Focal Therapy: Current Status and Future Directions

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Behfar Ehdaie, Jonathan A. Coleman, and Peter T. Scardino

20.1 Introduction

The widespread practice of screening for prostate cancer among asymptomatic men using the prostate-specific antigen (PSA) test is largely responsible for the dramatic rise in prostate cancer detection and survival [1, 2]. In the United States, the age-adjusted incidence of prostate cancer has increased considerably over the past two decades, rising from 92 cases per 100,000 men in 1975 to a peak of 240 cases per 100,000 men in 1992. Although the incidence of prostate cancer has remained stable at 180 cases per 100,000 men since 2001, annual age-adjusted mortality rates in the United States have drastically decreased, by more than 40 % [1]. Similarly, in the United Kingdom the incidence of prostate cancer has more than doubled, from 47.4 to 102.9 per 100,000 men, while the disease-specific mortality rate has decreased by 11 %, from 26.8 to 23.8 per 100,000 men [3].

B. Ehdaie
Urology Service, Department of Surgery,
Memorial Sloan-Kettering Cancer Center, New York, USA

Health Outcomes Group, Department of Epidemiology and Biostatistics,
Memorial Sloan-Kettering Cancer Center, New York, USA

J.A. Coleman
Urology Service, Department of Surgery,
Memorial Sloan-Kettering Cancer Center, New York, USA

P.T. Scardino (✉)
Urology Service, Department of Surgery,
Memorial Sloan-Kettering Cancer Center, New York, USA

Department of Surgery, Memorial Sloan-Kettering Cancer Center,
1275 York Avenue, Box 65, New York, NY 10065, USA
e-mail: scardinp@mskcc.org

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Despite worldwide improvement in mortality trends across continents, prostate cancer remains a lethal malignancy. In the United States, prostate cancer has been the second or third leading cause of cancer mortality in men in each of the last 75 years. In the European Union, prostate cancer was the third most commonly occurring cancer, causing an estimated 92,200 deaths in 2012 [4]. And although prostate cancer mortality in Asia remains lower than in Western countries, the rate of cancer mortality in Asian countries has been markedly increasing over the last 40 years [5]. Given these data, a diagnosis of prostate cancer continues to indicate a serious medical condition, regardless of the patient's age, health status, or disease risk, and management decisions for localized disease are complex, owing to the paucity of evidence comparing various treatment options.

20.2 Overdetection of Prostate Cancer

The adoption of recommended prostate cancer screening strategies has successfully shifted the detection of prostate cancer to an earlier stage of localized disease, at which point tumors are small and often identified as low-grade. This staging improvement has paradoxically highlighted the limitations in our ability to differentiate biologically aggressive tumors from low-risk, indolent tumors that may be discovered incidentally, using diagnostic techniques designed primarily to detect the presence of any prostate cancer. The lack of a more discriminating test that would distinguish indolent from aggressive cancers, coupled with the risk of treatment-related morbidities and societal costs associated with indiscriminate radical treatment of patients regardless of the threat posed by the disease, has increased awareness of the risks of overtreatment of prostate cancer. This heightened scrutiny has occasionally been taken to an extreme, with some questioning the utility of serum PSA-based prostate cancer screening, despite existing data that document the benefits associated with screening [6]. New, "smarter" screening approaches based on the best clinical and biological data are needed to accurately characterize prostate tumors and to guide appropriate therapies with less risk of overtreatment.

Overtreatment is a key concern in prostate cancer care [7]. Among men treated conservatively, those with moderately differentiated tumors and clinical stage <T2b cancer have less than a 10 % risk of dying from prostate cancer at 20 years and 57 % risk of dying from other causes, on average [8]. However, there has been a significant increase in the use of radical therapy with advanced treatment technologies, such as robotic-assisted surgical procedures and intensity-modulated radiation therapy, between 2004 and 2009, among men who have both low-risk cancer and a high risk of death from other causes [9]. A workshop convened by the FDA and composed of experts representing multiple stakeholders, including urologists, medical oncologists, radiation oncologists, industry representatives, and patient advocates, evaluated potential trial designs for the development of therapies for localized prostate cancer. The consensus recommendation on focal treatment strategies was that future clinical trials should investigate men with low-volume intermediate- and high-risk localized prostate cancer with life expectancy exceeding 10 years.

20.3 Treatment of Localized Prostate Cancer

Prostate cancer management is evolving in response to our improved understanding of the natural history and clinical features of this disease. Standard curative treatments have included radical prostatectomy and whole-gland radiation therapy. Although these treatments are clinically effective in eradicating tumors, patients risk a significant reduction in quality of life and increased posttreatment morbidity, including incontinence, erectile dysfunction, and bowel urgency [10–12]. The results of two recent clinical trials have demonstrated the safety – in the intermediate time frame – of active surveillance in men with localized prostate cancer, with delayed treatment occurring at the time of disease progression [13, 14]. The PIVOT trial reported no difference in cancer-specific and overall mortality at 12 years in men with prostate cancer randomized to radical prostatectomy or observation [14]. Although men on observation incurred an increased risk of bone metastases, especially in patients with high-risk disease, radical prostatectomy was associated with a significant increase in the rates of incontinence (17.1 % vs 6.3 %) and erectile dysfunction (55.9 % vs 18.9 %). Today active surveillance is widely recommended for primary management in men with low-risk prostate cancer (Gleason pattern 6 or less, PSA less than 10 ng/mL, and clinical stage T1c or T2a).

The challenge to clinicians is to accurately risk-stratify patients to distinguish between those who would benefit from immediate treatment and those who could safely be treated expectantly. The current approach to prostate cancer diagnosis is susceptible to systematic sampling errors, in which many tumors detected are low-risk, yet some high-risk tumors are missed, especially when they are located in the anterior and apical areas of the prostate. Prostate needle biopsy using transrectal ultrasound guidance has a false-negative rate (missing a high-grade cancer) of up to 30 %. In the absence of reliable techniques to accurately characterize tumors, it is difficult for physicians to reassure patients that their cancer poses minimal risk, and most urologists recommend immediate radical treatment. In a national registry study across 36 urology practices in the United States conducted in 2010, less than 7 % of patients chose active surveillance among 11,892 men diagnosed with prostate cancer [15]. The explanations for the apparent underuse of active surveillance are speculative, but presumably reflect an assessment of risk by physicians and patients who accept treatment-related morbidity as preferable to uncertainty about the risk of metastatic progression.

The desire to achieve cancer control with minimal side effects has driven current research into minimally invasive, innovative focal treatment modalities that ablate the local tumor without affecting surrounding structures crucial to normal bowel, urinary, and sexual function. Despite the recommendations of previous consensus panels on focal therapy to treat patients with very low-risk disease, today the most promising role for focal therapy is for intermediate-risk tumors, because active surveillance has been shown to be an effective management strategy for most patients with low-risk prostate cancer. The major advantage of focal therapy for intermediate-risk cancers is the reduction in treatment-related adverse effects, compared with radical prostatectomy and radiation therapy. It is unlikely that a trial of focal therapy

in low-risk prostate cancer could demonstrate a clinical benefit compared with active surveillance, in terms of reduced morbidity or better cancer control. The barriers to adopting focal therapy for treatment of intermediate- and high-risk prostate tumors include: accurate identification of the location of the high-grade lesions, appropriate management of incidental multifocal lesions (treat associated high-grade lesions but monitor low-grade lesions), and developing an effective way to monitor patients after treatment to be able to initiate timely whole-gland therapy when necessary to prevent metastases. Future research efforts should seek to identify molecular, genetic, and imaging characteristics that distinguish aggressive prostate tumors from indolent lesions. Recently, a study of men treated conservatively for prostate cancer identified cell cycle progression signatures on needle biopsy specimens as useful predictors of the risk of death from prostate cancer in men managed conservatively [16, 17]. Molecular profiles, along with optimal imaging and biopsy techniques, are valuable tools for prospective clinical trials using improved risk stratification and tumor localization to demonstrate the clinical utility of focal ablation of aggressive tumors and observation of indolent lesions.

20.4 Pretreatment Cancer Classification

To individualize treatment successfully for men with prostate cancer, it is essential to develop reliable methods for accurately identifying tumor location and characterizing biology. Diagnostic magnetic resonance imaging (MRI) is a promising tool for evaluating the location and extent of cancer within the prostate. MR imaging has also been used to direct focal therapy, assess treatment effect, and monitor for disease recurrence or progression. Currently multiparametric MRI (mpMRI) is the best studied modality; it is considered the most accurate imaging technique for detecting aggressive, clinically important cancer [18], and it has been used in risk stratification of low-risk prostate cancer when the image is normal or nearly normal [19, 20]. Using MRI to target lesions for biopsy may prove to be a particularly useful way to identify appropriate candidates for focal therapy [21]. If the negative predictive value of MRI in men with low-risk tumors who have a confirmatory biopsy is >90 %, then the best candidates for focal therapy would be those with a focal area of cancer on systematic biopsy with an MRI that shows no other suspicious areas [19]. The Prostate MRI Imaging Study (PROMIS) is a clinical trial currently accruing patients in the United Kingdom to evaluate the value of MRI in identifying cancer prior to prostate needle biopsy using a systematic template saturation biopsy to compare biopsy histology to imaging characteristics [22].

20.5 Rationale for Focal Therapy

Many urologic cancers (e.g., kidney or bladder) can be treated effectively with focal resection or ablation, in selected cases, as effectively as with whole-gland extirpation with radical surgery [23–25]. Prostate cancer may also be amenable to

organ-sparing focal therapies. The prostate is easily accessible through the perineum and the rectum, and many urologists are experienced in performing image-guided procedures in the gland to obtain diagnostic needle biopsies. The focal therapy's ability to preserve critical structures, including the neurovascular bundle posterolaterally and the rhabdosphincter at the apex of the prostate, could also preserve the patients' quality of life, compared with radical surgery. This therapeutic improvement may be most marked in patients undergoing salvage procedures for recurrent tumors after radiation therapy. Although the potential quality of life benefits of focal therapy makes it an attractive treatment option, future clinical trials are needed to demonstrate effective cancer control.

The most appropriate patients for focal therapy today are not those with low-risk disease that can be effectively managed with active surveillance but those with intermediate-risk lesions. Any biopsy-proven lesion that contains Gleason pattern 4 or 5 cancer, if limited in size and extent, can be treated by ablating the sector of the prostate that harbors the disease, offering patients an opportunity to defer or avoid radical therapy. The challenge for focal therapy is to demonstrate accurate targeting of the index lesion while avoiding serious understaging and subsequent undertreatment.

20.6 Understaging

Eighty-five percent of all prostate cancers are multifocal. Variations in reported rates of multifocality are probably related to patient selection and pathology sectioning technique [26]. However, index lesions account, on average, for 80 % of the total tumor volume and almost always represent the highest-grade lesion within the prostate, as well as 90 % of all lesions with extraprostatic extension [27]. The non-index foci tend to be smaller than 0.5 cm^3, low grade, and confined to the prostate – cancers that, in themselves, would be suitable for monitoring on an active surveillance protocol [28, 29]. In addition, the overall risk of disease progression is mainly associated with the characteristics of the index lesion rather than of the secondary tumor. In contemporary patients, the rate of unifocality appears to be increasing; 38 % of radical prostatectomy specimens contain a single disease site [30], albeit sometimes far too large for focal ablation.

The current diagnostic approach to prostate cancer is susceptible to sampling errors associated with systematic, regionally directed, nontargeted biopsies of the periphery of the prostate gland. Characterization of prostate cancer by stage, grade, and PSA level alone is insufficient to individualize patient management or to select patients appropriate for active surveillance, focal therapy, or radical treatment.

The role of systematic mapping biopsies has been investigated in a prospective study of men who underwent a three-dimensional prostate mapping biopsy after initial transrectal biopsy detected unifocal disease [21]. Among 180 men, 61 % had cancer detected bilaterally and 22 % had an increase in Gleason grade, including pattern 4 or 5. This study demonstrated that the complication rate was 7.7 %, reporting prolonged catheterization in 14 patients and hematuria requiring bladder

irrigation in two patients. Although sampling errors in a standard transrectal ultrasound-guided biopsy are reduced with mapping biopsy, this approach is burdensome for many patients and requires general anesthesia. Therefore, incorporating advanced imaging into the diagnostic approach for prostate cancer would be a useful noninvasive technique, if studies prove the accuracy of MRI to target significant tumors.

Multiparametric MRI demonstrates promising performance characteristics to identify clinically important prostate tumors – those larger than 0.5 cm or high-grade (Gleason ≥4 + 3). Targeting needle biopsy to lesions identifiable by MR imaging, either alone or in combination with a 12-core systematic biopsy, promises greater accuracy and is currently being widely explored [31]. Integrating multiparametric MRI-guided targeted biopsies (with or without systematic biopsies) with standard clinical and pathologic characteristics may add additional prognostic information and improve risk classification by distinguishing indolent from aggressive tumors [31].

The accurate assessment of disease risk remains imperfect with current biopsy and imaging modalities. Despite improvements in characterizing prostate cancer with confirmatory biopsies [32] or multiparametric MRI [33], more studies are needed to determine the accuracy of MR imaging and of MR plus targeted biopsies. These studies will require prospective reporting of MRI data, consistent criteria for identifying which patients to biopsy, and the use of systematic three-dimensional mapping biopsy as the diagnostic standard. Data from these studies will add to the evidence from landmark studies evaluating the accuracy of MRI compared with whole-mount radical prostatectomy specimens. Previous reports were limited by studying only patients who had been selected to undergo radical prostatectomy; therefore, the role of MRI in men with low-risk disease or no previous diagnosis of prostate cancer is unknown [33–35].

If targeted biopsy proves accurate, focal therapy may become an effective intermediate form of treatment for men with more aggressive disease who are ineligible for active surveillance to prevent the progression of disease requiring radical treatment. Refinements in targeted biopsy techniques will be vital for characterizing higher-risk tumors. The selection of patients for focal therapy should be able to extend beyond those with low-risk cancers who are reluctant to accept active surveillance. In the future, clinical trials should include patients with limited size intermediate- or high-risk disease, evaluating clinically significant endpoints, such as local progression or metastases, including time to intervention with radical or systemic therapy for documented progression. For phase III trials, a comparative cohort could include men treated with whole-gland radiation therapy, with the intermediate end points being sustained fall in serum PSA, periodic posttreatment MRI, and confirmatory systematic and targeted biopsies. In the focal therapy arm, re-treatment should be permitted if studies continue to show its low morbidity.

The patient best suited for a focal therapy clinical trial today would have a targetable region of disease or a clearly localized, Gleason 3 + 4 or higher lesion of relatively small volume amenable to focal ablation, who accepts the necessity of long-term follow-up with periodic imaging and repeat prostate biopsies. At

baseline, patients would be characterized by a multivariable risk model that includes PSA, Gleason grade, and clinical stage and extent of disease on biopsy and imaging. The ideal ablative technology would allow real-time visualization of the area of ablation during treatment, eradicate the tumor with minimal damage to surrounding structures, and not complicate future radical therapy, if needed. One caution is the effect of focal ablation on the accuracy of imaging during follow-up. Without evidence to support the superiority of any particular ablative technology, there is room to study a variety of approaches. Currently treatment strategies are largely based on the risk of side effects and the avoidance of potential damage to surrounding structures.

20.7 Thermal Tissue Ablation

Thermal tissue ablation devices create extreme temperature changes within tissue, freezing or heating it to cause necrosis. The effectiveness of hypothermic and hyperthermic forms of treatment is governed by the laws of thermodynamics and affected by tissue-dependant factors, including conductivity, vascularity, and the heat-sink effect.

Cryotherapy has evolved, with the advent of thermal monitoring probes and third-generation cryoprobes that use argon-based gas systems. The use of compressed argon gas rather than liquid nitrogen led to greater precision and mitigation of complications by achieving equivalent low temperatures critical for tissue ablation while enabling the freezing process to start and stop instantaneously, thereby decreasing damage to adjacent organs. Treatments can be delivered even more precisely with real-time ultrasound guidance, improving effectiveness and decreasing treatment-related morbidity. The extreme low temperature required to achieve tumor cryolysis and the surrounding temperature gradient remain disadvantages for focal cryotherapy because the area of ablation must be extended beyond the tumor. The necessity of extending the visualized leading edge of the ice ball at the periphery to achieve tumor ablation exposes surrounding structures to damage [36]. Therefore, achieving effective tumor ablation while limiting side effects such as erectile dysfunction, urethral strictures, and rectal injures has proved challenging [37, 38]. Unfortunately, the lack of rigorous clinical trials of focal cryosurgery prevents an adequate evaluation of oncologic efficacy and side effects. In selected cohorts of men, small retrospective studies report negative posttreatment biopsy rates of 75 % and potency rates ranging from 74 to 90 % [39, 40]. The advantages of focal cryotherapy include real-time assessment of treatment location using transrectal ultrasound and the ability to perform re-treatment safely. However, disadvantages include the inability to assess histologic changes during treatment, lack of precision at the leading edge of the ice ball to prevent collateral damage to surrounding structures, and destruction of local tissue anatomy, which complicates the planning and performance of subsequent radical surgery, should it become necessary. Although most patients recover erectile function with unilateral ablation, the effects of bilateral ablation are greater, should cancer appear in the contralateral lobe in the future.

High-intensity focused ultrasound (HIFU) produces thermal ablation with temperatures above 75 °C to achieve coagulative necrosis within the targeted tissue [41]. The effectiveness of treatment may be limited by interference from tissue factors, including prostate volume (specifically related to the distance from the probe to the anterior tumor) and calcifications. MRI integration with HIFU permits imaging of the tumor for accurate localization and targeting of malignant lesions for ablation. MRI technology permits real-time thermography as treatment proceeds and gadolinium contrast assessment of histologic effect by delineating areas of ischemia or necrosis so the treatment area can be extended or modified to ensure complete ablation of the target [42]. HIFU has been used as focal treatment in primary prostate cancer therapy and in salvage treatment following radiation, with patient outcomes significantly associated with pretreatment tumor characteristics, the patient's functional status, and whether the treatment is primary or salvage therapy [43].

The oncologic efficacy of focal HIFU treatment is difficult to evaluate, given the short follow-up periods in published reports. Recent studies have confirmed that focal HIFU is associated with fewer side effects, compared with whole-gland treatment [44–46]. Preservation of erectile function sufficient for intercourse was reported in 90 % of patients 1 year after treatment; however, larger studies are needed to evaluate the poorer outcomes described on subscales for orgasmic function and erectile satisfaction [45]. In addition, the Clavien classification of complications may underestimate the impact of side effects, including urinary retention or hematuria, especially in patients who are asymptomatic at baseline. Finally, reports of rectal-urethral fistulas in the early experience with focal HIFU suggest a significant learning curve that may limit the broad dissemination of this technology among urologists [46].

20.8 Nonthermal Tissue Ablation

Damage to surrounding structures by thermal tissue ablation spurred the development of chemical ablative treatments. Tumors are selectively targeted by the injection of chemical compounds that produce tissue necrosis without appreciable temperature change. The effectiveness of these treatments relies on the specificity of the compound for the targeted tissue and on sparing surrounding structures from the effects of therapy.

Vascular-targeted photodynamic (VTP) therapy for prostate cancer involves the intravenous injection of a light-sensitive compound that localizes in the targeted tissue and is activated by near-infrared illumination delivered by optical fibers. The treatment effect is mediated through the production of reactive oxygen species and the secondary activation of nitrogen species that initiate rapid necrosis and apoptosis of cells [47]. The advantage of VTP is the minimal toxicity profile reported in initial phase I and phase II studies [48]. The disadvantages of VTP include the inability to monitor treatment during therapy and uncertainty in identifying and retreating recurrences during follow-up. Phase III studies completed in Europe should provide more data to evaluate the efficacy of VTP in men with prostate cancer.

Electroporation transmits pulses of direct electrical current through localized tissue, at levels sufficient to damage cell membranes while sparing surrounding structures [49]. Studies of the use of electroporation in prostate cancer are preliminary at present; however, this treatment has been evaluated in diseases of other organ systems [50]. The main disadvantage of electroporation, as with VTP, is the inability to monitor treatment effect with imaging; the concern is damage to surrounding structures and difficulty monitoring the extent of injury during treatment.

Conclusions

Advances in understanding the natural history of prostate cancer have refined the recommendations for risk-stratified treatment, especially for men with low-risk localized disease. However, the sharp rise in the detection of prostate cancer attributable to routine screening of asymptomatic men ushered in an era of increased use of radical whole-gland treatments. Subsequently, less invasive therapies have emerged that selectively target prostate cancer lesions using organ-sparing techniques that could bring prostate cancer management into line with treatments used for many other solid-organ malignancies. Currently, the clinical experience in focal therapy is limited, and focal prospective trials are few. And although risks seem low, it is difficult to assess benefits. As focal ablative technologies continue to advance, the development of standardized treatment protocols and outcomes reporting will be essential to the accurate assessment of treatment efficacy. Clinical trials are needed to evaluate the benefits and risks of focal therapy for men with intermediate- or high-risk prostate cancer because active surveillance has been found to be a sufficient way to manage low-risk cancers. In this era of overtreatment, coordinated research is needed to personalize patient management by improving risk stratification and providing safe, reasonable, and effective treatment alternatives appropriate to the nature of each man's cancer and the risk it poses to life and health.

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