New Techniques and Management Options for Localized Prostate Cancer

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Prostate cancer is diagnosed in younger men who want treatment that does not compromise their quality of life, take time away from work, or cause worrisome side effects. Laparoscopic radical prostatectomy, robot-assisted laparoscopic radical prostatectomy, and third-generation cryotherapy are modifications of previously used techniques in the treatment of prostate cancer and are presented in this article. Although some or all of the outcomes might be expected to change in the future, the urologic surgeon is left to select an approach, presumably on the basis of the experience, level of training, and care pathways at his or her institution.
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The widespread acceptance and use of prostate-specific antigen (PSA) screening for the detection of prostate cancer has resulted in a well-documented downward stage and age migration, better treatment outcomes, and an increase in the number and type of treatment options available to men diagnosed with prostate cancer.[1-5] An increase in patients' desire for minimally invasive procedures can be viewed as an expected outgrowth from the fact that younger, healthier men are being diagnosed with prostate cancer. Patients' desire to be effectively treated, while maintaining their current level of quality of

life, intersects with the goals of minimally invasive treatment approaches: disease eradication, shortened time in the hospital and time away from work, and minimization of treatment-related side effects and their impact on normal daily functioning.[6] It must be kept in mind, however, that even when these criteria are satisfied, universal acceptance of any new technique also requires evaluation of its cost-effectiveness.

beam radiation therapy (EBRT) in patients with high-risk features.[10,11] Previously, most of the controversy surrounding the use of open RRP versus other management options had concerned whether radiation therapy treatments produced equivalent long-term outcomes. The current debate focuses on which surgical approach—open RRP, LRP, or RALRP—is the optimal management for prostate cancer.

A recent study showed that open radical retropubic prostatectomy reduces mortality compared with watchful waiting in early prostate cancer.

The push to identify minimally invasive techniques has resulted in the resurgence and modification of previously used techniques and the introduction of modifications to—and in some cases completely new takes on—tried and true "gold standards." Laparoscopic radical prostatectomy (LRP), robot-assisted laparoscopic radical prostatectomy (RALRP), and third-generation cryotherapy are the front-runners in this endeavor.

Rebirth of a Standard? Open Radical Retropubic Prostatectomy Versus LRP and RALRP

Among urologic surgeons, open radical retropubic prostatectomy (RRP) has long been viewed as the gold standard for the management of localized prostate cancer.[7] Reports of long-term follow-up indicate favorable biochemical progression-free survival rates ranging from 80% to 88% at 5 years and 69% to 75% at 10 years.[8,9] More recently, the scope of the indications for RRP have broadened, as more patients with advanced stages of prostate cancer receive primary treatment with open RRP. This increased use might reflect the establishment of a demonstrated benefit from post-prostatectomy external

Perhaps it is human nature that once the "kinks" have been worked out of a system, the next step is to replace that existing system with a novel, more high-tech approach. Refinements in surgical technique, intra-operative and peri-operative care, in addition to other advancements, resulted in reduced morbidity and improved functional and oncologic results. To that end, a recent study showed that open RRP reduces mortality compared with watchful waiting in early prostate cancer.[12] Proponents of open RRP attest that currently, patients can expect "an uncomplicated surgical procedure, a short and uneventful hospital stay, the lack of autologous blood transfusion, 'early' removal of the urinary catheter, full return to activities (including strenuous exercise) within 3 weeks and restoration of urinary continence."[13]

Since the late 1990s, radical prostatectomy has been increasingly performed laparoscopically[14,15] and more recently with robotic assistance. The cited advantages of LRP and RALRP result from the minimally invasive nature of the procedures and reportedly include reduced perioperative pain,[16] less blood loss and a reduced need for autologous blood transfusion,[16,17] shorter hospitalizations,[18] increased rates of preservation of the neurovascular bundles,[19,20] earlier Foley catheter removal and decreased time to recovery of continence,[20] and a faster return to normal levels of activity.[19,21,22] Perceived disadvantages of LRP include increased time in the operating room, increased time of anesthesia, loss of tactile sensation and queues, significant reduction in the degrees of freedom for manipulation of surgical instruments, a fixed, limited field of view, risk of postoperative ileus, risk of thermal injury to neurovascular bundles, and higher positive margin rates for pT2 disease.[23] In addition, virtually all published reports suggest that a significant learning curve is associated with LRP, with one group of investigators concluding, "Laparoscopic radical prostatectomy is technically demanding, with an initially longer operative time, higher incidence of rectal injuries and urinary leakage."[24] In other reports, the learning curve has been shown to be somewhat extended. Operative details from the surgeons at the Montsouris Institute, one of the pioneering institutions of LRP, suggest a continuation of significant experience-related improvements in technique and reductions in treatment-related morbidity, even after the completion of 300 cases.[25]

The introduction and commercial availability of the da Vinci Robotic Surgical System (Intuitive Surgical, Sunnyvale, CA) was associated with an increase in the number of cases of LRP performed and introduced the RALRP.[26-28] In addition to facilitating dissection and suturing, robotic assistance is reported to ease the learning of laparoscopic radical prostatectomy for urologic surgeons who have not had formal training in laparoscopic techniques.[21,27] Nonetheless, a moderate learning curve remains, and the

level of existing laparoscopic skills needed to master RALRP might have been underestimated.[21,29] In general, few if any functional or disease control advantages have been reported for RALRP over LRP, although like its predecessor, RALRP is suggested to outperform open RRP. Other than in the hands of select groups,[18,21,27,30] studies comparing LRP and/or RALRP with open RRP have failed to identify significant differences in treatment outcomes.[31,32] LRP patients have similar, but not improved, rates of perioperative complications (estimated blood loss, transfusion rates, hemoglobin levels, serum and drain fluid creatinine levels, length of hospital stay) when compared with similar open RRP patients.[33] Perioperative narcotic use and patient-reported pain were found to be low regardless of the surgical approach. RALRP was not associated with clinically meaningful decreases in pain compared with RRP, primarily owing to low pain scores reported in both procedure groups.[34] Operative times are initially longer with laparoscopic techniques, although as expected, operating room times decrease with experience.[24] No data exist that conclusively demonstrate better rates of continence or potency preservation with laparoscopic techniques. No significant differences in patient-reported general or disease-specific health-related quality of life have been documented between techniques.[35-37] Despite the fact that no prospective comparisons or matched pair analyses with long-term follow-up unequivocally support the superiority of LRP or RALRP, its use continues to increase. More perplexing still is that in a time of healthcare cost containment, the fact that both LRP and RALRP are significantly more costly than open RRP[38,39] has not dampened enthusiasm for their increased penetrance in either academic or community settings.

An older, less "high-tech," but equally efficacious minimally invasive twist on open RRP is the mini-laparotomy (mini-lap) RRP.[40,41] Theoretically, this approach should offer many of the same benefits as laparoscopic procedures, including a smaller incision, direct or magnified visualization of the operative field with the use of loupes or an endoscope, intraoperative temperature monitoring, shorter operating times, shorter hospitalizations, and reduced postoperative pain.[41-43] Mini-lap RRP costs significantly less than LRP and RALRP, largely because of lower hospitalization costs and lower equipment costs. Mini-lap RRP requires less training than laparoscopic prostatectomy procedures and can easily be adopted by most retropubic surgeons, effectively eliminating the human and monetary costs associated with the LRP/RALRP learning curve.[42,44-46] Associated morbidity is minimal, and treatment outcomes with mini-lap RRP compare favorably with those for open RRP and LRP.[42,47] If any information can be gleaned from the number of published reports on a technique, there seems to be a general lack of enthusiasm for the mini-lap approach. Given the level of concordance with the objectives of the various minimally invasive approaches, mini-lap RRP would seem to be a reasonable choice, particularly at those institutions where the laparoscopy learning curve and equipment expense cannot be overcome.

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Overall, when comparing open RRP with LRP and RALRP, the data to date seem to suggest that the 3 procedures do not differ significantly in terms of operative, postoperative, and pathologic outcomes. Furthermore, it has been reported that the majority of the differences can be attributed to the experience of the operating surgeon.[48,49] Although some or all of these outcomes might be expected to change in the future, at the moment the individual urologic surgeon is left to select an approach presumably on the basis of the experience, level of training, and care pathways at his or her institution.

Prostate Cryotherapy

Cryoablative approaches for the treatment of prostate cancer debuted in 1966[50,51] but very quickly fell out of favor owing to the high incidence and severity of treatment-related complications. Difficulties monitoring and controlling the temperature and the extent of freezing (isothermal dosimetry) resulted in uncertain levels of tissue destruction at the periphery of the treatment region, allowing for cell survival, repopulation, and tumor recurrence. Advances in imaging technology and surgical instrumentation and changes in freezing technology signaled a new era for prostate cryotherapy. A pivotal event was the approval of urethral warming devices by the US Food and Drug Administration.[52] The most significant change in third-generation cryotherapy machines might be the replacement of liquid nitrogen by gas-driven probes powered with argon and helium.[53,54] By harnessing the Joule-Thompson effect, an active thaw phase became possible. The ability to quickly transition from freezing to thawing increased control of ice-ball formation and shortened procedure times. The

use of smaller-diameter cryoprobes decreases perineal trauma, increases control of ice-ball formation, and permits more conformal coverage of the prostate gland.[55,56] Multi-focal real-time temperature monitoring, through the use of thermocouples, has also contributed significantly to improved treatment planning.[57] In the aggregate, the ability for transperineal, image-guided placement of cryoprobes into the prostate gland,[55,56,58] urethral warming, and more conformal freezing has resulted in more conformal coverage of the prostate, decreased morbidity, and encouraging biochemical control rates, as compared with earlier series.

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The weakness in the history of third-generation cryotherapy is insufficient follow-up. No definitive conclusions regarding long-term treatment efficacy can be reached. The lack of a standard definition of treatment failure makes comparative analyses difficult as well. The trial with the longest follow-up is a retrospective review of 590 patients with low-, intermediate-, and high-risk prostate cancer.[59] At a median follow-up of approximately 5.5 years, the 7-year actuarial biochemical disease-free survival rate (failure defined as PSA $\geq$ 0.5 ng/mL) for low-, intermediate-, and high-risk patients was reported as 61%, 68%, and 61%, respectively. Three prospective studies have been published. Second-generation cryotherapy devices were used in 2 studies and third-generation devices in 2 studies. Donnelly and colleagues[60] reported 5-year results from a prospective trial on 76 patients with low-, intermediate-, and high-risk prostate cancer treated with second- and third-generation systems. At a mean follow-up of 50 months (30 months minimum), the 5-year overall and cancer-specific survival rate was 89%. PSA levels were undetectable (defined as $<$0.3 ng/mL) in 60% of low-risk patients, 77% of intermediate risk patients, and 48% of high-risk patients. Aus and colleagues[61] reported a 39% biochemical recurrence-free survival rate and a 28% biopsy positivity rate at 59 months (mean) follow-up. The final multi-institutional study used third-generation cryotherapy exclusively but has only 12 months (mean) of follow-up.[62] Biochemical recurrence-free survival rates (failure defined as inability to achieve PSA nadir $\leq$ 0.4 ng/mL) overall were 75%: 78% for low-risk patients (Gleason score $\leq$ 7 and PSA $\leq$ 10 ng/mL) and 71% for high-risk patients (all others).

In each of the four studies described above, complication rates were lower with third-generation machines, with the exception of impotence rates. In men who were potent before treatment, 95%, 53%, 91%, and 87% became impotent.[59-62] Investigations into nerve-sparing cryotherapy are underway. Onik and colleagues[63] reported improved potency in a cohort of men treated with focal unilateral nerve-sparing cryotherapy. A study investigating neurovascular bundle preservation with active warming has shown feasibility but not reproducibility.[64] A significant concern is incomplete peripheral tissue ablation resulting from neurovascular bundle preservation. Reports on health-related quality of life after cryotherapy suggest similar quality of life at 3 years after treatment completion to that seen with men treated with "radical prostatectomy and radical radiotherapy," with the exception of decreased sexual function.[65,66]

As is the case for cause-specific, biochemical, and disease-free survival rates, additional follow-up is needed for reliable assessment of complication rates and post-therapy quality of life, and before cryotherapy can be considered a standard management choice for localized prostate cancer. Compared with open RRP and EBRT, the cost for cryotherapy treatment is significantly lower.[67]

Cryotherapy, like radiation therapy, might be considered a biologic approach to the management of prostate cancer, with both direct and indirect mechanisms of cell killing. As was seen with the combination of androgen deprivation and radiation therapy, efforts to improve the therapeutic ratio will undoubtedly involve the identification and evaluation of synergistic agents to increase levels of cell killing. In vitro studies with human prostate cancer cell lines (PC-3) have shown that exposure of the cells to sublethal doses of 5-fluorouracil before freezing led to significant increases in cell killing at temperatures at or below -40°C, as well as at higher temperatures.[68] Recent animal studies have suggested that cryoimmunotherapy—intratumoral injections of dendritic cells after cryotherapy of local tumors—might provide a more comprehensive approach to cancer treatment, combining local tumor destruction and systemic anticancer immunity.[69] Another potential niche for cryotherapy as a salvage treatment for disease recurrence after EBRT is an area of active interest.[70-72]

Cryotherapy Versus LRP Versus RALRP

No published reports comparing cryotherapy, LRP, and RALRP are available. Long and colleagues[73] published a 5-year retrospective pooled analysis of cryotherapy, brachytherapy, and EBRT, suggesting similar results. The absence of 10- and 15-year data, as well as the use of a failure definition of PSA of 1 ng/mL or greater, weakens their conclusion. One prospective longitudinal report comparing disease-specific and general quality of life after open RRP, LRP, and palladium-103 (^{103}Pd) has been published.[36] General quality-of-life scores were minimally affected by the choices; however, the disease-specific domains of bowel, urinary, and sexual function were adversely affected by all modalities. Post-treatment disease-specific domains were similar for open RRP and LRP, and urinary and sexual scores were lower than those for ^{103}Pd. At 12 months, 38% of open RRP and 46% of LRP patients had returned to baseline urinary function, compared with 75% of ^{103}Pd patients. At 12 months, 63% of ^{103}Pd patients had returned to baseline sexual function, compared with 19% of both the LRP and open RRP patients.

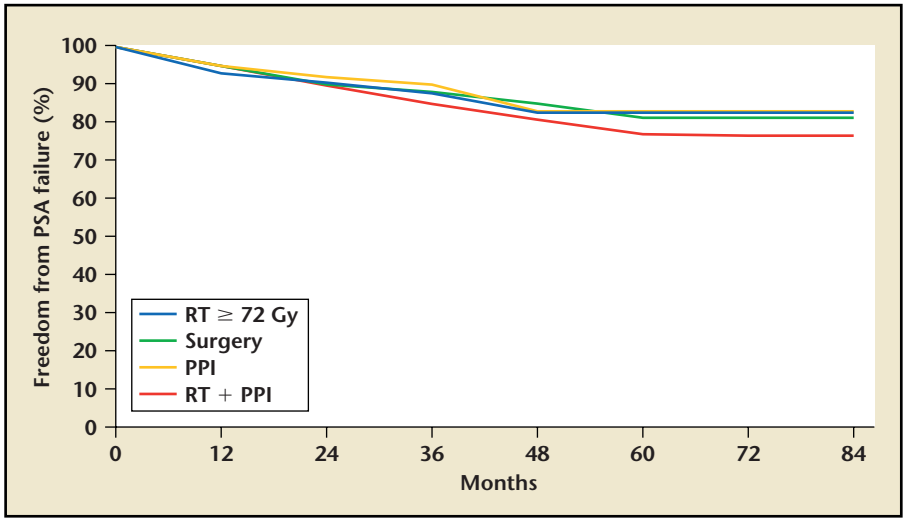
"Minimally Invasive" Radiation Therapy

Radiation therapy, a primarily noninvasive management option for localized prostate cancer, also offers a therapy comparable to LRP and RALRP: permanent seed brachytherapy. Prostate brachytherapy (BT) fulfills each of the criteria for a minimally invasive treatment: disease eradication, shortened time in the hospital and time away from work, minimal treatment-related side effects, and little if any disruption in normal daily functioning.[6] Permanent seed BT is an outpatient procedure usually requiring less than 1 hour for the transperineal insertion of radioactive seeds. Patients usually go back to work and can engage in their normal activities within 1 to 2 days. The predominantly urinary symptoms are self-limited and readily managed. The need for narcotic medications is rare. Longitudinal quality-of-life studies suggest that BT also satisfies patients' desires for an efficacious treatment that preserves their quality of life. Although patients treated with BT and RRP have a different spectrum of side effects, patient-reported overall long-term quality of life is similar, with urinary and sexual function being the primary determinants of this outcome.[35,74,75]

Like the other therapies, a learning curve exists for brachytherapy, and greater BT experience generally translates into shorter procedure times (average 45 minutes to 1 hour in our institution) and diminished treatment-related toxicity.[76] Careful juxtaposition of the posterior prostate and the rectal wall, visualization and avoidance of the urethra throughout its entire course, and avoidance of peri-prostatic veins during the implant procedure significantly impact urethral and bowel toxicity.

One significant distinction between BT and LRP or RALRP is the availability of long-term data that confirm equivalent biochemical and clinical control rates when compared with EBRT (Figure 1). The excellent rates of biochemical and clinical control achieved with BT monotherapy are also comparable to those achieved with RRP.[77-80] A retrospective analysis comparing biochemical control rates of 412 patients treated at the University of California, San Francisco, with permanent prostate seed implantation or EBRT demonstrates significantly better 5-year biochemical control rates with BT. This suggests that for low-risk patients, BT might be more efficacious than EBRT. This finding is supported by a comparative analysis of PSA nadir value and time to spectroscopic metabolic atrophy after treatment with EBRT (72–87 Gy) or BT monotherapy (144 Gy).[81-84] Patients with low-risk prostate cancer and treated with BT only (no androgen deprivation) achieved metabolic atrophy sooner and reached a lower PSA value when compared with patients receiving external beam radiation, suggesting a more pronounced

Figure 1. *Freedom from biochemical (prostate-specific antigen, PSA) failure according to treatment type. RT, radiotherapy; PPI, permanent prostate seed implantation. Data from Kupelian et al[87] and Sylvester et al.[88]*



metabolic and biochemical response associated with BT. If true, the probable etiology of the BT advantage is the ability to safely deliver higher total doses of radiation to the prostate, as well as a greater biologic effect of BT on prostate cancer cells. The dose–response relationship for prostate cancer and the characteristic radiation responses of prostate cancer (low α/β ratio) are well documented in the literature.[85,86]

Conclusion

The enthusiasm for newer minimally invasive techniques and the seeming willingness to adopt them as a standard of care for the management of localized prostate cancer in the absence of robust data supporting that change are somewhat surprising. Throughout history, the medical community has been cautious when it comes to the acceptance of new treatments and subsequent validation of a treatment as a standard of care. The practice of evidence-based medicine is the goal. It was not sufficient for a treatment to be "as good"; there was an expectation or at least the anticipation that a novel approach offered some additional benefit. This history has been played out time and time again in various oncologic situations, as evidenced by the move from extended radical mastectomy to modified radical mastectomy and breast-conserving therapy, the suggestion that pelvic lymphadenectomy might be omitted with low-risk prostate cancer, and the acceptance of prostate brachytherapy. However, it must be kept in mind that science and medicine must also respond to the demand for patient-specific therapies that maximize treatment outcomes, reduce treatment-related morbidity, and have minimal impact on health-related quality of life. In addition, patients want the option to select a treatment from among treatments that have comparable efficacy but differing side effects; physician and patient bias are formidable barriers. Under these auspices, perhaps "as good" is good enough. ■

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Main Points

- An increase in patients' desires for minimally invasive procedures can be viewed as an expected outgrowth from the fact that younger, healthier men are being diagnosed with prostate cancer.
- Despite the fact that no prospective comparisons or matched pair analyses with long-term follow-up unequivocally support the superiority of either laparoscopic radical prostatectomy or robot-assisted laparoscopic radical prostatectomy, their use continues to increase.
- Mini-laparotomy radical retropubic prostatectomy requires less training than laparoscopic prostatectomy procedures and can easily be adopted by most retropubic surgeons.
- Cryotherapy, like radiation therapy, might be considered a biologic approach to the management of prostate cancer, with both direct and indirect mechanisms of cell killing.
- Radiation therapy, a primarily noninvasive treatment option for localized prostate cancer, also offers a therapy comparable to laparoscopic and robot-assisted radical prostatectomy: permanent seed brachytherapy.

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