

The new era of minimally invasive interventions for prostate cancer: robot-assisted laparoscopic radical prostatectomy and focal therapy

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Abstract: Prostate cancer remains a common but highly treatable disease. Innovations in prostate cancer treatment have allowed a transition toward minimally invasive approaches in an attempt to avoid treatment-related morbidities. In the middle of the treatment spectrum between radical open surgeries and active surveillance lies robot-assisted laparoscopic radical prostatectomy (RALP) and focal therapy (FT). This review sets out the most current information on RALP and FT (including laser ablation, cryotherapy, high-intensity focused ultrasound, photodynamic therapy, and irreversible electroporation).

Keywords: PCa, RALP, FT, laser ablation, cryotherapy, high-intensity focused ultrasound, photodynamic therapy, irreversible electroporation

Introduction

Prostate cancer (PCa) is the most common nondermatological malignancy in males, with an estimated annual incidence of approximately 220,000 cases in the United States and 300,000 in Europe.^{1,2} Data from the SEER (Surveillance, Epidemiology, and End Results) registry indicate that the incidence of PCa in men under 50 years has risen steadily over the past 10 years, with an annual incidence of 9.5%,³ suggesting that more men will live a long time with the outcomes of their treatment.^{3,4} The goals of active therapy are oncologic control with minimal morbidities, and the latter has driven research on newer, minimally invasive approaches to PCa treatment. In the paradigm of radical therapy, radical prostatectomy remains the gold standard for localized disease, and several minimally invasive modifications have been added to the original technique including the robot-assisted laparoscopic approach.⁵ The newly emerging paradigm of focal therapy (FT) can be viewed as the middle ground between radical therapy and active surveillance (AS), offering the possibility of less morbidity than any other contemporary technique, while attempting to attain adequate oncologic control. Minimally invasive robot-assisted laparoscopic prostatectomy (RALP) and the rationale and practical considerations of FT will be discussed.

Materials and methods

The authors of this review performed a PubMed search for articles in English, using the terms robot assisted radical prostatectomy and focal therapy as an unrestricted search. Relevant articles regarding novelties in these two fields were reviewed and are presented below.

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RALP

Since the first case performed by Binder and Kramer in 2001,⁶ RALP has dramatically changed the surgical management of PCa. RALP is an established treatment modality for PCa, accounting for approximately 85% of radical prostatectomies currently performed in the United States. With the advantages of three-dimensional (3D) vision, tremor filtering, seven degrees of freedom, coordinated eye–hand movement, and superior surgeon ergonomics when compared with standard laparoscopy, robotic technology offers the potential of performing surgery in a precise and delicate way, especially in places with difficult access such as the male pelvis. However, the supposition that technological breakthroughs will be translated into improved outcomes has to undergo rigorous inspection and validation. In this context, the literature regarding RALP is becoming increasingly mature. With increased surgical experience, well designed prospective studies comparing RALP with open radical prostatectomy (ORP) have been recently published. In addition, a topic in the robotic literature which has received increasing attention is the way to report the results of radical prostatectomy. Patients undergoing surgery nowadays are at the prime of their life, and expect complete cancer cure and functional recovery. In this context, patients expect to be counseled regarding all three goals of cancer control, urinary incontinence, and erectile dysfunction. Below is a review of the most recently reported outcomes and concepts related to RALP.

Current outcomes of RALP

Although results of high volume centers have demonstrated that RALP offers results at least equivalent to those of ORP,⁷ the reproducibility of these findings in centers with lower caseload has been a matter of long debate. The publication of high impact studies, which have generally used poor methodology, have further increased doubts about the real benefit of robotic prostatectomy.⁸ Even though randomized trials provide the strongest evidence when comparing different treatment modalities, nowadays patient preference regarding treatment options is influenced by many factors, and there is real doubt whether such a study can be performed anymore. In the absence of randomized trials comparing ORP and RALP, the strongest evidence comes from prospective comparative nonrandomized trials.⁷ In this context, two well designed studies from centers with average caseload have been recently published.

A prospective nonrandomized trial by Ficarra et al⁹ compared 105 patients who underwent ORP with 103 who

had RALP. Patients in both arms were under the same data collection protocol, including serial validated questionnaires to assess urinary continence (ICIQ-UI), potency (IIEF-5) and complications (Clavien). Urinary and sexual functions were evaluated before surgery and at 12 months. Patients in the robotic arm were younger (61 versus 65 years; $P < 0.01$); the remaining preoperative characteristics including performance status, body mass index (BMI), prostate-specific antigen (PSA), and tumor stage and grade did not differ between the study arms. Main results for RALP versus ORP were: overall positive surgical margins (PSMs), 34% versus 21% ($P =$ not significant [NS]); PSM in pT2 disease, 12% versus 12% ($P =$ NS); perioperative blood transfusions, 1.9% versus 14.0% ($P < 0.01$); perioperative complications, 10% versus 11% ($P =$ NS); continent at catheter removal, 69% versus 41% ($P < 0.001$); continent at 12 months, 97% versus 88% ($P < 0.01$); and mean time to continence, 25 versus 75 days ($P < 0.001$). Among preoperative potent patients who underwent bilateral nerve sparing, 81% and 49% of those who underwent RALP and ORP were potent at 12 months. Similarly, the mean time to recovery of erectile function was 3.9 months versus 6.7 months respectively. An interesting aspect of this study is that surgeons from both study arms had different levels of experience. For example, the two robotic surgeons were during their learning curve, with a prior experience of 50 cases each, while the open surgeons had a prior experience of 400 cases each. While this certainly can explain some particular aspects of the results, such as the higher rate of PSM in the robotic group, improved functional outcomes seen with even relatively limited experience are encouraging.

In a study by Di Pierro et al,¹⁰ the authors prospectively included 150 consecutive radical prostatectomies using the same inclusion and outcome measurements. The first 75 were done in an open fashion by three different surgeons with a prior experience of 100 cases each, while the second 75 were done robotically by a single surgeon with comprehensive open experience and after a 6-month fellowship in robotic and laparoscopic surgery. Preoperative characteristics including age, PSA, and D'Amico risk group were comparable between the study groups. Patients in the robotic arm had longer operative time (330 minutes versus 253 minutes, $P < 0.02$), less node count after lymphadenectomy (12 versus 18, $P < 0.001$), lower PSM (16% versus 32%, $P < 0.001$), improved 3- and 12-month continence rates (95% versus 83%, $P = 0.003$; and 89% versus 80%, $P = 0.09$), and improved 3- and 12-month recovery of erectile function (68% versus 25%, $P = 0.001$; and 55% versus 26%, $P = 0.009$). Although overall complication rates were similar (RALP

40% versus ORP 37%), those occurring in the robotic group were significantly less severe, with 84% being Clavien I or II, versus 46% in the open group, $P = 0.005$).

New concepts in reporting results of radical prostatectomy

The goal of radical prostatectomy has been traditionally described as the ability to excise the cancer completely while achieving good recovery of urinary control and erectile function. While each of the former outcomes has been extensively reported individually, the concept of reporting the likelihood of achieving these three outcomes concurrently, the so called “trifecta,” has gradually spread since first reported by Bianco et al.¹¹ Subsequently, Eastman et al¹² evaluated the trifecta outcomes in 1577 patients who underwent ORP. The trifecta was achieved in 62% of patients at 48 months of follow-up. Patel et al¹³ reported the trifecta outcome in 404 patients who underwent RALP. The trifecta was achieved in 80.3% of patients at 12 months.

As PCa is more frequently diagnosed in younger and healthier men, the current demands and expectations of patients who desire surgical treatment of PCa are much higher and cannot be addressed with the current trifecta outcomes. For example, a patient with a rectal injury and temporary colostomy after RALP can still reach the trifecta. Therefore, patients who have reached the trifecta but have also experienced postoperative complications or positive surgical margins might not be completely satisfied after surgery. In this context, Patel et al¹⁴ proposed a new concept for reporting outcomes after radical prostatectomy: the “pentafecta,” which includes the outcomes of the trifecta in addition to negative surgical margins and absence of perioperative complications. In their report on 332 patients, the pentafecta was reached in 70.8% of the patients by 12 months.

The outcomes of RALP are encouraging when compared with traditional open methods, but more studies with adequate methodology and larger cohorts are warranted. This will allow more definitive conclusions about the advantages of RALP and its place in minimally invasive PCa treatment.

FT

Despite the high incidence of PCa, it is only responsible for 11% of all cancer deaths.¹ This can be attributed to PSA-era screening protocols that allow earlier diagnosis of PCa while it is still localized and treatable. However, many investigators question whether we should treat all cases and postulate that we are overtreating patients.¹⁵ Recent figures indicate that 48–100 patients must be treated to prevent a single cancer death,^{16,17}

and even the most recent surgical techniques discussed previously are associated with morbidity and perioperative complications. A recent study of radical prostatectomy specimens revealed that 78% of patients had indolent disease and could have been managed less aggressively.¹⁸

AS protocols are recommended for patients with low-risk disease, in an attempt to reduce overtreatment. In practice, the 10-year disease-specific survival of men who select AS is between 97% and 100%,^{19,20} but although small, there is always the risk of missing the curative window. Recent analyses reveal that men who defer treatment have higher incidences of biochemical progression following definitive treatment,²¹ with up to 50% treatment failure in a large cohort of patients.¹⁹ This could be a reason for poor acceptance and adherence to AS by patients and physicians. Less than 10% of candidates select AS even when classified as very low risk.²² One study found that more than half of patients following AS drop out to seek definitive treatment and most do have an oncologic basis for doing so.²⁰

FT can be viewed as the middle ground between radical therapy and AS. The concept of FT is extensively applied in other diseases, for example lumpectomy for breast cancer or local ablation of cervical cancer.^{23,24} The goal of FT is to ablate the tumor, specifically leaving nondiseased tissue and the surrounding critical structures unaffected. In doing so, FT could avoid the side effects of radical therapy and provide the oncologic control that AS lacks. By nature, FT is minimally invasive and should offer fewer perioperative complications compared with radical whole-gland treatments.

Although the number of patients that have been treated with FT is low, there are published results of an international panel stating which patients are prime candidates for FT.²⁵ Patients should have low- to moderate-risk disease and favorable tumor topography. Although unifocal or unilateral disease would be most effectively treated with FT, there is an increasing body of literature suggesting that even multifocal bilateral disease might be effectively controlled with FT. This arises from the “index lesion” hypothesis. This theory hypothesizes that progression and metastasis arise from a single aggressive focus, the index lesion.²⁶ Additional low-volume satellite foci are more likely to harbor less aggressive disease.²⁷ It follows that identifying and treating the index lesion will decrease risk of progression and cancer death.

Practical considerations of FT Accuracy of PCa staging

The indications for FT rely on accurate staging of PCa, but this is not always feasible. Studies of radical prostatectomy

specimens of patients initially considered to have clinically insignificant disease reveal that 25% of patients are reclassified and 8.5% have extra-capsular extension.²⁸ Understaging could have serious implications for patients managed conservatively with AS or FT, and this should be factored into treatment decisions.

Some of the inaccuracy of staging is due to biopsy sampling error associated with sextant biopsy. In some cases, extensive biopsy schemes have been shown to improve staging accuracy, but this is still a matter of debate.²⁹ A study of men initially diagnosed with insignificant disease underwent 32-core saturation biopsy, and 70% were reclassified.³⁰ Conversely, another study found no increase in prognostic information for tumor volume or extra-capsular extension in patients with >6 cores.³¹ A recent comparison of 24-core perineal and transrectal biopsy schemes revealed no significant differences in PCa detection.³²

Diagnostic imaging may play a role in identifying patients for FT.³³ Excellent soft-tissue contrast is attained with magnetic resonance (MR), but standard T2 weighted images miss the majority of foci <5 mm and around 10% of larger (>10 mm) foci.³⁴ More sophisticated techniques such as dynamic contrast enhanced MR, diffusion weighted imaging, and MR spectroscopic imaging offer better characterization of PCa focality, stage, and size.^{35–37} Some FT protocols have integrated these multiparametric MR techniques into pre-treatment staging in order to target and contour the lesion suspected of being the index lesion for accurate treatment targeting.^{38,39}

Another recently developed technique that combines the advantages of imaging and biopsy is stereotactic biopsy. Early trials of multiparametric MR transrectal ultrasound (MR-TRUS) fusion systems report 44% improved sampling of significant lesions over 12-core random biopsy alone.⁴⁰ Further, the targeted biopsy schema allow upstaging of lesions that may have been classified as insignificant by 12-core biopsy.⁴¹ MR-TRUS fusion systems with 3D/2.5D registration have reported 2.4 mm precision in phantoms and motion compensation using a closed-loop control system in humans.⁴² Real-time 3D ultrasound and multiparametric MR fusion have been reported in context of an FT trial. Stereotactic biopsy was used to select 14 patients for organ conservative high-intensity focused ultrasound (HIFU).⁴³ Stereotactic biopsies might also play an important role in the future in enabling targeted FT in patients where imaging is negative for cancer. Lastly, navigated stereotactic biopsy might play a role in validating complete ablation post procedure. One study reported feasibility of documenting biopsy

location with image fusion⁴⁴ and has shown the possibility of achieving consistency with re-biopsy sampling.

Evaluation of treatment efficacy

Efficacy of most contemporary treatments is evaluated by the previously described trifecta. This poses a challenge to FT evaluation as there is currently no validated PSA threshold that would be considered fulfillment of the oncological aspect of the trifecta. After lesion-targeted FT and even hemiablation, most of the gland remains vital,^{45,46} hence the PSA does not reach undetectable levels. New standards of treatment efficacy would have to be implemented. Follow-up with PSA kinetics might prove to be one solution, and success could be considered a stable PSA with long doubling time (>3 years).⁴⁶ Another option is using imaging as a surrogate endpoint with or without repeat biopsies.⁴⁶

FT strategies and results

Energy modalities currently being investigated for FT include cryotherapy, HIFU, focal laser ablation (FLA), photodynamic therapy (PDT), and irreversible electroporation (IRE). Cryotherapy uses extreme low temperature (typically -35°C to -40°C)⁴⁷ to cause freeze-thaw injury to target tissue. This technique requires percutaneous insertion of argon or nitrogen probes. HIFU is a noninvasive transrectal or transurethral application of high-intensity acoustic waves that damage target through hyperthermia and cavitation. FLA requires percutaneous insertion of a laser fiber and causes local photothermal destruction of the tissue. PDT causes reactive oxygen cytotoxicity when photosensitizing agents are excited by the output of a percutaneous laser fiber. IRE involves placing electrodes into the target lesion and delivering successive microsecond pulses of direct current. The process creates nanopores in the plasma membrane, inducing apoptotic cell death.

The outcome of these therapies tends to be related to the extent of the ablation and to accurate real-time monitoring of the ablation. The thermal ablative methods (HIFU, FLA, and cryotherapy) allow for close temperature monitoring to ensure that therapeutic temperatures are reached only in the target volume.

Organ-conservative cryotherapy has been reported with adequate oncologic control.^{47–49} Unilateral nerve sparing has been attempted, and data are now available for 48 patients followed for a mean of 4.5 years. Stable PSA was reported in 94% of patients, and of the 24 patients biopsied regularly, there was no evidence of local recurrence in the treated area. Excellent continence (100%) and preservation of preoperative

sexual function was reported (90% of men who were potent before treatment remained potent).⁴⁹ A similar study reported a 96% negative biopsy rate, 93% free of biochemical recurrence, and 88.9% potency preservation.⁴⁸ A study of 60 FT cases reported similar figures.⁴⁷

An FLA trial fused 3D ultrasound with MR imaging to guide transperineal FLA in 12 patients, and temperature was monitored with fluoroptic probes. No perioperative complications occurred, and mild, self-limiting side effects included fatigue, perineal discomfort, hematuria, and hematospermia. Investigators reported no significant decline in sexual or urinary function. Post-treatment biopsy indicated 67% of patients were free of disease in the target area.³⁹ Histopathologic analysis of radical prostatectomy specimens initially treated with FLA has validated treatment efficacy, revealing homogeneous coagulative necrosis of the target volume with no remaining viable cells.⁴⁵ Later, the same group performed fully MR-guided and monitored FLA in two patients without complication. Two weeks post-treatment contrast-enhanced MR imaging revealed devascularization of the target with no evidence of residual disease, damage to the rectum, or damage to the neurovascular bundles.³⁸

The majority of reports of focal HIFU have been hemiablation. In a long follow-up of hemiablation in 12 patients, five patients (41%) required subsequent treatment for recurrence or treatment failure, but not for 5–10 years after first HIFU. The authors report urinary tract infections in two patients and acute urinary retention in one, but a stabilization of international prostate symptom scores at 1 year and overall cancer-specific survival of 100%.⁵⁰ Another group reported early cancer control with a cohort of 20 patients treated with hemiablation. The trifecta of continence, erections, and cancer control was achieved in 89% of patients.⁴⁶ A comparison of whole to hemi-gland therapy revealed no significant differences in biochemical disease free survival, but no differences in quality of life measures were noted either.⁵¹ Conversely, Beerlage et al report that patients with selective lesion-targeted HIFU have reduced local control based on biopsy findings and increased PSA nadir.⁵²

There is one report in the literature regarding focal PDT. Six men were treated on this protocol. After injecting meso tetra hydroxyl phenyl chlorin, light was administered to the lobe with biopsy-proven PCa. Adverse effects were observed, including irritative voiding symptoms in all patients for 2 weeks following treatment, one case of sepsis and one case of stress incontinence. In terms of cancer control, PSA decreased in most patients but biopsy results revealed at least one positive core in each patient following treatment, but it

is unclear as to where the tissue was obtained.⁵³ Several trials using the PDT compound WST11 are underway in an attempt to better define the role of focal PDT in PCa patients.

IRE is a relative new ablative technology. Most investigations into IRE have been in-vitro tests on the PC3 cell line,⁵⁴ and more recently IRE for prostate has been evaluated in a canine model.⁵⁵ A cohort of 16 men with PCa underwent focal IRE, and no periprocedure complications were reported. Post-treatment biopsy showed no viable PCa remaining in the targeted region.⁵⁶ The most promising aspect of this nonthermal modality is that the IRE should not theoretically damage nerves or blood vessels while completely ablating the tumor parenchyma. Experimental models of the prostate revealed that the electric field inside vessels and axons was nil compared with the high field distribution in surrounding tissue.⁵⁷ Also, IRE does not damage extracellular matrix proteins, so the interstitial architecture remains intact. The possible impact of IRE on nerves is still a matter of debate. Electrophysiologic studies of a sciatic nerve contained within an electroporated zone reveal that they remain excitable and conductive both immediately after IRE and 2 weeks later.⁵⁸ In the human trial, potency was conserved.⁵⁶ A different group performed IRE on a porcine sciatic nerve to evaluate the effect of direct IRE on nerves⁵⁹ and reported signs of injury including axonal swelling, fragmentation, and loss, in addition to coagulative necrosis and immune infiltrate, but the electrophysiology was not assessed.

Thus far, neither therapy has emerged as most effective or free from morbidity. The recent interest in FT can be seen in the literature, but there are few reports of treatment efficacy.^{46,60–63} Each energy modality must be investigated with large cohorts and longer follow-up to determine their role in treating PCa and within the FT paradigm.

Conclusion

PCa is being increasingly diagnosed in younger and healthier men. These men are in the prime of their lives and desire an effective treatment that will leave them cancer free, reduce the impact on their quality of life, and allow them to go back to their normal activities shortly after the procedure. In this setting, new technologies have been developed to decrease the morbidity of traditional radical procedures. Robotic prostatectomy is an established procedure, while FT is a promising novelty that might shortly join as part of the armamentarium to treat patients with PCa.

Disclosure

The authors have no conflicts of interest regarding this publication.

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