free survival on the basis of fused scan results.[8] These data support the aggressive treatment of intermediate- and high-risk category patients without signal detected outside the prostatic fossa. It is hoped that a therapeutic application of this technology with the attachment of 177-Lu for both imaging and treatment of prostate cancer and that PSMA-based prostate cancer vaccines will be available in the near future. ■

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