Minimally invasive surgical techniques are moving into the mainstream of urological practice. Even less invasive techniques, some of which can involve no use of the knife whatsoever, are rapidly being developed and implemented for treating urological cancer. *Interventional Techniques in Uro-oncology* is the first text to cover these techniques in total and provides a comprehensive review of the state-of-the-art minimally invasive interventions.

This well-illustrated reference provides the basic science behind each technique before explaining when and how best to perform them. It examines their use in different clinical settings, the advantages and disadvantages of each technique in the management of specific tumor types, and their suitability for different patients. Future techniques are discussed including the potential of nanotechnology in the delivery of urologic healthcare. Each chapter is easy to navigate with key points and references.

*Interventional Techniques in Uro-oncology* is an essential reference for training and practicing oncologists, urologists and radiologists as well as the general physician with a keen interest in cancer care. Its approachable style will also inform non-experts on what is available and whether a particular intervention is suitable for their patient in the clinic.

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Interventional Techniques in Uro-oncology

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Preface to the First Edition

The face of urological cancers is changing. We are diagnosing disease earlier with the window of opportunity for cure that is much greater as a result. However, with such a change comes a shift in the pattern of malignancies with low-volume, low-risk disease increasingly found and treated. The need for refined interventions that carry accurate targeting through novel imaging, minimal side effects, and equal effectiveness to extirpative surgery is now more paramount than ever.

We have invited many eminent groups to write the chapters. These physicians not only practice the field they write about but are also endeavoring to forward the technologies and concepts within research programs that have patients with cancer at their heart. We are, indeed, very grateful to these experts.

This book provides a comprehensive review of the state-of-the-art in minimally invasive interventions. It is written for training and practicing oncologists, urologists, and radiologists as well as the general physician with a keen interest in cancer care. It is written to allow the nonexperts among this wider fraternity to understand what is available and whether a particular intervention is suitable for their patient in the clinic.

Hashim Ahmed
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2011
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 metastasis 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
CHAPTER 1

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).

Renal cell carcinomas 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.

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].

**Fig. 1.1** Diagrammatic depiction of the changing paradigm in treatment of renal tumors from whole-kidney radical nephrectomy (a) to partial ablative therapy to one (b) or multiple renal tumors (c). In the latter case, multiple ablative procedures would be most suitable for a patient with von Hippel-Lindau syndrome. (Images provided by Hashim U. Ahmed, University College London, UK.)
RATIONALE FOR MINIMALLY INVASIVE INTERVENTIONAL TECHNIQUES IN UROLOGICAL CANCER

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 [12] 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 13.7% 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
CHAPTER 1

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 urethrocaneous and rectourethral fistulas 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

**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 2.3%–4.5% 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.

Active surveillance with the potential for delayed therapy must incorporate several assumptions: (1) markers for disease progression are reliable, (2) patients are compliant, (3) the cancer will not progress at a speed exceeding follow-up windows, and (4) patients accept the potential anxiety associated with untreated cancer.

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 have died of their disease at a median follow-up of 7 years [53], and none have died of their disease in the UCSF series at a median follow-up of 3.6 years. 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% (310/1886) of patients met the criteria. And of those patients, only 9% (28/310) 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
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assessment of the techniques described (and new ones to be developed) are critical, if 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.

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RATIONALE FOR MINIMALLY INVASIVE INTERVENTIONAL TECHNIQUES IN UROLOGICAL CANCER

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Brachytherapy for prostate cancer

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Brief history

- In 1903 Alexander Graham Bell wrote, “... there is no reason why a tiny fragment of radium sealed in a fine glass tube should not be inserted into the very heart of the cancer, thus acting directly upon the disease material. Would it not be worthwhile making experiments along this line?”
- In 1910 Hugh Hampton Young (pioneer of the radical prostatectomy) used intrarectal radium for the treatment of prostate cancer, with encouraging results. Although known for the perineal radical prostatectomy, he performed only 25 radical prostatectomies from 1906 to 1927. He performed approximately 500 prostate brachytherapy procedures from 1915 to 1927.
- In 1930 Flocks first injected radioactive gold into the prostate for the treatment of cancer.
- In the early 1970s Willet Whitmore and Basil Hilaris at Memorial Sloan-Kettering Cancer Center (MSKCC), New York, were the first physicians to perform I-125 prostate seed implants. An abdominal incision was used to implant the seeds directly into the exposed gland.
- In 1983 Hans Holm, University of Copenhagen, Denmark, was the first physician to perform the “closed” or “nonsurgical” implant method, which utilized transrectal ultrasound (TRUS).
- In 1989 John Blasko, Peter Grimm, Haakon Ragde, and John Sylvester started regular training programs in the Seattle technique at Northwest Hospital in Seattle.
- In the 1990s a dramatic increase in permanent seed implantation occurred in the United States. Significant advances occurred in dosimetry, patient selection, and implant technique including stranded and linked technologies.
- Seed implantation is linked with dosimetry and patient selection. The past 23 years have led to a continual refinement in patient selection, dosimetry, and technique.

Introduction

Brachytherapy has been used as definitive treatment of prostate cancer since the early 1900s. One of the earliest reported experiences was a series of 100 patients treated by Denning in 1922 [1]. Due to inaccurate dosimetry in that era, complication rates were significant and cancer control rates poor. Brachytherapy lost ground to surgery as surgical and anesthetic technique advanced. During the 1960s to 1990s megavoltage external beam radiotherapy (EBRT) became more popular, as it had relatively fewer side effects than surgery and similar survival rates.

In the late 1960s Carlson and Scardino used permanent interstitial radioactive gold-198 combined with EBRT [2]. Memorial Sloan-Kettering Cancer Center
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Fig 2.1 Old open retropubic approach (a) and modern ultrasound-guided transperineal approach (b).

(MSKCC) pioneered the use of radioactive iodine-125 (I-125) seeds [3]. Using an open laparotomy retropubic approach, the seeds were placed directly into the surgically exposed prostate (Figure 2.1a). To achieve a uniform distribution of dose a nomogram table was used to calculate the appropriate number of seeds, of a given seed activity, for various prostate volumes. Those patients in whom orthogonal x-rays revealed a high-quality seed distribution and dose (matched peripheral dose of >140 Gy) achieved a local control rate of 60%. However, in those with a matched peripheral dose of <120 Gy the local control was only 20%. Hilaris and colleagues reported a 70% 15-year cause-specific survival in stage B1 patients treated with high-quality I-125 seed implantation [4–10]. These results were at least as good as the best contemporary surgical and EBRT series in that era. However, limited technology in the 1970s prevented this retropubic technique from consistently achieving high-quality implants. This inconsistency contributed to permanent seed brachytherapy falling out of favor.

The 1980s saw the introduction of multiple technologic advances that led to the rebirth of prostate brachytherapy [11]. Puthawala et al at Long Beach Memorial Hospital in Southern California, pioneered transperineal low-dose rate temporary interstitial brachytherapy (performed at time of open laparotomy) combined with EBRT [12]. Martinez et al used a transperineal applicator to guide the placement of the radioactive implant [13]. In 1983 Holm and colleagues were the first to perform I-125 seed implantation via a transperineal approach using transrectal ultrasound guidance for the placement of the sources [14]. This technique allowed for more accurate placement of radioactive seeds. In 1985 Blasko, Grimm, and Ragde pioneered preplanned transrectal ultrasound, template-guided transperineal permanent I-125 seed implant in the United States. Using improved technologic advancements, patient selection due to prostate-specific antigen (PSA) screening, and improved radiation treatment planning systems (Figure 2.1b) the group demonstrated that consistently high-quality implantation was achievable with appropriately staged patients and appropriate doses of radiation based on the MSKCC experience.

Patient selection

There are three key issues involved in the selection of patients for ultrasound-guided permanent prostate implant (PPI): oncologic issues, technical issues, and toxicity issues. The patient should be a good candidate in all three for PPI to be an ideal management option.

Oncologic issues

Oncologic issues deal with the extent of disease: local, regional, and distant. Patients with proven lymph node involvement (N1) or distant metastatic disease...
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(M1) are not going to benefit from the local control of PPI because they will not have any legitimate chance for cure. For PPI, this would exclude biopsy-proven pelvic lymph node and distal seminal vesicle involvement from being candidates for brachytherapy as monotherapy. Extracapsular extension does not exclude a patient from brachytherapy, as the treatment includes a margin around the prostate. In palliative situations where local disease progression is causing symptoms, the role of brachytherapy for control of local symptoms of disease progression are limited and more easily treated (with less toxicity) by surgical procedures, such as transurethral resection of the prostate (TURP) or transurethral laser therapy, androgen ablation or external beam radiation therapy, or a combination of these.

The ideal candidate for I-125, palladium-103 (Pd-103) PPI, or cesium-131 (Cs-131) monotherapy is a patient with a low risk of microscopic extension beyond 1–3 mm. The risk of microscopic disease extension outside the prostate has been reported by Partin and colleagues [15–17]. The Partin tables correlate the risk of extraprostatic extension (EPE), seminal vesicle (SV) involvement, and lymph node (LN) involvement with the pretreatment biopsy Gleason score, clinical stage by rectal examination, and PSA level. The nomogram was based on the pathologic examination of 5730 radical prostatectomy specimens. The original work has recently been updated with results showing a reduced risk of extraprostatic disease extension for each of the categories, as a result of earlier disease detection in the current PSA era [18].

Some patients with documented EPE at radical prostatectomy have a low biochemical relapse free survival (BRFS) rate and others a high BRFS. Davis [19], Sohaya [20], and Chao [21] separately published the results with trimodality therapy, including neoadjuvant androgen deprivation therapy, external beam radiation therapy (EBRT) or surgery, and androgen ablation. Whether this is an independent risk factor in PPI patients has yet to be proven.

Few studies have many patients in the high-risk group treated with monotherapy. The initial PPI experience of D’Amico at the Hospital of the University of Pennsylvania showed poor BRFS with the high-risk patients treated with monotherapy, but the quality of these initial implants is in question because of learning-curve issues, the relative lack of postoperative CT dosimetry, and surprisingly poorer results in their intermediate-risk patients, as compared to contemporary reports from the New York and Seattle groups [24, 25]. Data from Seattle with Pd-103 monotherapy showed better results than those published with three-dimensional conformal therapy (3D-CRT) or surgery, but it was a small number of patients and has not yet been duplicated by others [25]. Data reported from Mount Sinai Medical Center demonstrated promising results with tritomicl therapy, including neoadjuvant concurrent, and adjuvant androgen deprivation therapy, external beam radiation therapy (surgical vesicles plus prostate), and seed implant boost [16]. The standard brachytherapy treatment of high-risk disease, at this time, is EBRT + seed implant boost with I-125, Pd-103, or Cs-131 with or without hormone therapy. Long-term (15-year) BRFS outcomes

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were published by Sylvester et al and showed a rate of 67.8% BRFS in high-risk patients treated by 45-Gy EBRT followed by Pd-103 or I-125 boost [37].

While monotherapy is generally recommended for low-risk patients and combined therapy for high-risk patients, the choice of mono versus combined therapy is more difficult for men with intermediate-risk disease. Some studies show excellent 5- and 10-year BRFS with PPI monotherapy, whereas others (usually involving implants carried out during the initial learning curve) have not [24,25,30,37–40]. The Seattle group previously reported the outcomes of their intermediate-risk patients treated with PPI, with or without EBRT. The data did not show any statistically significant difference between the two regimens, but the patients treated with combined therapy had worse pretreatment risk factors and longer follow-up, yet enjoyed a 4% better BRFS (not statistically significant) [41]. In a recently published series, they showed that 9-year BRFS outcomes for intermediate-risk disease treated from 1998 to 2000 of 91.9% in both the seed monotherapy and the combination EBRT + seed implant boost cohorts (80 patients in each). This was not a randomized trial and selection bias favored the monotherapy cohort [42].

The intermediate-risk group is heterogeneous. The current definition in Seattle of a favorable intermediate-group subset, or “Low-Intermediate Risk Group”, includes those patients with Gleason 3 + 4 = 7, ≤1/3 core biopsies positive, PSA ≤10 or Gleason 6 and PSA 10–15 ng/mL. This group will tend to have high biochemical control rates with PPI monotherapy provided the quality of implant is high and lateral margins generous (~5 mm). [43] Intermediate-risk patients with worse prognostic factors such as a high percentage of positive biopsies may be served best by EBRT plus PPI, but the data are not yet conclusive for this patient-risk cohort. A second random con.

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Technical issues

Technical issues need to be evaluated before a patient becomes a candidate for PPI. The preoperative planing TRUS prostate volume study can determine the gland volume and assess for the presence of pubic arch interference (PAI). If the prostate is much greater than 60 mL, the implant becomes technically more challenging. Large prostates also require more needles and seeds to achieve adequate dosimetric coverage. This increases the bleeding and trauma within and around the gland. Intraprostatic and peri-prostatic bleeding during the procedure can interfere with prostate visualization on ultrasound, and therefore negatively impact the quality of the implant. Prostate swelling and bleeding into the perineum can also move the prostate further away from the perineum and template, making it difficult to track the base position of the prostate. This can lead to underdosage of the base if one fails to adequately utilize sagittal imaging. In addition, the increase in trauma and swelling can increase the risk of acute urinary symptoms, including acute urinary retention. Thus, ideally the prostate should be less than 60–70 mL or reducible to this with androgen ablation, or a combination of an oral antiandrogen and a 5-alpha reductase inhibitor.

Significant PAI can prevent proper placement of needles, and therefore seeds, along the periphery of the gland. This in turn can decrease the margin of tissue treated anterior and laterally along the prostate capsule, and may underdose microscopic extracapsular extension. The technique for assessing this risk is discussed in the ultrasound-planning section. Evaluation of the pubic arch in every patient is necessary since occasionally a patient with an average size (30–40 mL) prostate will have significant PAI. If necessary, medical downsizing can be used. Traditionally, a combination of LHRH agonist depot and oral antiandrogen is used. Approximately 30%–40% volume downsizing effect can be seen after 3 months of total androgen...