Focal Therapies for Localized Prostate Cancer

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Introduction

With the increased uptake of PSA testing within both formal and informal screening programs, and increased public awareness of the disease, men are being diagnosed with prostate cancer earlier in its natural history. As a result, there has been a major shift in the incidence and prevalence of low- to intermediate-risk prostate cancer [1]. The benefits of screening and early cancer detection are equivocal. The European Randomized Study of Screening for Prostate Cancer (ERSPC) showed a 20 % reduction in prostate cancer mortality in the screened population compared to the control arm [2]. However, this comes at a price as 1,410 men needed to be screened and 48 diagnosed and treated in order that one prostate cancer-related death was avoided over a 9-year interval.

At present, men diagnosed with low-risk localized prostate cancer face a difficult decision between two extremes of care: active surveillance and radical therapies. The former avoids the side effect risks of radical treatments but with the added burden of regular invasive tests (usually PSA blood tests 3–6 monthly and prostate biopsies every 1–3 years), the risk of progression, and the psychological morbidity of living with the disease. Radical therapies allow near certainty of cancer clearance but with an associated significant side effect profile including impotence, incontinence, and rectal toxicity. Thus, the screening related shift in disease profile has not been accompanied by an alteration in our approach to low-risk disease. Knowledge of which disease we need to treat, and which disease can be monitored over time, has not shifted in a parallel manner to the change in disease profile. As a result, the risk of overtreatment, and treatment-related harms, is significant. This risk becomes less of a problem if a treatment can be delivered that is cost-effective and associated with very low rates of harm, while eliminating potentially high-risk disease.

Focal therapy, the selective treatment of part of the prostate, may offer a middle way between these two extreme management strategies of active surveillance and radical therapies (Fig. 66.1). If cancerous tissue can be successfully and definitively treated while preserving normal tissue, men are potentially offered cancer treatment with minimal functional impact, as adjacent structures such as the neurovascular bundles, external urinary sphincter, bladder neck, seminal vesicles, and rectum are avoided. This move toward tissue-preserving therapies is a strategy that has well served other oncologic specialties. For example, there has been a move from mastectomy to lumpectomy for localized breast cancer and from nephrectomy to partial nephrectomy, or even focal lesion control (e.g., radiofrequency ablation) for localized renal cancers. Thus, the potential of focal therapy as a primary treatment for prostate cancer has been the focus of discussion by clinicians and researchers worldwide in recent years [3–13]. In addition, focal therapy may provide an option for cancer control in patients with recurrent disease, minimizing the acknowledged high rate of side effects that occur with other salvage treatments, while potentially delaying the need for systemic hormone ablation treatment.

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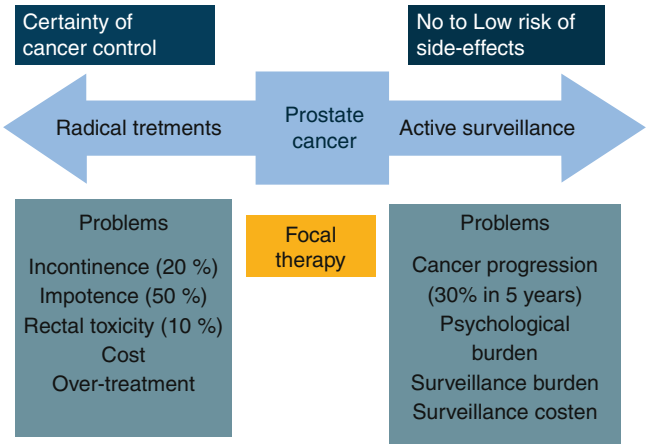

Fig. 66.1 Focal therapy as an alternative treatment option for localized prostate cancer (Figure first published in *BJU International*, 2010)

Focal Therapy as an Alternative Treatment Strategy to Current Standard Care

An international consensus expert panel recently defined focal therapy as "a type of treatment that aims to eradicate known cancer within the prostate and at the same time preserve uninvolved prostatic tissue with the aim of preserving genitourinary function" [14]. There are two patient cohorts that might potentially benefit from this strategy as a primary treatment: firstly, men with low-risk disease who opt for treatment over active surveillance and secondly, men with intermediate-risk disease for whom radical therapy has been offered, but who place particular value on preservation of functional status.

Defining who is and who is not a candidate for focal therapy is, in the absence of knowledge of the long-term outcomes of the intervention, a potentially contentious issue. The arguments are polarized to two schools of thought. First, that a novel intervention has, by definition, high levels of uncertainty associated with it and should only be offered to a group of men with a low chance of disease progression and thus a low chance of prostate cancer-related death (the active surveillance cohort). The second is to adopt the position that men with low-risk characteristics are not destined to die of prostate cancer over a 15–20-year window, [15] and therefore any intervention has a very low chance of conferring benefit and therefore can only confer harm. This position would encourage the inclusion of patients with characteristics that would increase their chances of disease progression if left untreated. In other words, a pragmatic strategy might be to incorporate men with higher-grade tumors but with an upper limit of tumor burden that is deemed feasible and safe to treat.

Focal Therapy as an Alternative to Active Surveillance

Active surveillance is a strategy that enables maximum tissue preservation and hence genitourinary function but with planned delayed treatment of low risk or occasionally low-volume intermediate disease. It involves a regular program of PSA blood tests and prostate biopsies, with the associated interventional and psychological morbidities that these procedures carry. Many men undertake this "watch and wait" strategy in order to preserve function as long as possible. While approximately 10 % of men on active surveillance choose to have intervention despite the absence of biochemical or histologic progression, questionnaire surveys have shown that there are conflicting findings about the anxiety levels present in such cohorts [16]. The latest report from a large active surveillance cohort in Toronto has demonstrated that of 450 on active surveillance, approximately a quarter of the population was treated radically, with a median follow-up of 6.8 years [17]. In these 117 men, the PSA failure rate was 50 %, a relatively high rate, and upgrading occurred in 30 % of men.

Active surveillance relies on accurate baseline characterization of disease burden. It is likely that a significant proportion of those men that "progress" within 5 years do so not due to true cancer progression but due to the poor accuracy of diagnostic transrectal ultrasound-guided biopsies in ascertaining baseline burden [18]. In any case, despite this significant level of "disease progression," the 10-year actuarial prostate cancer survival rate was high at 97.2 %, again suggestive of overtreatment in patients with low-risk disease. However, it may be possible to alleviate patient anxiety by selectively treating cancer lesions and extend the period without side effects if focal therapy were to be carried out either at diagnosis or at the time of disease progression instead of radical therapy.

Thus, the two main arguments for focal therapy as an alternative to active surveillance are firstly, to reduce the potential psychological morbidity of delayed intervention with the approach that "some form of treatment is better than none," and secondly, to reduce the cancer progression and/or reclassification rate that currently occurs in about one-third of men who undergo active surveillance.

The arguments against men who are suitable for active surveillance undergoing focal therapy are that any treatment within this group is liable to be overtreatment and regardless of the encouraging functional outcomes that it may demonstrate, will carry greater morbidity than a management strategy in which two-thirds of men with low-risk disease can avoid treatment while the others can delay such morbidity.

Focal Therapy as an Alternative Strategy to Radical Treatments

The benefit of "no treatment" versus radical treatment for localized prostate cancer remains uncertain. The Scandinavian Prostatic Cancer Group Study, which randomized 695 men to watchful waiting versus radical prostatectomy, demonstrated a reduction in disease-specific mortality of 14–9 % with radical surgery over a median follow-up period of 8 years [19] suggesting that radical therapies improve survival. However, the patient cohort in this trial involved mainly men with clinically palpable tumors and PSA levels of up to 50 ng/ml, a disease profile that differs from the PSA-screened population of today. In addition, the true effects of radical prostatectomy on disease-free survival should be tempered, as the result incorporated a higher percentage of men that were treated with hormone ablation therapy within the watchful waiting arm compared to the radical prostatectomy arm. In addition, the recent update showed no statistical difference in disease-related mortality in the two groups at a longer follow-up period of 12 years [20].

Even with significant recent advances in technology, and a move toward minimally invasive therapies, the functional outcomes and recovery periods for patients following radical therapies remain significant. Although there have been no prospective randomized trials comparing techniques, laparoscopic and robot-assisted laparoscopic data suggest that blood loss and length of hospital stay are favorable compared to the open radical prostatectomy approach [21]. However, the data does not currently support the belief that cancer control and functional outcomes will be significantly improved with the minimally invasive techniques. The side effect risks remain similar as the whole prostate is treated or removed, with unavoidable collateral damage to the surrounding structures. Radical surgery causes chronic urinary symptoms in one-third of men. The alternative radical therapy, i.e., radiotherapy, causes moderate anorectal and urinary side effects in 5–20 % of men. Both radiotherapy and radical surgery cause impotence in 30–90 % of men depending on which modality is used and the particular series looked at (high-volume centers of excellence generally get better results) [22].

A strategy that treats the cancer rather than the organ may reduce the side effect burden while allowing adequate cancer control. One strategy could be to selectively treat all clinically significant cancer and carefully monitor untreated tissue for *de novo* cancers and/or progression of clinically insignificant disease. This may obviate the need for any further radical therapies in future or delay it for a number of years during which the man is free of treatment-related side effects.

The theoretical problem posed by focal therapy is that selective treatment of a target volume of tissue deemed to contain a cancer may incur a miss due to poor targeting, poor staging, or both. The result would be that a cancer with metastatic potential may be given a time window to progress that would not have been available had radical whole-gland therapy been employed.

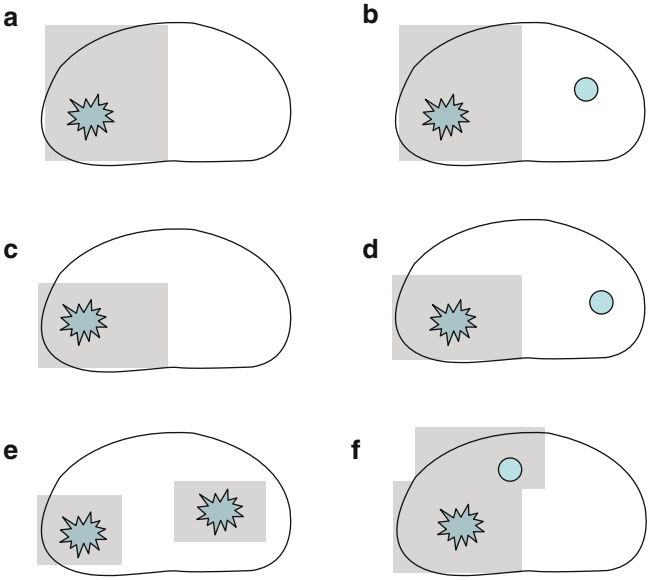

Fig. 66.2 Example treatment protocols for "focal" therapy. (**a**) Hemiablation (all detected tumour). (**b**) Index lesion hemiablation. (**c**) Quadrant ablation. (**d**) Index lesion quadrant ablation. (**e**) Bilateral focal ablation (sparing at least one neurovascular bundle). (**f**) Hemiablation with anterior extension ("dog leg")

Selecting Candidates for Focal Therapy

Focal therapy challenges our understanding of both the distribution of cancer foci within the prostate and which cancers we do and do not need to treat. As prostate cancer is a multifocal disease in most men, can targeted ablation really be a feasible option? One approach may be to treat only those men with unilateral or unifocal disease. An alternative approach may be to ablate only the "clinically significant" disease, with a surveillance strategy for the untreated "clinically insignificant" disease (Fig. 66.2). Both approaches require accurate methods for detecting, localizing, and characterizing cancer foci in order to plan treatment and for reliable follow-up of untreated foci.

Disease Profile

Multifocal Versus Unifocal Disease

A number of studies now show that prostate cancer in the PSA screened era is increasingly unilateral or unifocal.

Indeed, unilateral disease has been shown to exist in 20–40 % of men, while unifocal disease in contemporary series may be present in 10–44 % of men with newly diagnosed localized prostate cancer [23–28]. However, the data on multifocality arises from verification studies performed on men who have undergone radical prostatectomy. It is possible that the group of men who are recommended to undergo radical prostatectomy are likely to overrepresent the proportion of men who have multifocal disease compared to those men with screen-detected disease who opt for other management strategies (surveillance, radiotherapy/brachytherapy, minimally invasive treatments). Thus, this group is subject to work-up bias. Although this is more likely in European countries, and particularly in the UK in which active surveillance is well established, it is difficult to verify. However, a larger proportion of men than previously thought may be suitable for focal therapy whereby all of the known disease is treated.

The Index Lesion

Most men with multifocal disease have between two and three separate foci at diagnosis. Among these foci, there usually exists a dominant lesion that accounts for about 80 % of the total tumor volume (mean tumor volume varies between 0.5 and 2.3 cc) [29–32]. The implication of this observation is that the other 'nondominant' lesions account for 0.1–0.4 cc of tumor on average. By far, the majority of these small cancer foci will be of low grade and will conform therefore to most of the definitions of "indolence" [32, 33]. Lesions above 0.5 cc are the ones that tend to harbor Gleason scores of seven or greater and are responsible for extracapsular extension if present.

Epstein et al. [34] have classified foci into insignificant tumors and minimal, moderate, and advanced tumors using a radical prostatectomy series but drawing on the literature demonstrating pathological characteristics of tumors found in radical prostatectomy, autopsy studies, and cystoprostatectomy. Additional evidence pointing to the role of volume of cancer driving disease progression has emerged from retrospective cohorts evaluating rates of biochemical failure after surgery and radiotherapy [35–37]. Other studies have shown total tumor volume predicts failure on univariate analysis but not on multivariate analysis likely due to the strong influence of Gleason score [38, 39]. Evaluating the predictive power of the index lesion seems to demonstrate a relationship [40, 41]. This may explain some of the discrepancy evident in the literature.

Evidence from molecular genetic studies, which point to a single clone being responsible for metastases, demonstrates that there is usually only one clinically significant clone in the prostate and therefore presumably one clinically significant lesion. This study could not demonstrate whether the metastatic clone resided in the index lesion [42]. It may seem reasonable to propose that ablation of the dominant lesion(s) by volume and grade will give rise to disease control provided the remaining lesions can be well characterized in the pretreatment evaluation [43]. In fact, it could be argued that definitive knowledge of whether index lesions drive disease progression could only be answered within a clinical trial that involves careful selection and follow-up to ensure that progression of untreated areas of cancer is detected early.

Disease Localization and Characterization

In order to evaluate suitability of candidates for focal therapy, an accurate assessment of the target disease to be treated is required. Using the arguments above for the prognosis of prostate cancer by pathological characteristics and lesion size, the test needs to adequately sample or visualize all of the lesions of clinical significance. The current "gold standard" of TRUS-guided biopsies is likely to be inadequate for this purpose. A number of alternative biopsy strategies and imaging modalities have been proposed or are currently under evaluation.

Biopsy Techniques

TRUS-guided prostate biopsy techniques have advanced over the years, with improved ultrasound technology and an increase in the recommended number of cores taken. However, despite an increase from six cores to the current "extended" standard of between 10 and 12 cores, or even saturation biopsies, it is still recognized that this technique has a high false-negative rate, especially in the detection of anterior tumors [44]. In the context of focal therapy, accurate siding of the cancer lesions is a particular concern. Despite this, most focal therapy series to date have relied on TRUS-guided biopsies to assess eligibility, plan treatment, and assess response to treatment.

Some groups are now showing high cancer detection rates with the use of targeted transrectal biopsy of image-detected suspicious lesions [45]. If prostate imaging can meet the standards required to rule in and rule out "significant" disease, then this may provide the optimal diagnostic test, with histopathological confirmation of cancer on limited targeted biopsies of image-detected lesions. Until that time, an alternative approach may be required. The transperineal template-guided technique has been proposed as a more accurate method for "mapping" the prostate for cancer foci (Fig. 66.3). It involves biopsies taken via the perineal skin, with sampling of the prostate at 5 or 10-mm intervals through a brachytherapy grid, performed under general anesthetic. The technique has been shown to be approximately 95 % accurate in locating all significant tumor foci. Recently, the Colorado group demonstrated that prostate template mapping biopsies detected all tumor subsequently found on whole-mount radical prostatectomy specimens [46, 47].

As the prostate is sampled via a "clean" approach, sepsis rates are much lower compared with the transrectal approach.

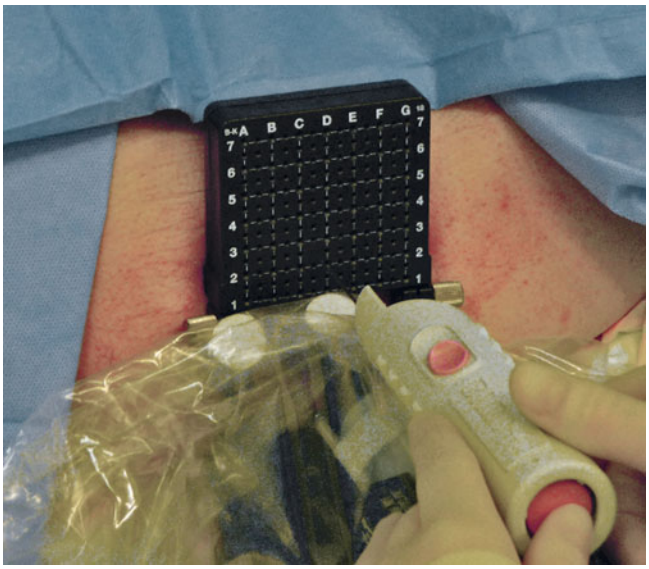

Fig. 66.3 Transperineal template prostate biopsies

The main acknowledged risk of acute urinary retention can be limited with the use of perioperative alpha-blockers. Thus, despite the need for general anesthetic and theater time demands, transperineal template-guided biopsies have been proposed (and accepted by some groups), as the standard to which trials in focal therapy should evaluate patients' eligibility [6, 48].

Imaging

As opposed to other solid organ cancers, imaging is not considered a component of the diagnostic pathway for prostate cancer. Instead, reliance is placed on histological sampling of the gland via prostate biopsies, with the aim of capturing cancer in a "blinded" manner. However, with improvements in technology and our understanding of the imaging phenotype of prostate cancer, imaging may now take an essential role in prostate cancer diagnosis and in the assessment of suitability for focal treatments.

Ultrasound

Although cancers often show up as hypoechoic lesions on normal gray-scale TRUS, this modality is currently neither sensitive nor specific enough to accurately evaluate disease burden or identify the index lesion for focal therapy purposes. However, the addition of color Doppler ultrasound, which assesses regional blood flow, may have a future purpose in identifying the index lesion [49]. Other techniques using ultrasound are now emerging that demonstrate improved accuracy for prostate cancer detection and localization over gray-scale ultrasound. One is contrast-enhanced ultrasonography (CEUS), which uses microbubble contrast agents to visualize prostate cancers through alterations in microvascularity. It has already been used in the context of focal therapy, for monitoring ablative lesion formation [50]. Another is HistoScanning™, a tissue characterization modality that detects and localizes the acoustic signatures produced by tissue of altered morphology, i.e., tumors, compared with normal tissue (Fig. 66.4). Pre-trained algorithms are applied that interrogate raw backscatter 3D ultrasound data and translate them into visual, interpretable signals indicating the presence or absence of disease. Retrospective analyses using whole-mount step-sectioned radical prostatectomy specimens as the reference standard have demonstrated that HistoScanning™ can reliably detect and locate clinically significant lesions of at least 0.5 cc in volume [51, 52]. Finally, elastography is a method that assumes that malignant tissues have different elastic properties to benign tissue and has demonstrated sensitivities of around 85 %, with improved detection of high-grade disease [53].

Multiparametric Magnetic Resonance Imaging

Traditional MRI uses T1- and T2-weighted sequences, but newer sequences such as diffusion-weighted (DW), magnetic resonance spectroscopy imaging (MRSI), and dynamic contrast enhancement (DCE) using intravenous gadolinium, have been used to improve the accuracy of this imaging modality (Fig. 66.5). A number of studies suggest that with the addition of these sequences, in the so-called multiparametric MRI (mpMRI), 90–95 % of lesions of greater than 0.2 and 0.5 cc in volume are detected [54]. Thus, imaging for prostate cancer with MRI has progressed from its initial use to stage the disease to its present-day capability to identify tumor burden and the precise location of tumor foci within the gland. In fact, a number of centers are now using mpMRI prior to prostate biopsies in order to detect, localize, and characterize prostate cancer [55]. Expert consensus is now being reached on the optimum conduct and interpretation of images for this purpose [56] in an attempt to standardize practice. In addition, mpMRI allows the morphological characteristics of the tumors to be visualized so that margins are better incorporated within a focal treatment plan [57].

Therapeutic Options for Focal Therapy

There are a number of energy sources that can be used to ablate tissue in a focal manner. An ideal focal therapy is one that offers precise ablation within millimeters of tissue volume, with quick delivery, minimal impact to the patient in terms of discomfort and side effects, and within a day-case setting. Several methods are demonstrating promise in delivering these ideals. Cryotherapy, high-intensity focused ultrasound (HIFU) (Fig. 66.6), and photodynamic therapy (PDT) are the most established techniques to date, all having been evaluated within phase II studies. These are discussed in the following section, together with other possible focal therapies of the future.

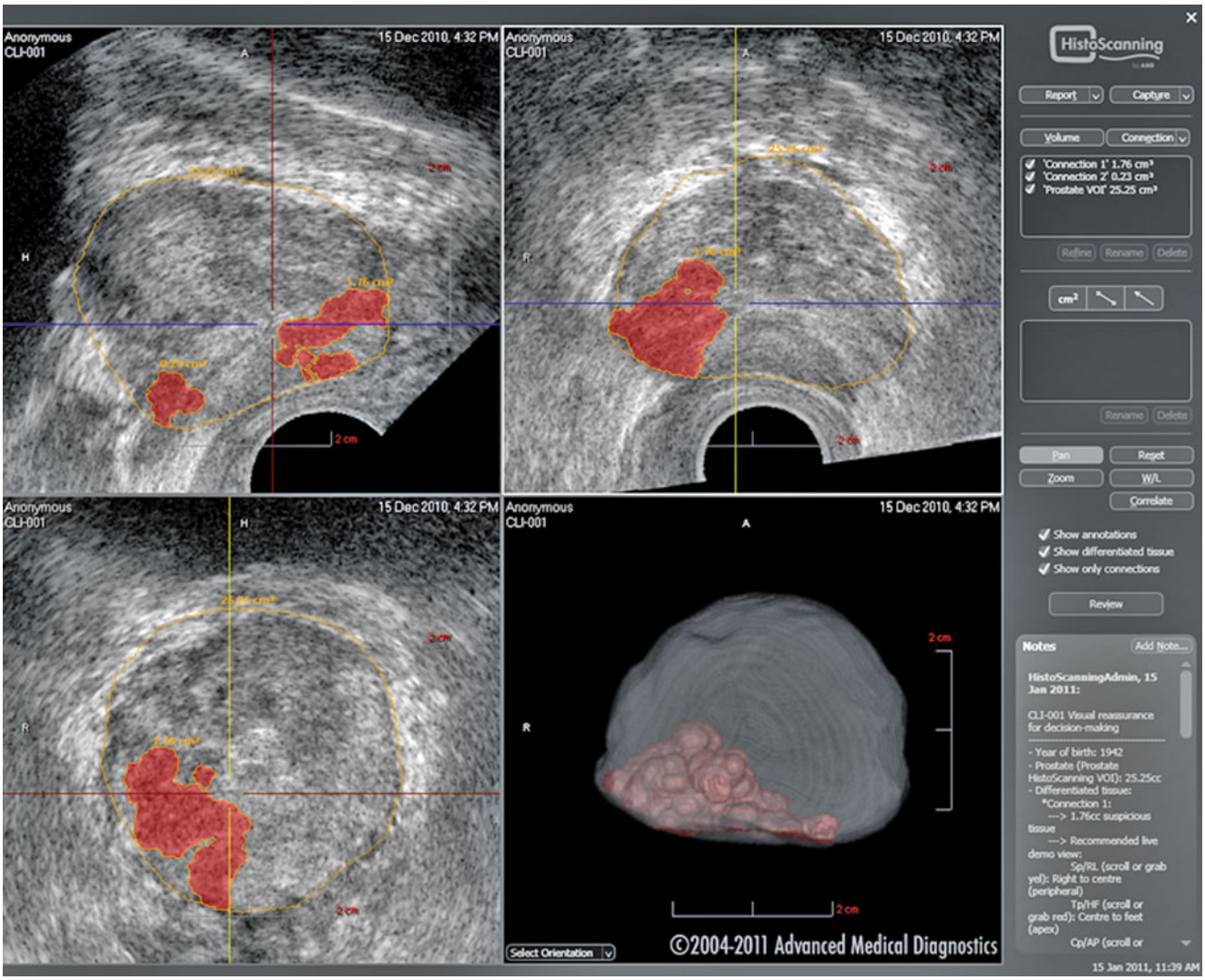

Fig. 66.4 HistoScanning™ images indicating right-sided prostate cancer (Courtesy of Advanced Medical Diagnostics, Waterloo, Belgium)

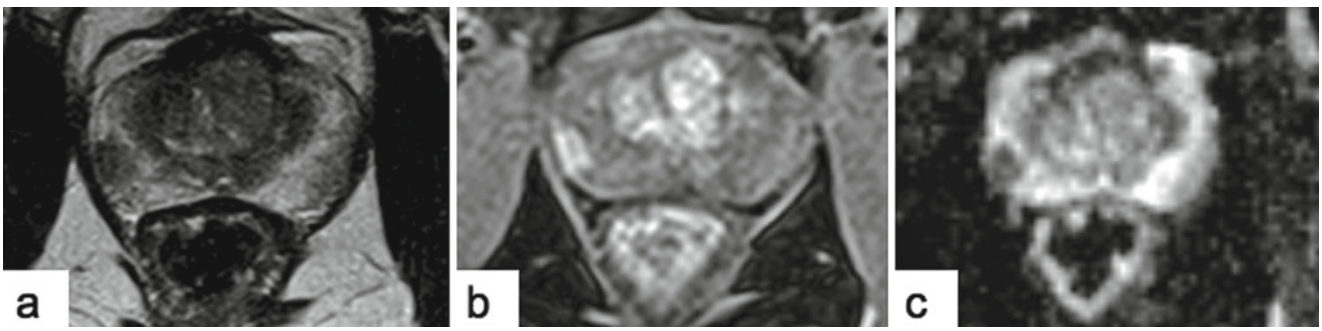

Fig. 66.5 Multiparametric MRI sequences showing a right peripheral zone lesion. (**a**) T2-weighted. (**b**) Dynamic contrast-enhanced. (**c**) Diffusion-weighted

Cryotherapy

Background

Cryotherapy uses extremely low temperatures to treat prostatic cancer via percutaneously placed cryoprobes (Fig. 66.7). It has been demonstrated as a successful primary and salvage treatment for localized prostate cancer with the advantages of minimal blood loss, shorter hospital stay, and the ability to treat "difficult" tumors, such as high burden disease involving the capsule, with more ease than radiotherapy and radical

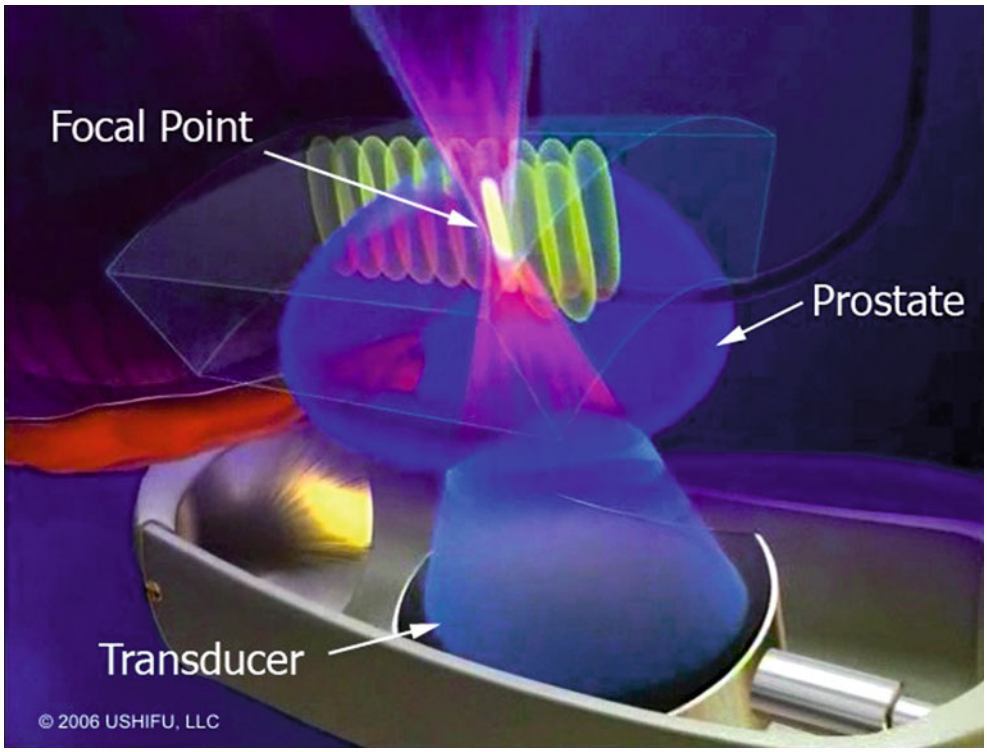

Fig. 66.6 High-intensity focused ultrasound (Sonablate 500®). The ultrasound waves are focused on a target area depositing large amounts of energy (Courtesy of US HIFU, LLC, Charlotte, USA)

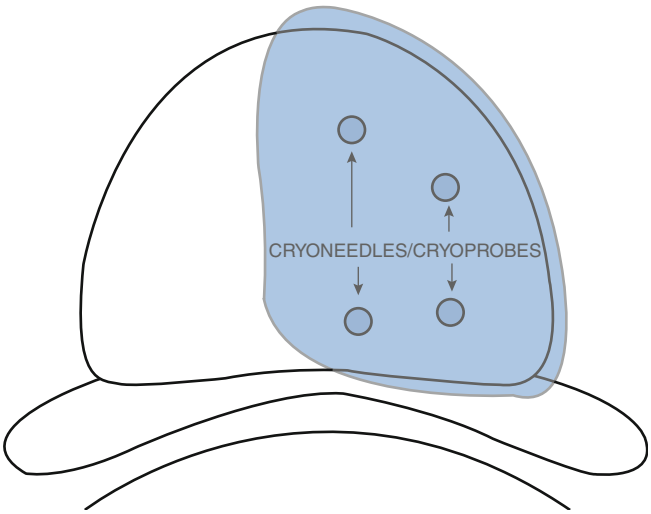

Fig. 66.7 Example of a focal cryotherapy treatment (Figure first published in *Journal of Urology*, 2007)

prostatectomy. Cryotherapy was approved by the Centers for Medicare and Medicaid Services (CMS) as an alternative primary whole-gland therapy in 1999. In addition, it has been granted approval by the Food and Drug Administration for the treatment of localized prostate cancers. Over the years, cryosurgery has taken its place as an alternative primary treatment option to "conventional" treatments for localized prostate cancer but with limitations on functional outcomes. Subsequently, the cryotherapists were the first to explore whether a focal ablative approach, with preservation of at least one neurovascular bundle, might improve functional outcomes without compromising cancer control.

Cryotherapy was first proposed as an alternative form of radical therapy for localized prostate cancer in 1966, by Gonder et al [58]. Initially, liquid nitrogen was used, with needles placed transurethrally via an open perineal technique but without accurate visualization of the needle placement and the real-time freezing effect. Subsequent treatment of 229 patients demonstrated reasonable cancer control but significant associated morbidity, with a high rate of fistulae (particularly urethrocutaneous), urethral sloughing, and incontinence [59]. The technique was temporarily abandoned due to poor functional outcomes. However, refinement of the technique by Onik et al. caused a reemergence of its application. Visual feedback was introduced with ultrasound imaging guidance, and there was a move toward a percutaneous route of probe insertion. This change in access required several smaller (3 mm) probes in place of the single 8-mm probe, with better and more precise tissue coverage. As a result, cancer ablation improved and fistulae rates declined. Further adaptations to technique and equipment have improved oncological and functional outcomes further; free-hand probe insertion was replaced by the use of a fixed template, urethral warmers have reduced urethral sloughing rates, thermosensors provide local tissue temperature feedback, and intraoperative injection of saline into Denonvilliers' fascia to separate the rectum from the prostate has permitted increased periprostatic freezing to be tolerated in patients with high-risk disease [60]. A change from passive freezing with nitrogen to active freezing and

thawing, via pressurized argon and helium gas, respectively, permitted a further decrease in probe size (17 gauge). It was then possible to insert the probes via a brachytherapy grid, with increased precision of placement and freeze contouring. Other conceptual changes in practice were suggested through expert opinion in an attempt to improve outcomes yet further [61]. However, despite a significant improvement in technology and conduct, potency rates remained poor, with persistently high rates of erectile dysfunction. Thus, a move toward tissue preservation, particularly of the neurovascular bundle, was considered to evaluate whether improved functional outcomes could be achieved without compromising cancer control.

Summary of Clinical Results

With nerve-sparing radical prostatectomy already demonstrating increased preservation of erectile function, the feasibility of nerve-sparing cryotherapy was addressed. A pilot study, published in 2002, was the first to attempt a "focal" approach to cryotherapy [62]. Patients with cancer confined to one lobe of the prostate (assessed on sextant TRUS biopsy as a minimum) were treated with sparing of the contralateral neurovascular bundle. Eleven patients in total received focal, nerve-sparing treatment, with 2 patients lost to follow-up. Of the remaining 9, all had stable PSA results over a mean follow-up period of 36 months (range 6–72 months); 6 received postoperative biopsies at 1 year, all of which were benign. Potency was preserved in 7 out of 9 men. Feasibility of nerve sparing was also assessed in canines by another group, with active warming of the nerve bundles demonstrating preservation of the neurovascular bundles on histopathological examination, albeit with adjacent unintentional preservation of prostatic tissue in some cases [63]. They also demonstrated more uniform and complete tissue ablation when a double freeze-thaw cycle was applied, compared to a conventional single cycle.

The notion of the "male lumpectomy" was first proposed by Onik et al., drawing on similarities with the tissue-preserving strategy by the breast oncologists in order to minimize the psychological and physical morbidities of losing a breast [64]. Focal cryotherapy was performed by his group in 48 men with localized prostate cancer with a follow-up period of at least 2 years. Of these, 94 % had stable PSA levels according to ASTRO criteria, and all 24 men who received postoperative biopsies at 1 year were cancer-free [65]. Four patients (8 %) with rising PSA levels and confirmation of residual disease on prostate biopsy received a second treatment. Pad-free continence was 100 %, and erectile function (defined as that sufficient for penetration and "satisfactory" sexual function, with or without oral agents) was maintained in 90 % of men.

Other groups were also adopting this technique. Lambert et al. retrospectively reviewed 25 patients who received focal cryosurgery confined to a single lobe at a single institution between 2002 and 2005 [66]. Patient eligibility was assessed on 12-core TRUS biopsy; those with Gleason grade 6 or 7 (3+4) confined to one lobe in up to two contiguous biopsy cores, and with a maximum tumor volume of up to 10 % had an ipsilateral lobe and neurovascular bundle treatment with sparing of the contralateral neurovascular bundle. The median follow-up period was 28 months (range 9–72 months). The median PSA level fell from 6.0 ng/ml to a median nadir of 2.4 ng/ml postoperatively. Sexual function outcomes were less favorable in this group. Of 24 previously potent men, 17 (71 %) remained potent, with the use of phosphodiesterase-5 inhibitors in 7. However, other than an episode of postoperative retention in 1 patient, no other adverse effects were reported.

Another small cohort received tissue-preserving cryotherapy between 1995 and 2004 [67]. This group of men were selected based on initial 6- or 8-core TRUS-guided biopsies, followed by color Doppler ultrasound with systemic and targeted biopsies of suspicious areas on ultrasound (including of the neurovascular bundle or seminal vesicle if extracapsular extension was suspected). There was no limitation to Gleason grade or PSA for inclusion. Over a mean follow-up period of 70 months (range 2–107 months) potency was preserved in 88.9 % (24/27) of men; 40.7 % required phosphodiesterase-5 inhibitors for preservation of function. Again, no patients suffered with incontinence (defined as leak at least 3 months following treatment) or other complications. Biochemical disease-free survival was defined by ASTRO criteria in this study, at a rate of 92.9 %. Of 25 patients receiving at least one postoperative set of biopsies, only one was found to have cancer on the contralateral side.

Ellis et al. treated 60 patients with stage T1 to T3 localized prostate cancer amenable to tissue-sparing therapy as assessed on standard TRUS biopsy [68]. Of 34 preoperatively potent men, 24 (70.6 %) retained potency at 12 months, with or without oral pharmaceutical assistance. The postoperative incontinence rate (with leak but pad-free) was 3.6 % in this cohort. ASTRO criteria were again used to define biochemical disease-free survival, with a rate of 80.4 %. However, cancer-free rates on follow-up bilateral biopsy were high with 14 of 35 men (40 %) having a positive result. Of 11 men who received a second focal treatment, following a period of impotence in 5 men, all regained potency by 12 months following re-treatment.

Thus, in small groups of men, improved functional outcomes compared to whole-gland therapy have been demonstrated as feasible with a focal approach, together with acceptable cancer control. Recently, the multicenter Cryotherapy On-Line Data Registry ("COLD") of whole-gland and focal treatments has begun. This has allowed analysis of outcomes in larger numbers of patients over a longer follow-up period. Focal results have been presented for 795 patients treated with "partial gland" cryoablation [69], with

reported "sexual activity", incontinence, and fistula rates of 65, 2.8 and 0.4 %, respectively, with a median follow-up period of 1 year. Accurate assessment of the data collected is difficult however, as the methods by which both functional and histological data have been obtained are variable. For example, only 18 % of patients underwent postoperative biopsies (performed at the physician's discretion). Of these, 25 % were positive for histology.

High Intensity Focused Ultrasound

Background

Due to the ability of high intensity focused ultrasound (HIFU) to treat small, localized areas of the prostate in a precise manner, this technology has shown promise as a focal ablative therapy, both as a primary treatment and as a focal salvage treatment for localized radio-recurrent disease. Additional prostate treatment is not precluded if cancer recurrence occurs after HIFU. Patients can either undergo further HIFU (whole gland or focal) or be considered for brachytherapy, cryotherapy, radiotherapy, or surgery. The majority of men choose redo HIFU, so the numbers undergoing other therapeutic modalities is low. Therefore, the outcomes of salvage radical therapies after HIFU are poorly reported but would be expected to be worse than for primary treatments.

Ultrasound applies cyclical sound pressures at varying frequencies passed through a piezoelectric material. The spectrum of frequencies allows ultrasound to be used for both diagnostic (1–20 kHz) and therapeutic purposes (0.8–3.5 MHz). Waves are propagated through tissue, causing alternating cycles of pressure, with compression and rarefaction of tissue. HIFU uses short wavelengths (mm) in combination with megahertz frequencies to cause a focused heating effect on a small volume of tissue. By applying heat over 55 °C for at least 1 s, irreversible tissue necrosis is caused. The heating effect is localized to ellipsoidal volumes of tissue measuring approximately the size of a grain of rice (as small as 1 × 8 mm).

HIFU uses the mechanisms of firstly, thermal ablation and secondly, cavitation to cause irreversible cell damage. The ultrasound waves are focused on a target area depositing large amounts of energy, which is absorbed by the tissue and converted into heat. Temperatures of up to 100 °C can be reached for a period of a few seconds causing necrosis and cell death within the target area without causing damage to the surrounding tissue. However, heats over 55 °C are sufficient for cell death. Some of the energy sourced at the transducer is deposited at the tissue interfaces that sit between it and the target tissue. However, as the frequency of the waves rapidly diminishes with proximity to the transducer, the heating effect is minimized to normal tissue. The vibrating effect of ultrasound on tissue causes rarefaction and the production of bubbles from released gas, with rapid collapse. The combination of thermal insult and cavitation causes tissue necrosis.

The therapeutic application of HIFU was first described in 1942 by Lynn et al. when neurological changes were noted in cats and dogs in whom brain tissue was treated [70]. The Fry brothers subsequently demonstrated successful ablation of neurological tissue with HIFU in both animals [71] and humans with neurological conditions [72] in the 1950s. In the same decade, HIFU was first considered as an ablative therapy for cancer tissue [73], and since that time, it has been evaluated in clinical practice for a number of benign and malignant pathologies. Currently, these include treatment of lesions in the liver, bladder, kidney, breast, uterus, brain, and bone. All of these treatments are at different stages of clinical development, with most undergoing evaluation of medium to long-term outcomes within ongoing clinical trials.

It was not until the 1990s that clinical application of HIFU on both benign and malignant prostate tissue is starting to become of interest. HIFU ablation of benign prostatic hypertrophy within phase II trials demonstrated only moderate medium-term improvement in lower urinary tract symptoms, and in one series, 43.8 % of men required a re-resection TURP (transurethral resection of the prostate), within 4 years [74]. Thus, HIFU was not proven as a successful alternative treatment of benign prostatic hyperplasia to TURP. However, it is its ability to ablate tumors with an acceptable side effect profile that has resulted in its adoption as a form of cancer therapy worldwide.

There are currently two HIFU devices available for the treatment of prostate cancer: the Ablatherm® (EDAP-TMS SA, Vaulx en Velin, France) and Sonablate 500® (Focus Surgery Inc, Indianapolis, Ind). There are differences in technology and conduct between them. However, both involve the delivery of treatment via a transrectal probe containing the transducer. Treatment effects can be monitored via real-time ultrasound. In most cases, the patient receives a general anesthetic. This allows for patient tolerance and restricts motion so that accurate targeting is possible. The rectum is cooled during treatment using continuous irrigation with degassed water in order to limit the potential adverse effects of heating such as fistula formation.

The Ablatherm® device consists of two "modules," the treatment module on which the patient lies in a lateral position to receive treatment and the control module at which the surgeon plans treatment and controls the position of the probe delivering HIFU. Treatment plans are automated to a preset protocol depending on whether it is a primary treatment, re-treatment, or salvage procedure.

The Sonablate 500® equipment consists of a monitoring module together with the transrectal probe which is inserted with the patient supine and in the lithotomy position on a

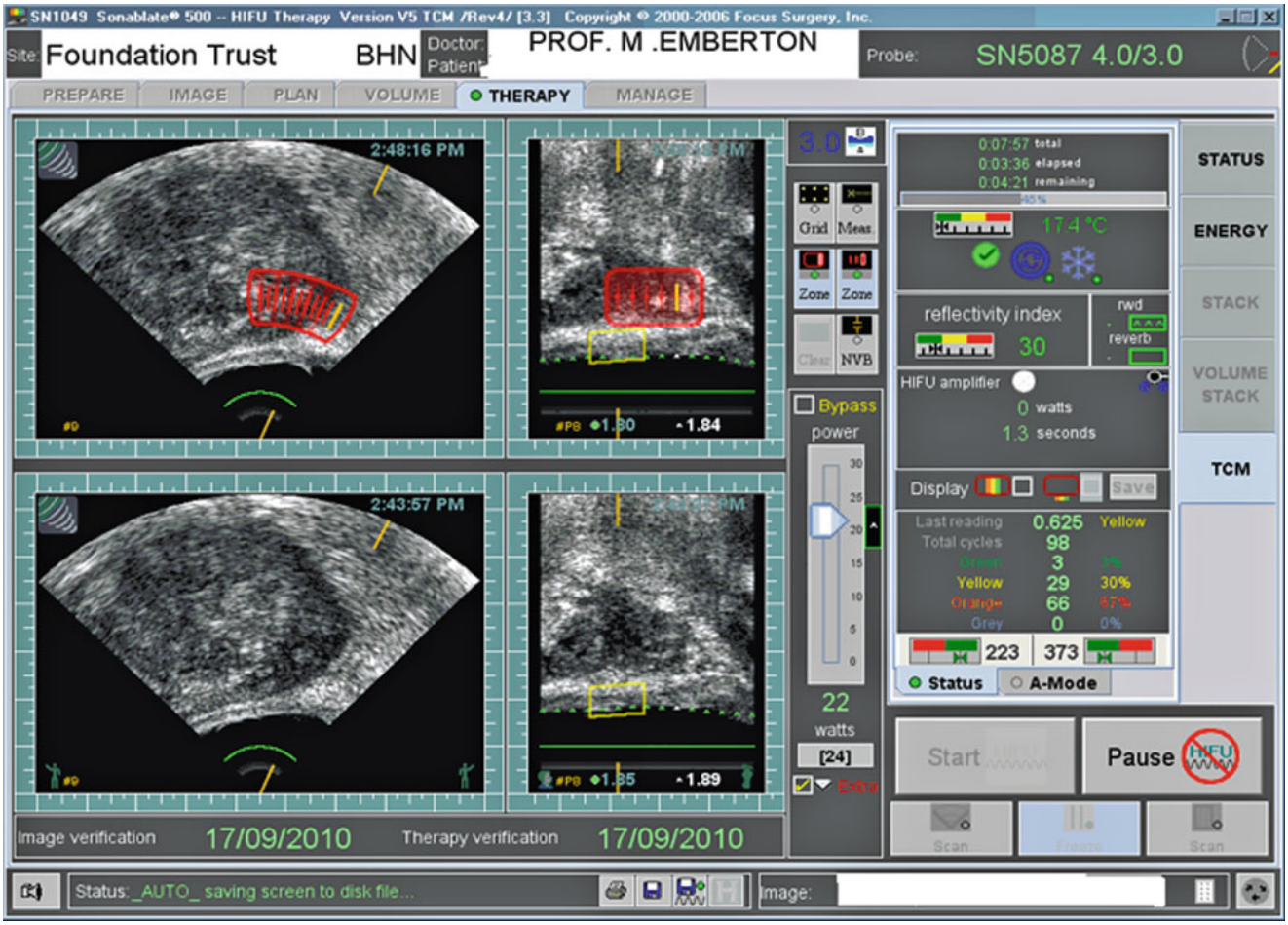

Fig. 66.8 Ultrasound images of a focal HIFU treatment (Sonablate 500®). Live images are seen in the sagittal and transverse views, and power levels can be adjusted according to the visual effects seen

standard operating table. The Sonablate 500® is controlled manually by the surgeon, and the power of HIFU pulses can be altered according to real-time visual feedback from the ultrasound images.

Ultrasound real-time feedback of treatment effect is seen as gray-scale changes as the heating effect causes tissue damage. These so-called "Uchida changes" are also known as the "popcorn" effect due to the visual appearance of circular areas of echo-poor tissue. The changes are classified into grades I–III depending on the extent of the gray-scale changes within the targeted area. The power delivered can be altered immediately by the surgeon according to the real-time effects seen (Fig. 66.8).

Prostate-related contraindications to HIFU treatment include a large prostate size whereby the focal length for treatment would not reach the anterior part of the prostate. Some surgeons perform a TURP prior to HIFU to reduce the prostatic volume. Also, large calcium deposits within the prostate can prevent ultrasound wave propagation causing undertreatment. Both of these factors can be assessed at a preoperative transrectal ultrasound of the prostate. Non-prostatic reasons for HIFU exclusion include any anatomical or pathological abnormality limiting insertion of the rectal probe, e.g., tight anal stenosis and previous anorectal surgery.

Summary of Clinical Results

HIFU is still a relatively new treatment for prostate cancer. The medium–long-term results of whole-gland treatment are now being published. Reported complication rates include urethral stricture 10–40 %, impotence 25–30 %, incontinence <2 %, and rectourethral fistula <0.5 %. As with other salvage procedures, the reported side effect profile and adverse functional outcomes of salvage whole-gland HIFU are greater, with cancer control of approximately 70 %.

As focal HIFU is a relatively new therapeutic concept, reported results are currently limited (Fig. 66.9). The results of focal HIFU were first reported in 29 men out of a total cohort of 70 that received HIFU for localized prostate cancer (low–high risk) [75]. The remaining 41 patients received whole-gland therapy. Treatment was evaluated and planned (whole gland versus focal) using 12-core tran-

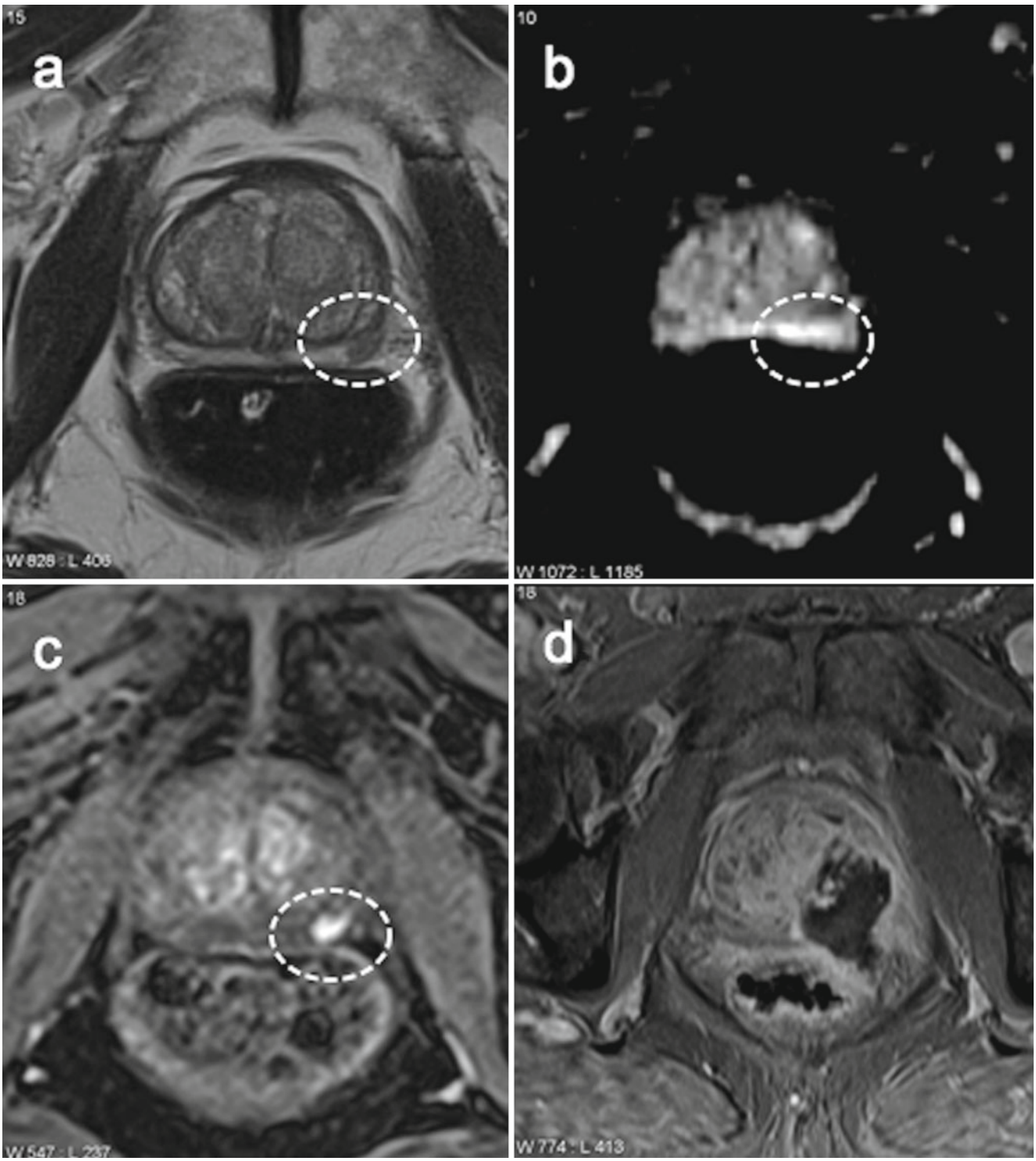

Fig. 66.9 Focal ablation of a left peripheral zone lesion. Multiparametric images showing the preoperative lesion on (**a**) T2-weighted, (**b**) diffusion-weighted, (**c**) dynamic contrast-enhanced sequences, and (**d**) necrosis of the area seen on the early (2 week) postoperative MRI

srectal biopsies. Men receiving focal treatment had unilateral disease on biopsy. A third (34.3 %) of patients in total were receiving hormone ablation therapy prior to treatment, including 24 % of those patients treated focally. Focal treatment involved bilateral peripheral zone ablation and ipsilateral transition zone ablation according to the laterality of the positive biopsy cores. This group demonstrated comparable cancer control between the two groups; 84.4 % of patients were disease-free on 12-month postoperative prostate biopsy in the whole-gland group, compared

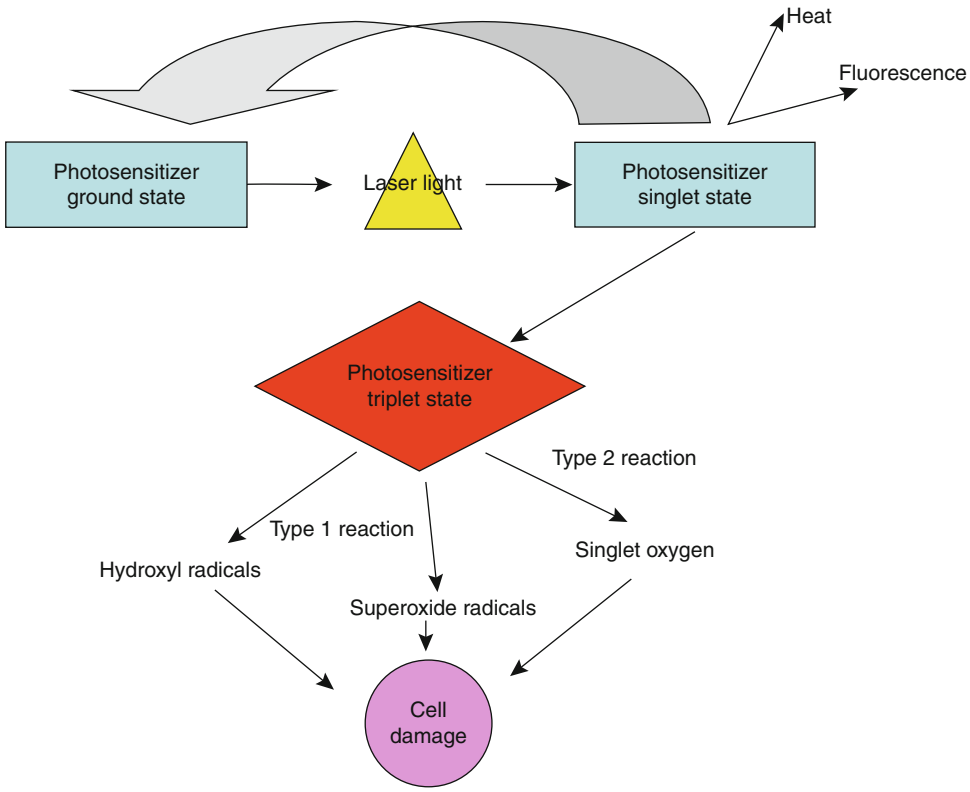

Fig. 66.10 Photodynamic therapy. Activation of the photosensitizer occurs on exposure to light of a specific wavelength, with conversion of the inactive product to an unstable energized (singlet) state (Figure first published in *World Journal of Urology*, 2010)

to 76.5 % of the focal group. Surprisingly, despite preservation of some normal prostatic tissue, 2-year biochemical disease-free survival rates according to ASTRO criteria were also similar between the two groups, at 90.9 and 49.9 %, respectively, for low- and intermediate-risk disease with whole-gland ablation and 83.3 and 53.6 %, respectively, with focal ablation. However, the group did observe that in the group of patients not receiving hormone ablation therapy, serum testosterone levels were maintained following focal treatment but diminished following whole-gland treatment. If this outcome is reproducible, it may account for some of the functional loss following whole prostate treatment.

Published data for focal HIFU is otherwise lacking, although it is currently being evaluated within phase II clinical studies with promising early results that demonstrate potency and continence rates of approximately 90–95 % with 90 % early cancer control. The results of the first two of these trials have recently been published [87, 88]. Two further phase II trials are ongoing at University College London, UK. The first involves treatment of the index lesion only, i.e., ablation of clinically significant cancer as assessed on transrectal or transperineal biopsies, while sparing clinically insignificant disease for future surveillance. The second is a multi-centre UK study. This will provide further phase II data on a larger group of men and with a longer follow-up period (3 years).

Photodynamic Therapy

Introduction

Photodynamic therapy is the ablation of tissue using a photosensitizing drug that is activated by light of a certain wavelength, in the presence of oxygen. Interaction of the activated drug and oxygen results in the production of reactive oxygen species, which cause localized tissue necrosis. Photosensitizers are administered either topically, orally, or intravenously in their stable inactive form. Activation occurs on exposure to light of a specific wavelength, with conversion of the inactive product to an unstable energized (singlet) state (Fig. 66.10) [76]. Energy is emitted in this state in the form of heat or light. Conversion to a triplet, or intermediate state, occurs prior to the return to the unstable form. From the triplet state, the photosensitizer is capable of two types of reaction: type 1 is the production of superoxide and hydroxyl radicals, and type 2 is the conversion of molecular tissue oxygen to singlet oxygen. The output of both reactions causes localized cell death.

Photosensitizers can either be activated in the vasculature or in the tissue itself. Tissue-activated photosensitizers take several days to reach a maximal concentration in the target tissue, in comparison to the surrounding normal tissue. However, due to accumulation of the drug in other nontarget tissue, such as the eyes and skin, careful precautions are required to protect these areas from activation of the drug by

light such as strong sunlight or indoor light. These drugs can take several weeks to be cleared, requiring skin protection for several weeks. An example of a tissue-activated photosensitizer is amino levulinic acid (ALA). The second form of photosensitizer (vascular-activated) is activated within the vasculature within minutes of administration. In addition, it is cleared rapidly. As a result, both the photosensitizer and the light source can be administered as a same-day treatment, with no requirements for prolonged protection from light. Examples of this type include the palladium bacteriopheophorbide photosensitizers, padoporfin, and padeliporfin (Steba Biotech, Netherlands).

Since that time, the development of a light delivery system via optical fibers enabled its use as a treatment of solid organ tumors, including of the head, neck, and pancreas. For treatment of the prostate, optical fibers (hollow plastic needles) are inserted via a transperineal route, using a brachytherapy template.

Summary of Clinical Results

The first clinical application of photodynamic therapy for prostate cancer was published in 1990 in the Lancet [77]. Two patients with localized prostate cancer were treated with tissue-activated PDT. Both patients were treated with tissue-activated hematoporphyrin-derivative photosensitizers, one with "Photofrin" (polyporphyrin) and the other with HpD. Light dosing was administered transurethrally 48–72 h later, 6 weeks after two separate prostatic resections (to ensure adequate resection). Follow-up prostate biopsies were benign 3 months postoperatively. PSA values fell from 10 and 6 μg/l preoperatively to 2.5 and 0.2 μg/l postoperatively, respectively. There were no adverse events reported. One patient died of previously undiagnosed lung cancer 6 months after treatment. However, the post-mortem evaluation of his prostate showed no histological evidence of residual cancer.

Another group at University College London, UK, performed two small clinical studies using PDT for localized prostate cancer. The first involved treatment of radio-recurrent localized disease with the tissue-activated photosensitizer temoporfin (meso-tetra-hydroxyphenyl-chlorine, mTHPC, Foscan®; biolitex AG, Jena, Germany) in 14 men [78]. A low light dose (20 J/cm) was given to the first 5 patients, 4 of which then chose to have a larger second dose after limited effects of treatment were seen on postoperative CT. The remaining 9 patients received a higher dose of 50 J/cm from the outset. Limited tissue ablation was performed based on preoperative biopsy and imaging results. Volumes of necrosis were variable on postoperative imaging, some of which were patchy, with a maximum treatment effect of 91 % necrosis for a bilateral treatment. Adverse events included one rectourethral fistula (possibly contributed to by, or caused by, a postoperative rectal biopsy), stress incontinence in 2 men, and acute urinary retention in 3 men. The second phase I/II study used the same photosensitizer (mTHPC) to treat primary localized disease in 6 men with Gleason 3 + 3 [79]. Focal treatment was given using up to four fibers inserted via the transperineal route and the positions checked using the open access MRI scanner. The light dose given was tailored to proximity of the treatment to the apex (50–100 J/cm). After a total of ten treatments (4 patients were offered re-treatment on the basis of cancer found on biopsy 1 month after the first treatment), the PSA fell after eight of these. Postoperative treatment effects were variable on the early postoperative MRI at 2–6 days. Healing of necrotic and edematous areas was seen at both the 1-month and the 2–3-month, postoperative MRI scans. The treatments were well tolerated. All patients had irritative voiding symptoms that lasted for up to 2 weeks, and two patients required temporary re-catherization after second treatments. One of these men developed transient incontinence that had resolved by 4 months.

Padorphin (WST-09, Tookad®; Steba Biotech, The Hague, The Netherlands) is a lipophilic vascular-activated photosensitizer. It requires a carrier in order to be given by intravenous infusion. It was also first evaluated within a phase I/II trial as a salvage treatment for radio-recurrent disease [80]. As this was the first application of this drug in humans, a dose escalation regimen was used. At an infused rate of 2 mg/kg, and with a half-life of about 20 min, photosensitizer levels were undetectable at 2 h. An increased volume effect of treatment was seen with the higher light dose, as assessed on early postoperative MRI scans. There was no residual skin photosensitivity, as assessed using a full spectrum of solar-stimulated light, 3 h after treatment. A similar dose-related effect was seen by the same group, when Padorphin was assessed as a whole-gland salvage treatment in 28 men with failed external beam radiotherapy (EBRT) [81]. In 13 men who received a light dose of at least 23 J/cm^3, 8 had negative biopsies 6 months following treatment. Two patients had rectourethral fistulae following treatment, one of which closed spontaneously at 6 months. Neither received a higher than average light dose compared to the rest of the group.

Padorphin has since been evaluated as a primary therapy within a dose escalation trial, and the results of this trial are awaiting publication [82]. Good volumes of necrosis were seen. Hypotension requiring fluid bolus and vasopressors had been seen previously. However, cardiovascular events (in two patients) and subclinical hepatotoxicity were additional adverse events seen in this study.

As a result of the systemic effect seen with padoporfin, a water-soluble version of the drug was developed, called padeloporfin (WST-11 Tookad® Soluble). This drug has undergone assessment within recent phase I/II clinical trials, within improved safety and tolerability levels seen compared to padoporfin. The results of these studies are awaiting publication. Furthermore, a European multicenter phase III trial

is underway, assessing the outcomes of PDT versus active surveillance in men with localized low-risk disease.

The Future of Focal Therapy

A number of different ablative techniques are underdevelopment as potential focal therapies for localized prostate cancer. They all aim to provide greater precision by which abnormal tissue is ablated, within a minimum treatment timeframe and with the minimal postoperative recovery period and discomfort to the patient. The method by which tissue is rendered nonviable may not be the priority question however, in the assessment of whether focal therapy will take a position within the current "standard" treatments for localized prostate cancer. Rather, the most pressing area of need may be in the ability to accurately detect, localize, and characterize those cancers requiring treatment, with the ability to rule out significant disease elsewhere, both at the diagnostic stage, for planning focal treatment, and for follow-up. Additionally, imaging tissue characterization and cancer detection at the time of treatment would allow accurate tissue ablation of the cancer areas only, minimizing the area requiring ablation and with maximum preservation of surrounding normal tissue. Some important technological advances are currently underway with the aim of transferring imaging datasets from the diagnostic to the treatment platforms, with the potential for more accurate targeting. Finally, the ability to receive real-time visual feedback of tissue response would allow accurate delivery of the energy source, eliminating the risk of undertreatment (and poor cancer control) and overtreatment (with increased risk of side effects).

Alternative Focal Therapies

Radiofrequency ablation (RFA) and brachytherapy are both established ablative techniques for renal and prostate cancers, respectively, with the ability to treat selective areas of the prostate. Transperineal RFA, using both monopolar and bipolar energy via needles of different configurations (to alter the volume of tissue treated), demonstrated effective focal ablation in the prostate, as published in 1998 [83]. However, this technique is not currently being evaluated as a focal therapy within prospective trials. Similarly, there is potential for selective treatment using different radiotherapy sources. For example, low-dose brachytherapy seeds could be placed in a selective manner, with maximal radioactivity delivered to distinct areas of the prostate. Similarly, CyberKnife is a new method for delivering hypofractionated sterotactic radiotherapy via a robotic arm. It allows dose distribution to be tailored to the tumor, with a steep dose gradient between the target tissue and the surrounding normal tissue. As a result, it is hoped that the bowel, urinary, and sexual function toxicities seen with external beam radiotherapy will be diminished. Although not designed as a form of focal therapy, the notion behind CyberKnife is equivalent, with maximum energy delivered to the tumor itself.

Microwave and laser therapies are examples of thermal ablative techniques with the potential for real-time monitoring of treatment effect using imaging. MR thermometry was used to monitor the temperature changes in tissue with microwave treatment radio-recurrent prostate cancer in 5 men [84], with good correlation between the visualized heating effect with the areas of tissue necrosis. More recently, after demonstrating the feasibility of photothermal laser ablation for low-risk prostate cancer within a phase 1 trial [85], one group subsequently performed real-time MR imaging-guided laser ablation in 2 patients [86] with successful ablation of the target area and correlation of the temperature changes seen on imaging.

Finally, direct injection of an antiandrogen into the prostate has been proposed as method of administering a maximum tissue concentration to the lesion itself with minimized systemic effects. Patients are currently being recruited for treatment with the antiandrogen 2-hydroxyflutamide (Liproca®, LIDDS pharma, Sweden) within a phase II trial.

Take-Home Messages

With increased awareness of the potential for overtreatment and treatment-related burden from "traditional" whole-gland treatments for localized prostate cancer, focal therapy is showing promise as a new treatment concept in order to limit these risks. The cryotherapists have been the first group to demonstrate focal treatment in men, with consistently improved side effect outcomes compared with whole-gland cryotherapy. Since then, HIFU and PDT have also demonstrated success in the ability to ablate discrete areas of the prostate within phase I/II studies, with verification of treatment effects seen on imaging and histopathological specimens at follow-up. Functional outcomes have been encouraging across all three therapies.

Histological outcomes, although good in most series, have been less consistent. This inconsistency may be partly due to staging errors – preoperative TRUS biopsies for focal therapy eligibility may have been inadequate to adequately assess disease burden. Imaging and alternative biopsy techniques, such as transperineal template or image-targeted biopsies, need to continue to be evaluated within the focal therapy context to minimize staging errors in these patients. Secondly, focal treatment poses a dilemma for oncological follow-up. With the preservation of some normal prostate tissue, PSA levels are not expected to decrease to a negligible level. Currently, there are no defined biochemical treatment

failure criteria for focal therapy, although most studies use one of the many definitions for radical therapies as a surrogate measure, e.g., ASTRO criteria, Phoenix criteria. In addition, postoperative biopsy strategies currently differ across published data, making comparison of outcomes difficult. Imaging has been used for verification of treatment effect in many studies to date, and in the future, this may become the dominant technique for monitoring oncological success of a focal treatment.

In order to continue to assess focal therapy as an alternative treatment option in eligible men, longer-term data is now required. Registry data collections, such as with the COLD registry, will provide crucial information. In addition, further prospective trials in larger groups of patients, using validated patient questionnaires and consistent biochemical and histological verifications of treatment success, are required. In the meantime, new methods for selectively ablating tissue continue to be developed, together with improved technological advances such as in the concomitant use of imaging for guiding and monitoring treatment.

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Suggested Additional Reading

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