Rationale for minimally invasive interventional techniques in urological cancer

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Introduction

The goals of cancer therapy are either to cure or control disease while minimizing side effects to the patient. One must balance the number of life years gained (quantity) with the risk of morbidity and mortality 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. Radiographic staging has been the cornerstone in renal cancer prediction, while nomograms incorporating multiple pathologic, laboratory, and clinical measures have become the basis for prostate cancer prediction. The predictions made from this information have, to a substantial extent, guided modern treatment. In modern urologic oncology practice, a continuing movement toward maximizing survival while minimizing morbidity has been seen.

This movement is seen clearly when examining the increasing use of laparoscopic and, more recently, robot-assisted laparoscopic techniques in the treatment of renal and prostate cancers as well as conformal and intensity-modulated radiation therapy (IMRT), cryotherapy, high-intensity focused ultrasound (HIFU), and brachytherapy in the treatment of prostate cancer. More recent interest in focal, percutaneous techniques (i.e., radiofrequency or cryotherapy) reflects this evolution in management.

Minimally invasive interventional techniques are attractive since the risks of local progression and thus metastases are, in theory, decreased compared to surveillance, while the morbidity associated with radical (partial or complete) resection are also decreased. Other advantages regarding localized renal tumor management include technical ease compared to minimally invasive partial nephrectomy, no renal ischemia requirement, relative ease in locating endophytic lesions, the unique opportunity for retreatment with no significant increased morbidity of a second procedure and, finally, decreased convalescence.

The morbidity associated with radical prostatectomy and radiotherapy is well described and is primarily a result of treatment effects on adjacent structures [1]. Therefore, minimally invasive interventional techniques stand to have the greatest impact with respect to cavernosal nerve preservation, and limitation of extraprostatic radiation leading to advantages in erectile function preservation, improved continence, as well as hospital stay and return to normal daily activities and work. These techniques hold similar advantages to those for renal cell carcinoma with the added benefits of relatively easy access to the gland and discrete ablation that could facilitate less than whole-gland treatment.

Renal and prostate tumors are biologically unique and demand individual consideration for possible surveillance, local tumor treatment, or radical tumor
treatment. Select patients that would fall into each of these populations are now being considered for local tumor treatment with minimally invasive interventional techniques. The rationale for use of these modern techniques must be based on the following principles:

1) The technique offers similar disease control compared to the current standard.
2) The technique decreases morbidity compared to the current standard.
3) The technique offers improved outcomes compared to patients managed conservatively.
4) The technique is more cost-effective and, therefore, benefits healthcare services by reducing the overall healthcare financial burden.

Renal cancer
Disease control
With 54,390 newly diagnosed cases annually and 13,010 deaths in 2008, renal cell carcinoma is the most lethal of all genitourinary malignancies [2]. The majority (48%–66%) of new cases are diagnosed incidentally on imaging. Surgical resection remains the standard of care for clinically localized renal cell carcinoma with patients having pathologically small, localized tumors (pT1a) enjoying 5-year cancer-specific survival rates of ≥ 95% [3]. The importance of treatment for renal cell carcinoma localized to the kidney is heightened by the lack of adequate systemic therapy, once the disease has metastasized. This knowledge has historically led urologic surgical oncologists to follow Halstedian principles of wide, en bloc excision. More recently the field has moved toward organ-sparing techniques. Partial nephrectomy has now become the procedure of choice at many institutions for small tumors due to its capacity for renal preservation and similar cancer-specific survival compared to radical nephrectomy for small, localized tumors [4] (Figure 1.1).

Radiofrequency ablation (RFA) and cryoablation remain the primary modes of ablative therapy for the management of renal masses, although investigation is underway using HIFU, laser interstitial thermal therapy, and microwave ablation. Cryoablation appears to be preferred by most urologists over RFA for renal tumors [5] due to its lower retreatment rate (0.9% vs. 8.8%) [6], real-time monitoring, and excellent short-term oncologic outcomes with regard to local recurrence (4.6% vs. 11.7%) or metastatic progression (1.2% vs. 2.3%) [7]. Many series show encouraging, short-term results with ablation carrying a slightly higher risk of recurrence and persistence, but no change in the risk of metastasis as compared to partial nephrectomy.

A major problem with interpretation of data from these series is incomplete tissue staging making it difficult to compare outcomes to surgical extirpation. In most series, a successful ablation is defined as the absence of contrast enhancement [8]. A recent study shows a radiographic success rate of 85% for RFA and 90% for cryoablation at 6 months follow-up. Of the patients who underwent renal biopsy at 6 months, pathologic success (no cancer present) was found in 65% of those managed with RFA and 94% in those treated with cryoablation. This led the authors to conclude that radiographic outcomes were accurate and postoperative renal biopsy unnecessary in those managed with cryoablation [9].
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Morbidity
The driving force behind the current trend toward more minimally invasive methods in treating localized renal cell carcinoma is an attempt to minimize the morbidity associated with open, radical, and partial nephrectomy. Laparoscopic and robot-assisted partial nephrectomy, although oncologically acceptable methods, remain technically difficult for many and can be associated with significant morbidity. The overall complication rate for laparoscopic partial nephrectomy was 19.7% in a large series from experts in the field at the Cleveland Clinic [10]. In select patients, ablative therapies have shown significant advantages with regard to complications. The overall complication rate of partial nephrectomy (majority open) in comparison to ablative techniques for tumors of similar size was found to be 16.3% vs. 2.2% for ablative procedures [11].

Complications have been primarily minor and few in addition to minimal effects on renal function for both RFA and cryoablation [13]. Renal ablative therapies do carry further risk of complications due to the need for renal biopsy before and occasionally after the procedure. Image-guided renal biopsy complications include hematoma (1.3%), transfusion (1.7%), and pseudoaneurysm formation (0.7%) [14]. In addition, one must consider the risks, albeit small and difficult to quantify, associated with radiation exposure during the numerous follow-up studies that are required for proper monitoring postablation.

Comparison with conservative management
Active surveillance for small renal masses, including those that are malignant, has been assessed. Incidental radiographic detection of renal masses has resulted in stage migration downward and an increase in surgical intervention [15]. But is this significantly changing the natural history of small renal masses? Chawla et al have reported a median overall growth rate of 0.28 cm/year for masses ≤ 4 cm, and only a 1% rate of progression to metastatic disease at a median follow-up of 3 years [16]. Volpe and colleagues noted that approximately one third of small masses progress on surveillance [17]. Most surveillance studies, however, are performed using retrospective data from elderly populations. Significant selection bias would be present in studies such as this comparing surveillance to surgical intervention.

Costs
Renal cancer treatment has been estimated to cost $40,176 per patient per year with a monthly cost of $3080 for patients diagnosed with localized disease. Inpatient hospitalization accounted for 42.1% of this cost [18]. Minimally invasive interventional techniques stand to decrease cost substantially by decreasing the hospital stay to 24 hours of observation and decreasing the cost of treating perioperative complications. In a detailed analysis, Panharipande et al concluded that RFA was more cost-effective than partial nephrectomy in the treatment of small renal masses, as long as the relative local recurrence rate remains only 48% greater than that of partial nephrectomy and the cost of partial nephrectomy did not drop more than $7500 [19]. Critical assessment of this study reveals that some series have reported a difference in local recurrence of 11.7% for RFA compared to 2.6% for partial nephrectomy (relative difference of nearly 450%) [7]. In addition, cost-effective analysis must include the rigorous imaging follow-up schedule after ablation, which currently includes CT or MRI scans 3–4 times during the first year based on retrospective data showing 70% of recurrent or residual disease identified within 3 months of initial treatment and 80% within the first year [20].

Prostate cancer
Disease control
Approximately 94% of low-grade prostate cancer patients receive treatment in the modern era [21]. Widespread screening has led to an increasing prevalence of localized disease associated with an improved biochemical free survival [22]. Stage migration with an increased incidence of low-risk disease may allow for new treatment paradigms for low-risk, low-volume prostate cancer. Standard treatment whether surgery or radiation may not be needed in some of these patients. Many could potentially have been treated with a minimally invasive interventional technique or managed with active surveillance.

The earliest minimally invasive interventional technique introduced as prostate cancer treatment was radium brachytherapy, which first appeared in 1913 [23]. Since that time, brachytherapy has undergone profound refinements in implantation accuracy and
dosimetry. Several potential advantages over radical prostatectomy and external beam radiotherapy have been noted. First, it is minimally invasive requiring no incisions and can be done under spinal anesthesia. Second, perioperative morbidity is limited and the procedure, when done using permanent seeds, is performed during a single outpatient visit. Third, recovery is generally rapid with most men returning to normal activities within 48 hours. Fourth, real-time imaging during implantation allows for accurate radiation delivery even during gland movement, preventing unwanted exposure. Oncologic outcomes for brachytherapy alone are associated with 8-year disease-free survival rates of 82% for low-risk and 70% for intermediate-risk disease [24]. Another study reported 12-year disease-free survival at 66% in a series with 80% cT2 patients [25].

Another percutaneous technique is whole-gland cryotherapy. It shares many of the same advantages noted with brachytherapy since its application is essentially identical. A significant advantage over brachytherapy is the creation of a discrete ablative lesion allowing for improved observation of the treatment effect in real time. Early outcomes using this modality were worrisome with major complications reported, such as urethrocutaneous and rectourethral fistula prior to refinement of the technique. Further refinements in monitoring, urethral warming, and probe technology have brought about resurgence of interest in this technique. 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 the cryoablation arm [26]. The major disadvantage to whole-gland cryotherapy was the morbidity profile, most notably with respect to erectile dysfunction.

Other whole-gland interventional techniques have included HIFU and vascular targeted photodynamic therapy. The study with the longest follow-up for patients treated with HIFU reported an actuarial disease-free survival of 59% using the ASTRO-Phoenix definition of biochemical outcome at a mean follow-up of 6.4 years in patients with low- and intermediate-risk disease. Cancer-specific survival was reported at 98% and overall survival 83% [27]. By comparison, another series reported a biochemical disease-free survival of 78% at 5 years [28]. Photodynamic therapy (PDT) was first introduced in urology as treatment for superficial bladder cancer [29]. Although first described as a treatment for localized prostate cancer in 1990 [30], there is renewed interest due to the introduction of novel photosensitizers. The therapeutic effect of these compounds is theoretically limited to the vascular bed and, therefore, should be thought of as vascular-targeted photodynamic therapy (VTP). Phase I/II studies are currently underway assessing the efficacy of this modality in patients who have failed radiation and in low-risk primary disease [31].

Currently, there is considerable interest in focal, rather than whole-gland therapy. Focal therapy involves the local application of therapy to a specific focus under real-time image guidance (Figure 1.2). Therapy can be applied ranging from a small focus to subtotal ablation thereby decreasing morbidity [32,33]. Several factors have to be considered before focal therapy can be considered as an option for early

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**Fig 1.2** Diagrammatic representation of the changing paradigm in treatment of prostate cancer from whole-gland radical therapy (a) (using surgery, radiation therapy, HIFU, cryotherapy) to focal therapy in which all lesions are targeted individually (b) (using HIFU, cryotherapy, photodynamic therapy, photothermal therapy) or the largest index lesion targeted (c). The avoidance of the neurovascular bundles, external sphincter, bladder neck, and rectal mucosa from the treatment zone is likely to lead to less impact on genitourinary function. (Images provided courtesy of Hashim U Ahmed, University College London, UK.)
stage prostate cancer. First, prostate cancer can be a multifocal disease. However, large studies have shown that between 10% and 44% of prostatectomy specimens harbor unilateral or unifocal tumor. There is growing evidence that the majority of progression is driven by the size (≥0.5 cm³) and grade (Gleason ≥7) of the index tumor [34], and that 80% of multifocal tumors outside the index lesion have a volume of <0.5 cm³, making their clinical significance questionable. Some have argued that tumors <0.5 cm³ may not need immediate treatment [35], thus creating a large population of patients that could benefit from focal ablation of the index or unifocal tumor with subsequent surveillance of the smaller “insignificant” lesions if present. A recent study characterized 1000 RP specimens from men with early-stage prostate cancer who had undergone surgery and found that 18% had unilateral disease. In those with unilateral disease, the largest focus of cancer (index lesion) contained 80% of the total cancer present and of the cases with extracapsular extension, 90% of the tumors outside the capsule were associated with the index lesion [36].

If focal therapy is to be considered, accurate localization of the index tumor is imperative. Both improved biopsy, as well as imaging techniques, may allow for clear localization. Small prostate masses (<1 cm) 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 as will be described in subsequent chapters (Figure 1.3). Crawford has described the use of transperineal-guided prostate biopsy at 5-mm intervals (mean of 80.7 cores/prostate) and has shown 95% sensitivity for detecting clinically significant (≥0.5 cm³) cancers [37].

Morbidity

Overall, each of the whole-gland radical treatments can be associated with significant morbidity. Radiotherapy causes short-term moderate bowel and/or urinary toxicity in almost 50% with most having limited toxicity [38]. Five to twenty percent of patients with bowel toxicity have long-term persistence. Select surgical series report as high as 27% risk of chronic urinary symptoms while both radiotherapy and surgery have a near 50% reduction in sexual function, though the reports are widely variable [39]. In addition, newer techniques have shown very little change in the toxicity profiles [40,41]. A recent analysis evaluating outcomes from minimally invasive (laparoscopic and robotic) and open prostatectomy showed that incontinence and erectile dysfunction may be slightly higher in the minimally invasive group [42]. These and similar series should be the standard for which minimally invasive interventional techniques are compared.

Comparison with conservative management

Prostate cancer has significant mortality worldwide [43], yet has an incidence-to-mortality ratio of 8.6 in the United States and 3.0 in the United Kingdom [44]. 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 [45]. Additionally, incidental prostate cancer is found in 23%–45% of men undergoing cystoprostatectomy for the management of bladder cancer [46]. Most recommend early treatment of prostate cancer, although the trend may be changing in recent years as more compelling data becomes available for surveillance.

Surveillance, in lieu of immediate treatment, is likely to become a more popular option for many reasons. 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% [47]. Albertsen and colleagues assessed 767 patients managed conservatively and showed that those with Gleason 6 or less tumors, had a cancer-specific mortality of approximately 30% at 15 years [48]. This is a historical series based on biopsies using sextant cores, and so will have included many men with higher risk disease that was under-sampled. Another often-quoted study by Johansson et al. used to justify active treatment showed that cancer-specific survival dropped from 79% to 54% as patients managed conservatively.
Fig 1.3 Multiparametric MRI in a man with two previous negative prostate transrectal biopsies on a background of a rising PSA (3.6 ng/mL to 5.8 ng/mL) and a positive family history. (a–d) All MRI sequences (T2W, ADC map and high b-value diffusion weighted, dynamic contrast enhancement) on a 1.5 T scanner demonstrate an anterior tumor.
(e) This was confirmed on transperineal template biopsies (circles with lines and the circle with dots; numbers representing maximum cancer core length involvement). (f) The patient subsequently had surgery in which the tumor was again shown to be in the anterior transition zone. See also plate 1.3. (Images provided courtesy of Hashim U Ahmed, University College London, UK.)
were followed past 15 years [49]. Further evidence supporting active treatment is seen in a study describing 192 men who died of prostate cancer, 46% had early-stage tumors (T1-T2a) at the time of diagnosis, and 33% were Gleason ≤ 6 [50]. Finally, the Scandinavian Prostate Cancer Group conducted a randomized trial of patients with prostate cancer detected in the pre-PSA era treated by radical prostatectomy or watchful waiting, which revealed significant relative risk reductions in overall mortality, prostate cancer-specific mortality, metastasis, and local progression in the former group. Notably, only 12% had T1c and 20% had an initial PSA ≥ 20 [51].

A large population of patients are excluded from active surveillance protocols due to the following characteristics: PSA doubling time < 3 years, PSA > 10 ng/mL, tumor in >50% of any biopsy core, tumor present in >33% of all cores, and any pattern Gleason grade of 4 or 5. These strict criteria were relaxed in the Toronto active surveillance cohort of 229 men followed with intervention criteria for biopsy upgrading to Gleason grade ≥ 8 and for PSA DT of ≥ 2 years. In this study 34% dropped out of surveillance due to: PSA DT < 2 years (15%), histologic progression (4%), clinical progression (3%), and patient preference (12%) [42]. Furthermore, the PSA doubling time parameter in the Toronto protocol was changed to 3 years rather than 2 years in order to intervene earlier and because of concerns that more adverse PSA kinetics predicted poorer outcomes. The UCSF active surveillance series used more strict criteria and revealed a secondary treatment rate of 24% at 3-year median follow-up, though 37% met criteria for progression and 12% elected treatment without evidence of disease progression [52]. It must be noted however that of the patients in the Toronto active surveillance protocol only 3/331 (99%) disease-specific survival remains 100% at 10-year follow-up in 42 patients.

Another consideration for those on active surveillance is the relatively large voluntary crossover rate in most series as exemplified by the 12% rate in the Toronto series, and another study finding 45% of men on a surveillance protocol seeking therapy prior to evidence of progression [34]. When strict criteria are applied to candidates for surveillance, Epstein et al found that pathologically indolent disease was present at prostatectomy in 79% of patients [55]. Unfortunately, when these same criteria were examined retrospectively in the large, community and university based cohort of the CaPSURE database, only 16.4% (3101886) of patients met the criteria. And of those patients, only 9% (28310) chose a surveillance strategy [56]. Thus, between the years 1999 and 2004, only 1.5% of patients in this cohort were actually undergoing surveillance in what appeared to be a very appropriate profile for such therapy.

Cost

The cancer-attributable costs associated with the first 6 months of treatment in 1999 demonstrated the costs of radical prostatectomy to be $8113, external beam radiotherapy $6116, and brachytherapy $7596 [57]. 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 exists in hospitalization costs of $2348 for radical prostatectomy and $682 for cryotherapy [38]. 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 radical surgery. Cryotherapy, brachytherapy, and other forms of minimally invasive interventional techniques may have the advantage of being performed in a single, outpatient setting and could reduce treatment costs substantially.

Conclusions

Due to widespread screening and imaging, many prostate and renal malignancies are smaller and more focal in nature. Given the stage and tumor volume migration that has occurred for these malignancies, functional as well as cancer-specific outcomes are being assessed. Minimally invasive interventional therapies provide an avenue for cancer control that may well fit the biologic aggressiveness of such early disease. Evidence is growing that novel techniques, when applied to appropriate patients, may offer similar disease control as the current "gold standards" while the treatment morbidity is considerably less in properly selected patients. Further development of minimally invasive interventional techniques is the next logical step in this progression. Refinement and longer term
assessments of the techniques described (and new ones to be developed) are critical, as we are to better understand the role of such therapy in the management of patients with renal and prostate cancers. If minimally invasive interventional techniques prove efficacious in the long-term, they may very well be the preferred treatment modality for many patients. Given the rapid and impressive growth in our understanding of the biological processes unique to individual cancers and patients, targeted therapy, whether applied locally, regionally or systemically will play an increasingly important role in the management of patients with a variety of cancers.

References

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