SECTION I

Is there a role for Focal Therapy in Localised Prostate Cancer?

CHAPTER 1

The Rationale for Focal Therapy of Prostate Cancer

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Introduction

The goals of cancer therapy are either to prevent, cure, or control disease while minimizing the side effects of treatment. One must balance the number of life years gained (quantity) with the morbidity of a given treatment technique (quality). The ultimate goal is to match treatment type with the biological aggressiveness of the disease in an individual patient. A difficult initial hurdle is predicting disease aggressiveness. Nomograms and other risk-prediction instruments incorporating multiple pathologic, laboratory, and clinical measures have become the cornerstone in prostate cancer risk assessment. Accurate risk assessment guides treatment. In contemporary practice there is a continuing movement toward maximizing survival while minimizing morbidity.

This movement is seen clearly when examining the increasing use of laparoscopic and, more recently, robot-assisted laparoscopic techniques in the treatment of prostate and renal cancers as well as conformal and intensity-modulated radiation therapy (IMRT), cryotherapy, brachytherapy, and experimental modalities such as high-intensity focused ultrasound (HIFU) and photodynamic therapy in the treatment of prostate cancer. Minimally invasive techniques that deliver therapy to the cancer alone, with a margin of normal tissue, are attractive since the risks of local progression and thus metastasis are, at least in theory, decreased compared to surveillance, while the morbidity associated with radical resection or whole-organ ablation decreased.

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The therapeutic dilemma

The morbidity associated with radical prostatectomy and radiotherapy is well described and is primarily a result of treatment effects on adjacent structures [1]. Overall, each of the whole-gland radical treatments can be associated with significant morbidity. Radiotherapy causes short-term moderate bowel and urinary toxicity in almost 50% with most having limited toxicity. However, 5–20% with bowel toxicity have long-term persistence. Select surgical series report as high as 27% risk of chronic urinary symptoms. Both radiotherapy and surgery have a near 50% reduction in sexual function, though the reports are widely variable. Additionally, newer techniques and increasing refinement in technology have shown very little change in the toxicity profiles [2].

Therefore, minimally invasive techniques applied to discreet tumor areas, rather than the whole gland, stand to modify treatment impact the most with regard to urethral, rectal, and cavernosal nerve injury. Additional advantages could include reduced hospital stay and earlier return to work. Prostate cancer is biologically unique given the indolent nature and protracted natural history of many lesions. This demands individualized treatment decisions that include active surveillance or active treatment currently in the form of whole-gland therapy. Although the trend is changing in recent years as more compelling data becomes available, few patients elect to defer initial treatment. Between 1989 and 2008, 11,892 men with localized prostate cancer were registered in the CaPSURE multi-institutional database, and of those, only 810 (6.8%) elected to defer treatment and be managed with watchful waiting or active surveillance [3]. The rationale for use of minimally invasive therapies must be based on the following principles:

1. The technique offers similar disease control compared to the current options.
2. It is less morbid.
3. It offers improved outcomes compared to patients managed conservatively.
4. The technique is cost effective.

Prostate cancer has significant mortality worldwide, yet has an incidence-to-mortality ratio of 8.6 in the United States, 3.0 in the United Kingdom, and 1.2 in Africa [4]. Such differences may reflect many factors, one of which is screening rates. This is supported by multiple autopsy series showing that 30–40% of men suffering nonprostate cancer related deaths harbor prostate cancer [5]. Additionally, incidental prostate cancer is found in 23–45% of men undergoing cystoprostatectomy for the management of bladder cancer.

The difficult choices faced by men who have localized prostate cancer are further confounded by the findings from the recent publication of the

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third interim analysis from the European Randomized Study of Screening for Prostate Cancer (ERSPC). This demonstrated a reduction in prostate cancer specific mortality from PSA screening and treatment [6]. However, the healthcare policy implications of screening need to be tempered. First, a randomized controlled study in the United States has shown no difference between PSA screening and control [7], although the control arm had a high degree of contamination since many men had already undergone a PSA test prior to enrolment. Second, there are considerable harms associated with a screening strategy. These include overtreatment and treatment-related harms. The ERSPC showed that 1410 men need to be screened and 48 diagnosed and treated in order that one prostate cancer related death is avoided over a 9-year interval. Overtreatment becomes less of a problem if the treatment is cost effective and associated with very low rates of harm, while eliminating potentially high-risk disease.

Cost

The cancer-attributable costs associated with the first 6 months of treatment in 1999 demonstrated that radical prostatectomy cost $8113, external beam radiotherapy cost $6116, and brachytherapy cost $7596 [8]. Another study from the same time period found mean hospital charges of $5660 for radical prostatectomy compared to $4150 for cryotherapy. Most of the cost savings for cryotherapy arise from hospitalization costs of $2348 for radical prostatectomy and $682 for cryotherapy [9]. Most cost analyses do not take into account lost productivity from multiple treatment visits required for radiation therapy or postoperative visits and urethral catheter time associated with surgery. Costs for newer forms of radiation such as IMRT and proton therapy are higher. Insurers and public interest groups are paying more attention to the costs of care in conjunction with their utility and wide variation in application [10,11]. Minimally invasive interventional techniques delivering focal therapy may have the advantage of being performed in a single, outpatient setting with fewer downstream costs of dealing with side effects, but this may need to be balanced with the rate of salvage therapies in the event of failure.

Conservative management

Active surveillance with the potential for delayed therapy must incorporate several elements:

1 Markers for disease progression are reliable.
2 Patients are compliant.

3 The cancer will not progress at a speed exceeding follow-up windows.
4 Treatment at the time of progression is effective.
5 Patients accept the potential anxiety associated with untreated cancer.

A meta-analysis including 828 patients on surveillance protocols found the risk of metastasis at 10 years after diagnosis in those with well-differentiated tumors to be 19% and cancer-specific mortality 13% [12]. Albertsen and colleagues have shown that many men with prostate cancer die of other diseases. Further, those with low-risk disease (well-differentiated tumors) managed conservatively can expect 10-year prostate cancer specific mortality of 8.3% [13]. Other studies suggest that men with prostate cancer may be at higher risk. Johansson et al. showed that cancer-specific survival dropped from 79% to 54%, as patients managed conservatively were followed past 15 years [14]. In addition, the Scandinavian prostate cancer group randomized trial of patients with localized prostate cancer in the pre-PSA era treated by radical prostatectomy or watchful waiting, revealed significant relative risk reductions in overall mortality, prostate cancer specific mortality, metastasis, and local progression in the former group. However, the benefit to treatment was seen in those less than 65 years of age. In addition, the patients in this trial were notably different than those currently detected with aggressive screening in the United States. For instance, only 12% had T1c disease and 20% had an initial PSA $\geq$20 ng/mL [15].

In the Toronto active surveillance cohort of 450 men overall survival was 78.6%. The 10-year prostate cancer actuarial survival was 97.2%. Overall, 30% had been reclassified as higher risk and offered definitive therapy [16]. The UCSF active surveillance series used stricter criteria and reflected a secondary treatment rate of 24% at 3-year median follow-up, although 37% met criteria for progression and 12% elected treatment without evidence of disease progression [17]. None have died in the UCSF series at a median follow-up of 3.6 years.

Minimally invasive therapies

Minimally invasive interventional techniques have been applied to whole-gland therapy for many years in order to find a middle ground between active surveillance and radical surgery or radiotherapy. The earliest such technique introduced for prostate cancer was radium brachytherapy in 1915. Another percutaneous technique is whole-gland cryotherapy. It shares many similar advantages with brachytherapy. Early outcomes using cryotherapy were worrisome with major complications reported such as urethrocutaneous and rectourethral fistula. Refinements in monitoring, urethral warming, and probe technology have brought about resurgence in interest in cryotherapy. A prospective randomized trial comparing

cryoablation to external beam radiotherapy found near equivalent disease-free survival at 8 years and a significantly higher negative biopsy rate in those managed with cryoablation [18]. Katz et al. reviewed 5-year biochemical-free survival among patients treated with brachytherapy, conformal radiotherapy, radical prostatectomy, and whole-gland cryoablation in different series. When stratified according to low-, medium-, and high-risk disease, cryotherapy was equivalent to other modalities for low- and medium-risk patients and superior for high-risk patients [19]. The major disadvantage to whole-gland cryotherapy is the morbidity profile, most notably with regard to erectile dysfunction (approaching 100% in the whole-gland setting). Third generation, prostate cryoablation techniques have been in use since 2000 and have shown lower complication rates compared to previous techniques except for impotence. Reported complications include bladder outlet obstruction 3–21%, tissue sloughing 4–15%, and impotence 40–100% [20].

Other whole-gland techniques include HIFU and vascular-targeted photodynamic therapy (VTP). Early studies have yielded mixed results regarding efficacy and morbidity for these modalities [21]. For instance, HIFU whole-gland therapy seems to have incontinence rates (requiring pad usage) of less than 1%, impotence rates are still 20–50% [22]. However, application in a focal setting for well-selected patients may prove highly beneficial.

Focal therapy—the middle way?

Currently, minimally invasive modalities are receiving considerable interest applied as focal, rather than whole-gland, therapy [23,24]. Focal therapy involves the local application of therapy to a specific focus with a margin of normal tissue. Therapy can be applied ranging from a small focus to subtotal ablation thereby theoretically decreasing morbidity [25]. Several factors must be considered before focal therapy can be implemented as a routine option for early-stage prostate cancer. First, prostate cancer is often a multifocal disease. However, large studies have shown that between 10% and 44% of radical prostatectomy (RP) specimens harbor unilateral or unifocal cancers [26]. There is growing evidence that the majority of progression is driven by the size ($>$0.5 mL) and grade (Gleason $\geq$7) of the index tumor [27], and that most multifocal tumors outside the index lesion have a volume of $<$0.5 mL, making their clinical significance questionable. Some have argued that tumors $<$0.5 mL may not need immediate treatment [28], thus creating a large population of patients that may benefit from focal ablation of the index or unifocal tumor with subsequent surveillance of the smaller "clinically insignificant" lesions if present. (Figures 1.1a–h).

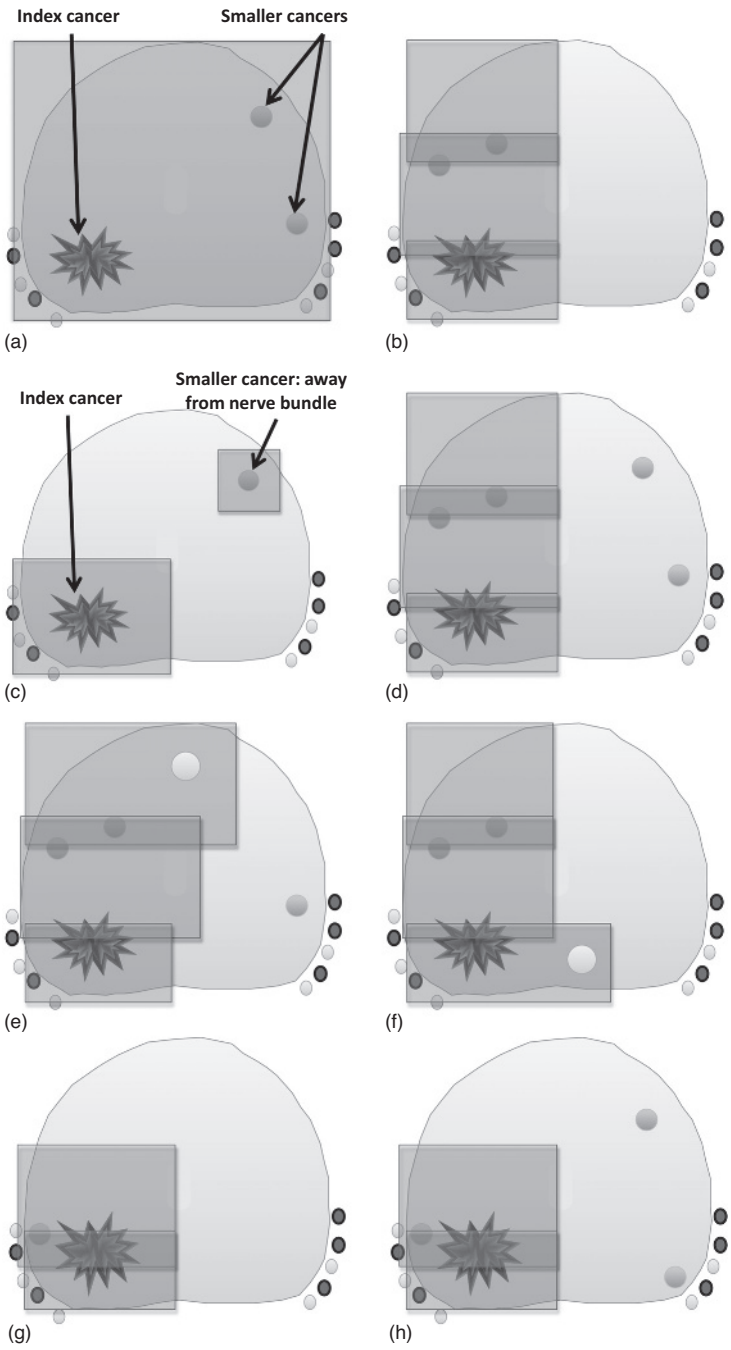

Figure 1.1 (a) Standard whole-gland strategies treat the entire prostate regardless of the risk category, volume, or disposition of cancer. (b–h) These figures illustrate the different strategies that could be employed using focal therapy to ablate either all areas of cancer or just the index lesion.

If focal therapy is to be considered, accurate localization of the index tumor is critical. Both improved biopsy as well as imaging techniques may allow for clearer and more accurate localization. Small prostate cancers have in the past proven to be very difficult to accurately detect radiographically, forcing most clinicians to rely on prostate biopsy to derive location and volume information. This trend is rapidly changing with improved imaging [29] and biopsy techniques such as transperineal template prostate mapping [30]. Given that benign PSA-producing tissue is spared with focal therapy, what constitutes appropriate cancer control measures (other than mortality) to be used in clinical trials is yet to be established. Composite definitions incorporating biochemical, histological, and imaging outcomes are likely to be needed until mature datasets demonstrate whether efficacy is maintained with respect to metastases and mortality [31].

Conclusion

Due to widespread screening, many contemporary prostate malignancies are small and focal in nature. Given the stage and tumor volume migration that has occurred, functional as well as cancer-specific outcomes are being critically assessed. Evidence is growing that novel techniques may offer similar disease control as the current "gold standards" while the treatment morbidity may be considerably less. Refinement and long-term assessment of the techniques described are critical if we are to better understand the role of such therapy in the management of prostate cancer.

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