Focal Therapy for Prostate Cancer

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**Overview**

The prostate cancer pathway from screening and diagnosis through to treatment has recently been critically questioned in light of level 1 evidence pointing toward pathway-related harms that may outweigh the benefits in many men. As a consequence, guidelines on screening in prostate cancer have recommended limiting the systematic use of screening based on prostate-specific antigen (PSA) testing to avoid overdiagnosis and overtreatment. There is a clear requirement to improve the current therapeutic ratio with novel interventions. Recent interest has focused on applying magnetic resonance imaging (MRI) in men at risk, before biopsy; targeted biopsy based on MRI-derived suspicious lesions, active surveillance of low-risk disease, and tissue-preserving focal therapy in those who require treatment and have suitable disease.

Minimally invasive focal therapies in localized prostate cancer offer the potential to reduce side effects and the health care burden and costs associated with radical modalities such as surgery or radiotherapy. This chapter reviews the role of these approaches and the therapeutic dilemma that men with localized low-volume prostate cancer currently face, in the context of novel therapies that aim to find a middle ground—tissue-preserving focal therapy—that follows the paradigm of almost all other solid-organ cancers.

**Conclusion**

For most men with localized prostate cancer, there exists a challenging decision-making process. Currently, the options often straddle two ends of a spectrum with active surveillance at one end and radical therapy, such as prostatectomy or radiotherapy, at the other. For those men with high-risk disease, there is an absolute risk reduction in disease-specific death—of approximately 5% over 10 to 15 years—between watchful waiting (a lesser form of active surveillance that is palliative in its intention) and radical surgery, as demonstrated in the Scandinavian Prostate Cancer Group’s SPCG-4 randomized controlled trial (RCT) (Bill-Axelson et al., 2005, 2008). The more recent Prostate Cancer Intervention versus Observation Trial (PIVOT), which randomized men diagnosed in the early PSA screening era between watchful waiting and radical prostatectomy, showed no overall survival or prostate cancer–specific survival advantage over an 11-year period (Wilt et al., 2012). PIVOT did show a survival benefit for men with intermediate- and high-risk disease, and although these were subgroup analyses, they confirm the findings of SPCG-4 that treatment should be directed toward those men with clinically significant disease. However, although there is a small survival advantage for these men, it could be argued that the morbidity from treatment (urinary incontinence, sexual dysfunction, rectal problems) questions the wholesale application of radical therapy to all men with intermediate- and high-risk disease.

The overtreatment of low-risk prostate cancer and limited effect on disease-specific mortality were further brought into context by two recent RCTs assessing the efficacy of population PSA screening. The North American Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial showed no difference in prostate cancer–specific mortality between the screened and unscreened arms with a mean follow-up of 7 years. This trial was significantly flawed because there was considerable contamination (informal PSA testing) in the control arm, potentially diluting any survival advantage of PSA screening. The fourth interim analysis from the European Randomized Study of Screening for Prostate Cancer (ERSPC) showed that 781 men would need to be screened and 27 men diagnosed (and often treated) to save 1 life within a 13-year period (Schröder et al., 2014). The effect was predominantly nested in a minority of countries, suggesting heterogeneity of study conduct, delivery, health care systems, and possibly disease types based on ethnic grounds. Although arguments rage about the strengths and weaknesses of each study, what is very clear is that any advantage from screening and treatment is likely to be small if all cancers are treated uniformly. We are therefore left with a stark choice: either to abandon the screening and diagnosis of prostate cancer as recommended by many high-level health care bodies that provide guidance to governmental institutions, or to find ways to identify men who are likely to benefit from treatment, and to these men offer therapies that reduce the impact on genitourinary and rectal function if they are suitable. Tissue-preserving strategies aim to target the cancer and not the whole organ when it is morphometrically possible to do so and thus reduce damage to collateral tissues.

**Errors in the Current Diagnostic Pathway**

Men at risk of prostate cancer are those with an elevated PSA level, abnormal digital rectal examination findings, a positive family history of prostate cancer, or a specific ethnic profile. Once a risk factor has been identified, patients are advised to undergo a transrectal ultrasound (TRUS)-guided biopsy. Annually, about one million men in Europe and one million in the United States undergo a TRUS biopsy. The problem with TRUS-guided biopsy is that the operator is unable to accurately determine the location of any significant cancer. The ultrasound examination is used to identify the prostate itself and not the suspicious lesion; this results in 10 to 12 biopsy specimens being taken blindly throughout the prostate. This is in contrast to the approach taken in most other
solid-organ cancers, wherein the lesion is identified, usually on imaging, to direct biopsies to the area of suspicion. The random and systematic errors in diagnosis, which are inherent in TRUS-guided biopsies of the prostate, lead to a number of problems. TRUS biopsies overdiagnose clinically insignificant prostate cancer. A man who undergoes TRUS biopsy has a 1 in 4 chance of being diagnosed with prostate cancer (Thompson et al, 2003; Bangma et al, 2007). This compares with a 6% to 8% lifetime risk of having prostate cancer that will affect a man’s life. These small low-grade lesions are detected by random chance (Djavan et al, 2001) (Fig. 117-1).

TRUS-guided biopsies miss clinically significant cancers. They have an estimated false-negative rate of 30% to 45% (Djavan et al, 2001; Scattoni et al, 2007). The clinician takes 10 to 12 biopsy specimens in a manner that attempts to obtain representative tissue from the peripheral zone (see Fig. 117-1). However, this systematic error leads to several parts of the prostate not being well sampled. First, the anterior part of the gland is missed as a result of its greater distance from the rectum. Second, areas in the midline are under-sampled owing to efforts to avoid the urethra. Third, the prostate apex is often inaccessible by the transrectal route (Crawford et al, 2005; Onik et al, 2009; Barzelli et al, 2012; Lecornet et al, 2012).

TRUS-guided biopsies can cause harm. It is associated with a p0090 number of complications, the most important being urinary tract infection (1% to 8%) that can result in life-threatening sepsis (1% to 4%). Hematuria (50%), hematospermia (30%), pain or discomfort (most), dysuria (most), and urinary retention (1%) can also be expected (Abdelkhaled et al, 2012; Batura and Gopal Rao, 2013; Loeb et al, 2013b; Pepe and Aragona, 2013).

**Conceptual Basis for Focal Therapy**

Overtreatment becomes less of a problem if the treatment is inexpensive and is associated with low rates of toxicity. Most current treatments do not share these attributes. At present, men can expect the following rates of toxicity from radical therapies on average: 30% to 90%, erectile dysfunction; 5% to 20%, incontinence; and 5% to 20%, rectal toxicity. Indeed, men may be willing to accept higher rates of genitourinary functional preservation with lower rates of survival. This is reinforced by data from a recent discrete choice experiment showing that men are willing to consider tradeoffs between survival and side effects; for instance, on average men would wish to see 25.7 additional months of survival conferred by treatment if that treatment leads to severe urinary incontinence (King et al, 2012).

Two strategies can be used to reduce this treatment burden. First, molecular characterization and imaging modalities may be used to identify men who have high-risk cancer that requires treatment. This has yet to prove fruitful, although imaging is showing some early promise (Kurhanewicz et al, 2008; Macura, 2008; Ahmed et al, 2009a; Turkbey et al, 2009). Second, minimally invasive therapies may be used in an attempt to reduce the side effects of treatment. Although this trend has resulted in intensity-modulated radiotherapy being promoted as the preferred method of care from the radiotherapeutic perspective, on the one hand, and robotic surgery on the other, these treatments are associated with high capital and considerable recurrent costs. For instance, a recent analysis has demonstrated that there were no statistically significant differences in quality-adjusted life-years (QALYs) among the various surgical methods; surgical methods tended to be more effective than radiation, although combined external beam and brachytherapy radiation treatment for high-risk disease was the exception.
Radiotherapy techniques were consistently more expensive than surgery, although both were expensive, with costs ranging from $19,901 (robotic-assisted prostatectomy for low-risk disease) to $50,276 (combined radiotherapy for high-risk disease) (Cooperberg et al, 2013). Others have shown that cost savings are not realized, at least in the first year and in the United States, between open and minimally invasive surgery (Lowrance et al, 2012). Others have shown that proton beam therapy is significantly more expensive, even if it theoretically improves cancer outcomes, compared with photon beam standard radiotherapy (Konski et al, 2007). In addition, there is little robust evidence that the toxicity profile has changed (Sanghani and Mignano, 2006; Berryhill et al, 2008). One way of reducing the side effects of radical therapy may be to direct treatment to only areas of cancer, to preserve tissue and avoid damage to key structures such as neurovascular bundles, external sphincter, bladder neck, and rectum (Ahmed et al, 2007; de la Rosette et al, 2010; Eggener et al, 2010; Lindner et al, 2010b; Karavitakis et al, 2011a) (Fig. 117-2).

When compared with other solid-organ malignancies, prostate cancer is an outlier. Breast, renal, thyroid, liver, and pancreatic cancers all involve tissue-preserving therapies, if appropriate, which are dependent on location and burden of cancer. It is clear that these areas of oncologic surgery developed tissue preservation, as opposed to Halsted principles for wider surgical margins, as a result of upstream diagnostic tools that are reliant on finding measurable—by palpation or imaging—disease that would undergo targeted sampling followed by targeted treatment. The transrectal biopsy has facilitated the reverse for the prostate. Random blind sampling has forced our hands as clinicians so that we have to apply radical whole-gland principles. So, if multifocality is overlooked in other organs by targeting just the measurable index lesion—the lesion that is largest and has elements of the highest grade—it is a reasonable hypothesis that targeting these lesions in prostate cancer will be sufficient in leading to acceptable cancer control rates, possibly equivalent to whole-gland therapy. In prostate cancer, a safe strategy may be to target those lesions that meet widely acceptable thresholds for clinically significant cancer. Focal therapy certainly leads to fewer genitourinary and rectal side effects, if the results of early prospective studies are found to be reproducible across populations, centers, and surgeons (Ahmed et al, 2011a, 2012d; Bahn et al, 2012).

To balance the unfavorable risk-benefit ratio of current standard treatments, new approaches and novel technologies are being explored. Hitherto, prostate cancer therapy has been traditionally directed toward the whole gland rather than to the area of the gland harboring cancer. It is one of the outliers in terms of cancer therapy, with most other solid-organ cancers having therapy directed toward the tumor and not primarily toward the whole organ in the majority of cases. For the prostate, a consequence of whole-gland treatment is that surrounding structures are usually damaged, with related urinary, erectile, and bowel side effects. However, new evidence has highlighted that only the index lesion—largest by volume and/or grade—drives the natural history of the disease, although prostate cancer is multifocal in most men (Ahmed, 2009). Thus a new approach delivering treatment only to the area of the gland affected by significant disease might be a reasonable approach and the best way to preserve function while retaining the benefits of cancer control. This approach has been called focal therapy (Ahmed et al, 2007; Eggener et al, 2010).

It follows that treatment could be patient specific. It is straightforward to envisage hemic ablative therapy in unilateral prostate cancer in which the entire lobe that is affected, regardless of volume or position of cancer, is ablated. Indeed, this is the treatment that retrospective case series of cryotherapy have delivered (see later). True focal ablation in which the tumor alone is ablated with a margin of normal tissue is also probably without contention, with the main difficulty arising from the greater precision in localization and targeting leading to potentially greater residual cancer or undertreatment rates. However, unifocal ablation is possible in only 10% to 20% of men, whereas hemic ablative therapy may be possible in 30% to 40% of localized prostate cancer. Because most men have two or three lesions per prostate, a hemic ablative or unifocal ablative approach would limit the patient population that could potentially benefit from focal therapy.

If tissue preservation criteria cannot be met owing to the disposition of secondary small tumors near the neurovascular bundles or sphincter muscles, it could be argued that the index lesion in which the largest and highest-grade tumor is ablated is warranted (Figs. 117-3 and 117-4). This could be justified to derive the benefits of lower toxicity, provided cancer control is not compromised by not treating all secondary cancer foci (Scardino, 2009). What is the justification for the inclusion of index lesion ablation? First, there is evidence that the volume of a tumor determines disease progression and that this volume equates to about 0.5 mL (Stamey et al, 1993; Epstein et al, 1994). Second, within multifocal disease is the inclusion of a large proportion of small tumors that probably
This represents a radical shift in how we treat the disease, but it certainly is in tune with the paradigm shifts we have witnessed in breast, thyroid, kidney, and liver cancers, to name just a few. The concept of the index lesion therefore runs to the very core of attempts to reduce the harms of screening for and treatment of prostate cancer, because systematic biopsies that inadvertently detect indolent disease will need to be replaced by targeted precision biopsies directed at a lesion of concern.

**Clinically Significant Disease and Tumor Multifocality**

Tumor multifocality in solid organs is not a novel phenomenon. It is not only found in prostate cancer, but it is also well recognized at various rates of incidence in breast, thyroid, lung, and even renal cancers. In these cancers physicians have taken an approach to treat only the cancer that will cause harm, leaving small indolent tumors (often unknown of) and preserving healthy tissue. In breast cancer, lumpectomy and localized radiotherapy might now be favored over whole-breast adjuvant radiotherapy because recurrences predominantly occur in the area of surgical resection after lumpectomy (Vaidya et al, 2014). The importance of preservation of healthy thyroid tissue is well recognized by endocrinologists and has led to the renaming of clinically insignificant disease as papillary microcarcinoma (Piersanti et al, 2003). The small lung tumors found at high rates at autopsy that would have caused more harm by investigation and treatment are commonly called pseudodisease in recognition of their nonmalignant behavior. Such a concept is made easier because the diagnostic pathway in those malignancies involves detection of the clinical phenotype visually, with palpation, or by imaging. In other words, diagnosis and treatment are directed at measurable disease.

In stark contrast to this, prostate cancer is typically detected by a somewhat random deployment of 10 to 12 transrectal needles, and the disease is confirmed histologically via these microscopic samples. This technique was deemed adequate because the presence of disease in the prostate was all that was required to inform treatment directed at a whole-gland level. By virtue of finding many lesions through this biopsy strategy, the multifocality of the disease has been used as a rationale to treat the entire prostate. However, informed treatment decisions based on biochemical and pathologic parameters cannot be made when systematic errors in sampling of the prostate can lead to overlooking of significantly malignant disease (disease that will lead to a reduction in quality or quantity of life) or undersampling, or when, conversely, clinically insignificant disease (disease that will never cause harm) is oversampled by clustering of the biopsy sites. In addition, even when disease in the prostate has been well characterized, it is sometimes difficult to predict the biologic behavior of individual cancers.

Along with multifocality, the idea that within the prostate separate cancers are behaving differently has long been recognized. In 1963 Halpert and colleagues surveyed 5000 autopsies following death from all causes (Halpert et al, 1963). In their survey they identified the presence of focal and diffuse tumors within the prostate gland. In younger men, focal tumors outnumbered diffuse tumors, but the researchers were not able to determine whether the focal tumors were precursors of diffuse tumors or if, indeed, the two types of tumors represented two forms of cancer with different biologic behavior. Thirty years after this publication, Villers and colleagues from Stanford University published their 3-mm step section analysis of 234 consecutive prostatectomies performed because of clinically detected prostate cancer from 1983 to 1989 (Villers et al, 1992). In this series a total of 500 adenocarcinomas were identified. A single cancer was found in 117 of the prostates analyzed. The remaining 117 specimens contained the clinically detectable lesion plus an additional 266 incidental tumors. Here, despite earlier studies describing diffuse tumors, the authors observed the distribution of normal tissue indicating expansion of the tumor from a single region of the gland.

Examinig the Gleason grade of the dominant and secondary lesions in 100 consecutive radical prostatectomies, Karavitakis and colleagues (2011b) identified a total of 270 lesions. In the 170 satellite, secondary lesions identified, 87% were less than 0.5 mL and

**Figure 117-4. Sections taken from radical prostatectomy specimens and pathology diagram showing dominant Gleason pattern 4+3 lesion with secondary satellite Gleason pattern 3+3 prostate cancer.**

This figure shows sections from a radical prostatectomy specimen. The dominant lesion is a Gleason pattern 4+3, while secondary satellite lesions have a lower Gleason score. This demonstrates the multifocality of prostate cancer and the importance of systematic biopsies to identify all clinically significant lesions.
99.4% had a Gleason score of 6 or less. In the 25 specimens in which two or more foci of cancer were identified, none contained the higher-grade, more aggressive disease in the secondary lesion.

Considering how size and growth of the index lesion affect outcomes in prostate cancer, Karavitis and colleagues (2012) examined the extent of positive surgical margins involving the index lesion and secondary lesions. Ninety-five consecutive whole-mount specimens from laparoscopic radical prostatectomy were examined. A total of 269 tumor foci were identified. Two of 160 (1.3%) lesions of volume less than 0.5 mL were involved in the positive surgical margin, whereas 0 of 132 lesions of volume less than 0.2 mL were involved. In the 19 cases in which multifocal cancer displayed a positive surgical margin, the index lesion was the cause in 13 cases and the index lesion plus a satellite lesion in the remaining 6 cases. In the other cases, the satellite lesion had a volume greater than 0.2 mL.

Tumor size was also found to be an important factor in PSA failure in a study by Nelson and colleagues, who analyzed 431 consecutive patients undergoing radical prostatectomy for localized prostate cancer (Nelson et al., 2006). In a multivariate analysis, tumor size was found to be an independent predictor of PSA recurrence. The mean tumor volume for PSA recurrence was 6.8 mL.

When Wise and colleagues compared the impact of small independent cancers and the index lesion on PSA failure in 486 men treated with radical prostatectomy, they found that 83% of men had multifocal cancer within the prostate (Wise et al., 2002). Fifty-eight percent of these smaller secondary cancers were less than 0.5 mL in volume. Factors that independently predicted PSA failures were the presence of any Gleason grade 4 or 5 and the volume of the index lesion. Multiple small cancers appeared to reduce the risk of PSA failure by 14% for each additional cancer. An explanation for this is that as the index lesion increases in volume, smaller, indolent cancers are assimilated into it. There might also be a paracrine growth inhibition effect between the largest index and smaller secondary lesions, although both of these theories remain to be investigated. From these studies, it is apparent that each tumor is a separate independent lesion, being multifocal, individual cancers within the prostate appear to express different behavior and that perhaps the most aggressive cancer is originating from a single site.

Index Lesion

There are two theories that explain multifocality of prostate cancer. One is of monoclonal expansion whereby tumors arise from the same original cell clone and multifocality is the result of intraprostatic metastasis. The other is of multiclonal expansion whereby each tumor is a separate independent lesion, genetically distinct, arising in a prostate that is predisposed to cancer through a field effect.

Specifically addressing this question, Cheng and colleagues examined the pattern of allelic loss for a tumor suppressor gene on chromosome 8p and the BRCA1 gene on chromosome 17q in 19 patients with two or more distinct prostate tumors (Cheng et al., 1998). The pattern of allelic loss was compatible with independent tumor origin in 15 of 18 informative cases. The remaining 3 were inconclusive and could have occurred as a result of independent origin or monoclonal origin.

This raises the question: If multifocal tumors in the prostate do arise independently, do they exhibit differential behavior, and does the index lesion behave differently than the smaller secondary lesions? When one evaluates the evidence with respect to the hallmark of malignancy, there is striking evidence demonstrating that small low-grade lesions (usually secondary) exhibit few of the traits that would qualify their status as cancer.

Reclassification of Low-Grade Low-Volume Prostate Lesions

The errors in the current pathway have been well described—namely, overdiagnosis, underdiagnosis, misclassification of risk, and overtreatment. These errors could be overcome by a recalibration of what is classified as malignant. A recent National Institutes of Health–National Cancer Institute expert group meeting on active surveillance stated that “because of the very favorable prognosis of low-risk prostate cancer, strong consideration should be given to removing the anxiety-provoking term ‘cancer’ for this condition” (Ganz et al., 2012). Eisenman and colleagues (2009) stated that “minimal risk lesions should not be called cancer,” with perhaps these lesions being called “indolent lesions of epithelial origin (IDLE).” Similar sentiments have been proclaimed elsewhere (Klotz, 2012b; Nickel and Speakman, 2012). As yet, there has been a lack of a systematic evidential approach having a contentious standpoint based on the current level of evidence.

The prostate is far from being an outlier. In lung cancer, there is a 1 in 6 incidence of what looks to be malignant lesions histologically when autopsies are conducted. These lesions are now coined pseudodisease in recognition of their nonmalignant behavior (Black, 2000; MacMahon et al., 2005). In the thyroid, the autopsy incidence of indolent lesions is 1 in 2, leading to a different label of papillary microcarcinoma (Pierotti et al., 2003), and in the bladder, low-grade papillary tumors have effectively been reassigned as nonmalignant by the term papillary urothelial neoplasia of low malignant potential (PUNLMP) (Jones and Cheng, 2006). Furthermore, another NIH consensus statement suggested that ductal carcinoma in situ should drop the term carcinoma from its terminology for the same reason (Albertsen et al., 2010).

Prostate cancer is, in general, multifocal and consists of a dominant (as measured by tumor volume) focus—denoted the index lesion—and one or more separate, secondary tumor foci of smaller volume (see Figs. 117-3 and 117-4). Much bench-side and clinical evidence demonstrates that we need to rethink how we regard low-grade and low-volume lesions (Karavitsik et al., 2011a). In this section, we discuss why low–Gleason pattern lesions with low volume—which in the current era are being designated as prostate cancer—could be regarded as nonmalignant, and perhaps a lack of a systematic evidential approach has been shown not to meet the hallmarks of cancer or lack robust evidence to that effect, as opposed to the index lesion—the largest lesion with the highest grade—which seems to be primarily responsible for metastatic disease (Fig. 117-5).

The redesignation of low-volume Gleason 3+3 disease as a benign entity may represent another incremental step in the way the grading system has evolved over the years. Gleason patterns 1 and 2 are rarely assigned to prostate cancer in the current era (Egevad et al., 2012). For instance, there has been a shift upward—so-called Will Rogers phenomenon (Albertsen et al., 2005)—in other words, the changing definition of Gleason pattern 4 has led to the regrouping of cases previously considered Gleason 6 into the Gleason 7 category. In many cases of pattern cancers previously assigned to the lowest Gleason grade 1, recent advances in immunohistochemistry have demonstrated the presence of basal cells, identifying the cases as atypical adenomatous hyperplasia, a benign mimic of cancer (Epstein, 2000). Moreover, lesions with grades 1 and 2 have been recognized as biologically similar to grade 3, further discouraging the use of these grades. Here we discuss key evidence structured within the framework of the original six “hallmarks of cancer” famously elucidated by Hanahan and Weinberg (2000, 2011) (Fig. 117-6).

Tumor cells can generate their own growth signals and reduce their dependence on stimulation from the surrounding tissue microenvironment. Ross and colleagues (2011), using laser-capture microdissection, extracted neoplastic cells from radical prostatectomy specimens of 23 men with either Gleason grade 3+3+3+3 or 4+4+4+4 index lesions. mRNA expression of 18,344 unique genes was then elucidated in these extracted cells. 670 genes were discovered to be differentially expressed between Gleason sum 6 (3+3) and 8 (4+4) index lesions. The profile of upregulated genes in high-grade lesions resembled the pattern observed in embryonic, neuronal, and hematopoietic stem cells. It is important to note that endothelial growth factor (EGF) and endothelial growth factor receptor (EGFR) overexpression stimulates independent cell proliferation.
Numerous papers have demonstrated that low-volume, low-grade lesions do not demonstrate the hallmarks of malignancy as exemplified by Hanahan and Weinberg. EGFR, epidermal growth factor receptor; ERG, ETS (erythroblast transformation-specific)-related gene; MVD, microvessel density.
proliferation and cell motility through several signal transduction mechanisms including the MAPK, AKT, and RAS pathways. In addition to the upregulation of the EGFR itself in Gleason 4+4 index lesions, the group also demonstrated overexpression of MAP2K4 and RALA20, the latter of which is a migration-promoting gene activated by EGFR. Also, the downregulation of RISP2 (which inhibits EGFR actions by resulting in its internalization, dedifferentiation, or apoptosis) was established. The investigators also noted that two genes that inactivate phosphor-AKT—PHLP and PML—were downregulated in Gleason 4+4 cancer.

Cancer cells must be able to resist the normal antigrowth signals that push them into a quiescent phase of the cell cycle or enter into postmitotic phases that ensure specific cell differentiation. The D-type cyclins are involved in the regulation of transition from G1 to S phases during the cell cycle. It has been reported that cyclin D2 is a direct target of Myc and that accumulation of cyclin D2 promotes the sequestration of p27, which is a cell cycle inhibitor, and this subsequently results in entry to the cell cycle. Inactivation of cyclin D2 may be a result of aberrant promoter hypermethylation. Using 101 radical prostatectomy specimens, Guo and colleagues reported that cyclin D2 in comparison with those containing Gleason patterns 4 or 5. Transforming growth factor-β (TGF-β) can impede growth by the induction of inhibitors of cyclin-CDK complexes including p27. Using radical prostatectomy specimens, Guo and colleagues (1997) showed that there was progressively diminished p27 immunostaining with increasing Gleason score in prostate neoplasms. All Gleason pattern 5 foci were totally negative for p27immunostaining, suggesting that these cells are unresponsive to the growth-inhibitory effect of TGF-β. This loss of p27 was associated with an increase in the proliferative index of the higher-grade prostate cancers.

The ability of cancer cells to resist programmed cell death (apoptosis) is key to ensuring continued growth and proliferation. The mechanism by which some cancers (2006) used laser capture microdissection to acquire specific subpopulations of prostate cancer cells consistent with lesions containing Gleason patterns 3, 4, and 5 from 29 radical prostatectomy specimens. The group profiled transcript abundance levels using cDNA microarray analysis and developed an 86-gene model capable of differentiating between lesions containing Gleason pattern 3 from higher-grade patterns 4 and 5. This model was observed to be 76% accurate in characterizing an independent set of 30 primary prostate tumors. One specific discrimina-
tory gene identified was DAD1, a gene encoding a protein that plays a role in programmed cell death, which is a downstream target of the nuclear factor-κB (NF-κB)-related pathway and displays an ant apoptotic function. DAD1 protein expression was subsequently elucidated by immunohistochemistry in tissue microarrays comprising formalin-fixed radical prostatectomy specimens, which, in combination with the expression of DAD1, demonstrated a strong correlation with Gleason grade, with tumors of patterns 4 and 5 more likely to show inflammation compared with Gleason pattern 3. Another new marker that is associated with higher grade and increased sensitivity to therapy, BCL2 (Cbl-2), its role in carci-
nogenesis and development of androgen resistance in prostate cancer has been well established. Recently, Fleischmann and colleagues (2012) performed immunohistochemical analysis on tissue microarrays of 3261 radical prostatectomy specimens. BCL2 expression was significantly upregulated in those lesions with a high Gleason score—that is, those lesions that included metastatic prostate cancer, which may reflect dedifferentiation and explain the clinical association of grade of the index lesion with prognosis. Hendriksen and colleagues (2006) also reported lower androgen signaling in high-Gleason pattern prostate cancer compared with low-Gleason pattern lesions. They suggested that localized prostate cancer cells become more aggressive by selectively downregulating androgen-responsive genes, resulting in increased tumor cell replication and proliferation. They concluded that androgen receptor overexpression in high-Gleason tumors was associated with aggressive features and suggested that androgen receptor as a target in prostate cancer. The association between ERG gene rearrangements and aggressive prostate cancer is controversial.

Neangiogenesis is a normal physiologic process that takes place during embryonic development and wound healing. The process is also required for solid tumors to grow beyond 1 mm in diameter and for their subsequent rapid growth (Folkman, 1995). Malignant prostate cells secrete angiogenic molecules such as vascular endothelial growth factor (VEGF), fibroblast growth factor-2, TGF-β, and cyclooxygenase-2. Raised levels of VEGF and increased microvessel density (MVD) are related to a poorer prognosis in prostate cancer (West et al, 2001; van Mooijeren et al, 2002). Several observations suggest that that higher-grade and larger prostate cancer lesions are associated with increased angiogenesis. For example, there is a strong correlation between elevated MVD and higher Gleason score (Brawer et al, 1994; Erbersdobler et al, 2010). In addition, Mucci and colleagues (2009) established that poorly differentiated tumors demonstrated greater MVD and irregularity of the blood vessel lumen with smaller vessels. In this study, during a 20-year follow-up period, bone metastases or cancer-related death occurred in 44 of 572 men. Lethal prostate cancer was 6 times more likely to occur in neoplasms exhibiting the smallest vessel diameter (based on quartiles). Also, cancers with the most irregularly shaped vessels were 17 times more likely to result in mortality. MVD was not linked to cancer-specific mortality after adjusting for clinical factors.

Cancers must exhibit the ability to invade local tissues and spread beyond the tissue and organ of origin. Evidence exists pointing to the lack of invasive and metastatic behavior of most prostate cancer lesions. For instance, when individual prostate cancer lesions, derived from one patient’s primary prostate cancer specimen, were implanted into a murine model, only one lesion showed characteristics of local invasion and eventually formed tumor nodules. CXCL12, a chemokine CXCR4 receptor, has been found to be upregulated in localized high-grade Gleason 4+4 index lesions in comparison with Gleason 3+3 index lesions. This CReceptor plays a key role in the directional migration of cancer cells to specific metastatic sites in response to its ligand CXCL12. The CXCR4 receptor has been associ-
prostate cancer, possibly through activation of the RAS oncopogene family member RAP1A, which has also been found to be upregulated in Gleason pattern 4 tumors relative to those containing solely a Gleason pattern 3. In addition, studies have suggested that hypoxia induces CXCR4 expression in tumor cells via hypoxia-inducible factor-1α (HIF-1α) (Scirri et al. 2003; Staller et al. 2003). Larger-volume tumors, specifically the index lesion in prostate cancer, are significantly more likely to have central hypoxic areas. This results in the expression of the CXCR4 receptor on the tumor cell membrane, allowing the cancer cells to migrate or metastasize away from the area of low oxygen tension, down a CXCL12 concentration gradient, to areas of high oxygen concentration. The ligand CXCL12 is secreted at particularly high levels by lymph node and bone marrow stromal cells.

Investigators from Stanford (Stamey et al, 1999; Wise et al, 2002) have reported that percentage of Gleason pattern 4 and 5, cancer volume of the largest tumor, positive lymph node findings, and intraprostatic vascular invasion were independently associated with prostate cancer progression. Another group observed that 80% of secondary foci are less than 0.5 mL and have the same volume distribution as tumors found incidentally in patients who have undergone cystoprostatectomy for bladder cancer (Nevoux et al, 2012). It has been proposed that tumor volume is associated with PSA recurrence (Nelson et al, 2006) and that prostate lesions smaller than 0.5 mL are clinically insignificant owing to the long doubling time of this cancer, so that it does not metastasize (Schmid et al, 1993b). Smaller tumor volumes that theoretically lead to distant metastases tend to be at least 4 mL (McNeel et al, 1990). In that case, with an estimated tumor volume doubling time of 2 years, it would take about 12 years for a 0.5-mL lesion to reach a volume of 4 mL. There also seems to be a strong correlation between pathologic and staging volume. In tumors more than 0.5 mL, investigators observed that 79% of men with previously untreated prostate cancer of all clinical stages who underwent serial PSA measurements during a period of at least 12 months had a tumor-doubling time greater than 24 months (Schmid et al, 1993b). Primary tumor volumes that theoretically lead to distant metastases tend to be at least 4 mL (McNeal et al, 1990). In that case, with an estimated tumor volume doubling time of 2 years, it would take about 12 years for a 0.5-mL lesion to reach a volume of 4 mL. There also seems to be a strong correlation between pathologic and staging volume. In tumors more than 0.5 mL, investigators observed that 79% of men with previously untreated prostate cancer of all clinical stages who underwent serial PSA measurements during a period of at least 12 months had a tumor-doubling time greater than 24 months (Schmid et al, 1993b). Primary tumor volumes that theoretically lead to distant metastases tend to be at least 4 mL (McNeal et al, 1990). In that case, with an estimated tumor volume doubling time of 2 years, it would take about 12 years for a 0.5-mL lesion to reach a volume of 4 mL. There also seems to be a strong correlation between pathologic and staging volume. In tumors more than 0.5 mL, investigators observed that 79% of men with previously untreated prostate cancer of all clinical stages who underwent serial PSA measurements during a period of at least 12 months had a tumor-doubling time greater than 24 months (Schmid et al, 1993b). Primary tumor volumes that theoretically lead to distant metastases tend to be at least 4 mL (McNeal et al, 1990). In that case, with an estimated tumor volume doubling time of 2 years, it would take about 12 years for a 0.5-mL lesion to reach a volume of 4 mL. There also seems to be a strong correlation between pathologic and staging volume. In tumors more than 0.5 mL, investigators observed that 79% of men with previously untreated prostate cancer of all clinical stages who underwent serial PSA measurements during a period of at least 12 months had a tumor-doubling time greater than 24 months (Schmid et al, 1993b).
(Dahabreh et al., 2012) and disease-specific mortality of 1% at 8 years while on surveillance (Klotz, 2012a) for men with low-risk disease as classified by a diagnostic TRUS-guided biopsy. The Toronto active surveillance series showed that all prostate cancer-related mortality occurred in men who had been reclassified as higher risk and who were offered radical treatment (Klotz et al., 2010). However, only one patient in this series who was treated after a relatively prolonged period of observation subsequently experienced progression to metastatic disease and death. Therefore, it is likely that reclassification of disease risk and subsequent radical treatment reflect undersampling of the prostate rather than true progression. Two recent reports from active surveillance cohorts from three regions that participated in the ERSPC study add a further shade of uncertainty for intermediate-risk disease. The first from Rotterdam and Helsinki looked at 509 men; 381 were low risk and 128 intermediate risk (Bul et al., 2012). During a median 7.4 years of follow-up, 221 men (43.4%) switched to deferred treatment, with 152 (39.9%) in the low-risk group undergoing treatment and 69 (53.9%) of the intermediate-risk group. Distant metastases were found in 1 low-risk and 3 intermediate-risk men. The other study looked at 439 (54.4%) men managed with surveillance from a total of 968 in the screening group (Godman et al., 2013): 224 (51.0%) were very low risk, 117 (26.7%) low risk, 92 (21.0%) intermediate risk, and 6 (1.4%) high risk. Two hundred and seventy-seven men continued on surveillance, of whom 133 (59%), 58 (50%), 46 (50%), and 3 (50%) were still on surveillance at study end in each group, respectively. Sixty men died during follow-up; only 1 man (intermediate risk) died from prostate cancer 12.7 years after diagnosis after having developed distant metastases at 8.6 years. However, despite a significant body of evidence demonstrating that this is a safe approach (Dahabreh et al., 2012), active surveillance seems to be infrequently offered to or chosen by men, with only 1 in 10 in the United States and 4 in 10 in the United Kingdom with low-risk disease undergoing active surveillance (Cooperberg et al., 2004; McVey et al., 2010). This may be physician or patient related but likely is a combination of both. With the uncertainty around longer follow-up, especially in the intermediate-risk group, this is hardly surprising, but it does point to the need for improved therapeutic interventions that can minimize the harms of treatment if that is what men and their physicians choose.

**Identifying the Patient Population for Focal Therapy**

Any man with localized prostate cancer suitable for curative therapy should be regarded as suitable for some form of focal therapeutic intervention. Such a pragmatic approach would not limit the age to a lower or an upper boundary. However, focal therapy has been seen by many, predominately in the United States, as an alternative to active surveillance, whereas others, predominantly in Europe, have argued that focal therapy should also be regarded as an alternative to radical therapies (Ahmed and Emberton, 2008).

The arguments for focal therapy to be carried out only in men suitable for active surveillance are (1) reduction of the potential psychological morbidity associated with men not having treatment for a cancer—that is, for patients, “some form of treatment is better than none,” and (2) reduction of the surveillance of cancer progression (about one third require delayed intervention within 5 years). Although up to 10% of men on active surveillance choose to have intervention within 5 years despite the absence of biochemical or histologic progression, questionnaire surveys have shown conflicting findings about the level of anxiety present in such cohorts. Furthermore, despite the progression rate, the mortality rate has been negligible, so it can be argued that most men can avoid treatment and those who have delayed intervention have a period of time free of treatment-related side effects. However, the period of low side effects could be extended if focal therapy were to be carried out at diagnosis or, indeed, at the time of disease progression after a period of surveillance. The argument against men who are suitable for active surveillance undergoing focal therapy is that any treatment within this group is liable to be overtreatment. Any treatment, 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 side effects of treatment and the others can delay such morbidity. Nonetheless, active surveillance is not without harm and burden, with surveillance blood tests and biopsies performed every 1 to 2 years [with their concomitant risk of complications], although the specific evidence with regard to repeat biopsy in active surveillance is conflicting (Fujijita et al., 2009; Bergman et al., 2012; Hilton et al., 2012; Loeb et al., 2013a).

It can be argued that the emergence of focal therapy as a strategy to reduce the side effects of conventional whole-gland therapies requires us to evaluate its potential within men who, as a result of harboring intermediate- to high-risk localized disease, would undergo radical therapies (Figs. 117-7 to 117-10). Despite the higher-risk disease status, evidence suggests that the oncologic benefits of radical therapies would be seen only after 10 years. A strategy that treats the cancer and carefully monitors untreated tissue for de novo cancer may obviate the need for any further radical therapies in the future or delay it for a number of years, during which the man is free of treatment-related side effects. The problem with such a proposal is the risk of progression to metastases in intermediate- to high-risk disease. Any undertreatment of cancer foci resulting from poor localization of the tumor may allow a window of opportunity in which focal curative treatment may not be successful. The prolonged natural history of prostate cancer, even in these groups, precludes such an argument.
Localization of Disease

Focal therapy requires accurate localization of disease to drive precision ablation. Localization of disease requires histology and imaging, either alone or in combination, and therefore represents an additional health care burden that forms part of focal therapy intervention. An accurate localization strategy will more clearly define the patient population in terms of stage, grade, and disease burden.

Before discussing the performance characteristics of different biopsy strategies, it is important to define what level or threshold of disease we are expecting biopsy strategies to find. A number of definitions of significant disease have been published (Table 117-1). The Epstein, Stamey, Harnden, Goto, and Ahmed/University College London (UCL) definitions all vary and have been validated using different reference standards—that is, TRUS, radical prostatectomy, or transperineal prostate mapping (TPM) (Stamey et al, 1993; Epstein et al, 1994; Goto et al, 1996; Harnden et al, 2008; Ahmed et al, 2011b). Overall, however, it seems that most studies have a widely used definition of clinically significant prostate cancer of 0.5 mL or greater in volume and/or Gleason grade 3+4 or higher. Several studies report on the detection rates of any cancer between biopsy strategies as opposed to the detection rate of clinically significant and clinically insignificant cancer.

A definition for clinically significant disease that has been validated using an accurate sampling strategy (either TPM or radical prostatectomy) must be agreed on. Biopsy strategies can then be compared using this definition to determine the most accurate method able to guide focal targeted therapy. It is likely that definitions will vary according to the patient's baseline characteristics and other risk factors.

Biopsy

When considering focal therapy, the role of prostate biopsy is not only in cancer diagnosis but also in characterization and localization of individual lesions (Ho et al, 2011). Biopsy strategies have evolved considerably to accurately identify, characterize, and localize lesions while trying to minimize risks to patients and reduce overall costs. Some of these strategies include taking biopsies via different anatomic approaches (transrectal, transperineal), as well as increasing the number of cores taken (saturation, mapping) and decreasing the number of cores but improving their deployment into the gland (targeted).

Systematic Transrectal Ultrasonography-Guided Biopsy

Currently, systematic TRUS-guided biopsy is still the standard of care (Heidenreich et al, 2014a). However, several studies have reported on the limitations of TRUS biopsy that hinder its ability to guide focal therapy. First, TRUS biopsy may miss up to 30% of clinically significant prostate cancer. Anterior regions of the prostate are frequently overlooked by TRUS biopsy, and it has been estimated that this is where approximately 30% of cancers reside (Bouye et al, 2005; Anastasiadis et al, 2006). Repeating TRUS biopsies because of negative results and a rising PSA level places men at increased risk of sepsis as well as causing anxiety from the uncertainty and delayed diagnosis. Second, TRUS biopsies are taken in a random manner and therefore cannot accurately localize individual areas of disease. Mayes and colleagues found that sextant TRUS biopsy has a low positive predictive value of 28%, with a high false-positive rate of 72% for detecting unilateral disease (Mayes et al, 2011). Washington and colleagues (2012) showed that although TRUS biopsy could identify lesions on the same lobe as the dominant lesion 81% of the time (95% confidence
interval [CI] 0.7 to 0.9), in only 22% was the correct location identified. The median number of cores per biopsy increased with successive biopsies: 14 cores for the first biopsy, 16 for the second round, and 17 for the third round. Because the patient is often in the left lateral position for TRUS biopsy, subsequent targeted treatment is somewhat difficult because there are no proper landmarks to clearly identify specific locations. Third, it is difficult to interpret whether the tumor is of small volume (and potentially insignificant on histology) or of large volume or high Gleason score (and potentially pathologically advanced) (Andriole et al. 2007). Indeed, when compared with the gold standard prostatectomy specimens, TRUS biopsy has been shown to underestimate disease, with prostate cancer detected in up to 30% of cases (Epstein et al., 2005; Chun et al., 2010). Last, some of the additional harms of TRUS biopsy include rectal bleeding and potentially life-threatening postbiopsy sepsis.

### Saturation Biopsy

Prostate saturation biopsy was initially introduced by Borboroglu and colleagues (2000) and consisted of taking at least 20 biopsy cores to address conflict in showing whether saturation biopsies provide more accurate disease diagnosis.

### Transrectal Saturation Biopsy

De la Taille et al. (2003) compared the cancer detection rates of taking 6, 12, 18, and 21 systematic TRUS biopsy samples. Overall, cancer detection rates for these groups were 22.7%, 28.3%, 30.7%, and 31.3% respectively. The 21-sample procedure statistically improved the cancer detection rate by 37.3% relative to the 6-sample procedure. There was no correlation between the detection rate of clinically significant cancer detection rates in this study.

Epstein and coworkers (2005) performed saturation biopsy on consecutive radical prostatectomy samples. Using Epstein's criteria of insignificant tumor less than 0.5 mL, organ confined, seminal vesicles not involved, lymph nodes negative, and Gleason pattern 4 or 5, 71% of the cancers at radical prostatectomy were classified as insignificant, and 29% had been misclassified using standard biopsy schemes. The false-negative rate of saturation biopsy for clinically significant cancer was also reported as 11.3% with sensitivity and specificity of 71.9% and 95.8%, respectively.

Li and colleagues (2014) retrospectively compared 3338 men with a 12- to 14-core biopsy scheme (extended biopsy) with 438 men with a 20-core biopsy scheme (saturation biopsy). A higher rate of low-grade prostate cancer as defined by Gleason score 6 was detected in the saturation biopsy group compared to the extended biopsy group (50.0% vs. 41.4%; P = .015). However, using Epstein's criteria for clinically insignificant disease, the saturation biopsy group did not detect a higher rate of clinically insignificant prostate cancer compared with the extended biopsy group (21.2% vs. 17.9%; P = .223).

Irrani and colleagues (2013) performed an RCT comparing 12-versus 20-core TRUS biopsy. Patients were biopsy naive and had PSA levels less than 20 ng/mL and no nodule on digital rectal examination. No significant difference was found between the groups for cancer detection rate or for Gleason score, tumor length, and proportion of cancer affecting both lobes. Using D'Amico criteria for low-risk cancer (Gleason 6 and PSA level less than 10 ng/mL and T1c or T2a clinical stage), there was no significant increase in low-risk cancers detected in the 20-core biopsy group compared with the 12-core biopsy group (47% vs. 39%; P = .32).

### Transperineal Saturation Biopsy

Novara et al. (2010) examined 143 men with previous negative TRUS biopsy who underwent a 24-core freehand transperineal saturation biopsy; 26% of patients were found to have cancer. The majority of these (65%) had Gleason grade 6 disease, and only 1 patient had Gleason grade 8 disease. Twenty-one of 37 patients with cancer had radical prostatectomy; 8 of these were found to have pathologically locally advanced disease (pT3ab N0) cancers and 4 to have ECE. It was not made clear whether this correlated with biopsy outcome. Eight of the 17 patients with a Gleason grade 6 on biopsy were found to have Gleason grade 7 on radical prostatectomy review.

### Transperineal Saturation versus Transrectal Ultrasound Saturation Biopsy

Abdollah and colleagues (2011) matched 280 patients who underwent either TRUS or transperineal saturation biopsy taking 24 cores. Overall, the prostate cancer detection rate or for Gleason score, tumor length, and prostatectomy review.

### Transperineal Template Prostate Mapping Biopsy

For transperineal template prostate mapping biopsy, the patient is placed in the lithotomy position with a brachytherapy grid against the perineum to guide the procedure. This has several advantages over the problems associated with TRUS biopsy (Fig. 117-11).

Firstly, the brachytherapy grid has 5-mm holes, allowing for p3050 systematic sampling of the entire prostate. This can ensure comprehensive coverage of the prostate and can sample areas commonly missed by TRUS biopsy (apex, anterior horn of peripheral zone, transition zone). Crawford and colleagues (2013) performed a computer-simulated study on 40 autopsy prostate specimens. The computer-simulated study used TPM with either 5-mm or 10-mm sampling. Overall, 5-mm sampling identified more cancers than 10-mm sampling (76% vs. 45%, respectively) and also detected tumors with a higher Gleason grade 4/5 (77% vs. 40%).

### Transperineal Prostate Mapping Biopsy versus Transrectal Ultrasound Biopsy

Lecornet and colleagues (2012) also performed computer simulation studies comparing standard TRUS biopsy, optimized TRUS biopsy, and TPM in the detection of clinically significant cancer using two definitions: (1) Gleason score of 7 or higher and/or lesion volume of 0.5 mL or more, and (2) Gleason score of 7 or higher and/or lesion volume of 0.2 mL or more (Ahmed et al, 2011b). Random localization error (RLE) to simulate errors introduced by imperfect needle placement, for example because of human error and needle deflection, was also incorporated into the analysis. The area under the curve (AUC) to detect and rule out definition 1 cancer was 0.69, 0.75, 0.82, and 0.91 for standard TRUS with RLE 10 mm, standard TRUS with RLE 10 mm, optimized TRUS, and TPM, respectively. For definition 2 cancer, the AUC was 0.57, 0.67, 0.74, 0.81, and 0.91, respectively (see Figs. 117-4 and 117-5). The difference in AUC between the different biopsy strategies was greater for anterior lesions. Standard TRUS missed 47% of lesions 0.5 mL or greater and 79% of those 0.2 mL to 0.5 mL. Another similar simulation study performed by the same group showed that the accuracy...
of TPM vs. standard TRUS (RLE 15 mm) was 0.91 versus 0.70, respectively, for lesions 0.2 mL or larger and 0.5 mL or larger (Hu et al, 2012).

Barzell and Melamed (2007) reported on 80 patients previously diagnosed with prostate cancer on TRUS biopsy who were considering focal cyrotherapy and who were rebiopsied with TPM biopsy and repeat TRUS biopsy. Patients were deemed suitable for focal cryoablation if only unilateral cancer was found after repeat TRUS and TPM. TPM biopsies detected 36 of 36 (100%) unsuitable candidates; repeat TRUS biopsies picked up only 5 of 36 (14%). Sixty-one of 66 (92%) were considered suitable for focal cryoablation by repeat TRUS findings; however, only 30 of 66 (45%) were deemed suitable by TPM findings. Thus, repeat TRUS-guided biopsies had a false-negative rate of 47% (31 of 66) in excluding patients from focal cryoablation. The template map was reported as crucial in providing cryotherapy treatment to eligible men. It permitted selective targeted ablation of the areas of cancer while sparing uninvolved parts of the prostate. Recently, our own group has shown that in 291 men who underwent TPM biopsies and had previously undergone TRUS biopsy, about 90% were suitable for focal therapy if this included index lesion ablation (Singh et al, 2014).

Reported drawbacks of TPM, however, include the laborious process in terms of setup, anesthesia requirement, and greater histopathology processing time as a result of the increased number of samples, with the consequent costs. Complications of TPM include urine retention (5% to 10%), hematuria (2%), and temporary erectile dysfunction, although rates of sepsis are very low (0.5%) (Hara et al, 2008; Merrick et al, 2008).

**Imaging: Advances in Ultrasound**

Increased vascularity or changes in blood flow are an important feature of prostate cancer and have been associated with higher Gleason grades (Wilson et al, 2004; Heijmink et al, 2006). These features have driven improvements in diagnostic imaging. In terms of TRUS, color Doppler imaging measures blood flow velocity and direction. Contrast-enhanced transrectal ultrasonography (CE-TRUS) involves detecting the difference in acoustic impedance between the contrast agent and adjacent tissue (Jakobsen et al, 2001). Elastography demonstrates the higher cell and vessel density in prostate cancer based on increased stiffness in comparison to the surrounding normal tissue (Aigner et al, 2012). Prostate HistoScan

![Figure 117-11. Diagram demonstrating how transperineal template-guided biopsies are carried out. If the sagittal length of the prostate is longer than the throw of the biopsy needle, then two biopsy specimens are taken from the same coordinate. U/S, ultrasound.](image-url)
92.9% of these lesions—either hypoperfusion (48.2%) or hyperperfusion (46.6%). Overall, if an RTE-positive target lesion showed a suspicious perfusion pattern, the likelihood of detecting cancer was 89.7%. A combination of RTE followed by CEUS reduced the false-positive detection rate from 34.9% to 10.3%.

Walz et al (2011) specifically evaluated the accuracy of RTE in identifying the index lesion for focal therapy in 32 patients. Criteria for the index lesion defined by this study were as follows: the largest suspicious lesion on RTE; on biopsy data, the lesion present in the lobe with positive cores (if the contralateral lobe had no positive cores); the lobe with the higher percentage of positive cores or the higher percentage of cancer on core length (if positive cores were present in both lobes); and/or the lobe with the higher Gleason score. Of all patients, 87.5% had clinically significant prostate cancer defined as Gleason pattern 4 or 5 and/or cancer volume exceeding 0.5 mL and/or extraprostatic extension. The sensitivity, specificity, negative predictive value, positive predictive value, and accuracy of RTE alone were 58.8%, 43.3%, 54.1%, 48.1%, and 51.6%, respectively. TRUS biopsies alone achieved 67.8%, 48.4%, 56.8%, 60.0%, and 58.1%, respectively. The combination of RTE...
and biopsy data increased these values to 84.9%, 48.4%, 61.9%, 75.8%, and 66.1%. Overall, however, RTE alone would miss 40% of index lesions. This study did not perform target biopsies of the suspicious lesions observed on RTE, making it difficult to predict whether a combination of RTE-targeted biopsies with systematic biopsies may have increased accuracy to detect the index lesion.

There have been a few studies reporting on PHS. Hamann and colleagues (2013) looked at 80 men who consecutively underwent a systematic 14-core prostate biopsy supplemented by three PHS-directed TRUS and transperineal biopsies. Twenty-eight men (35%) were found to have cancer. Targeted transperineal biopsy detected more lesions than targeted TRUS (82.1% vs. 53.6%). However, systematic TRUS and targeted transperineal biopsies performed almost equally in the detection of cancer (22 vs. 23; P > 0.99). The study was unable to report on the accuracy of PHS. De Coninck and colleagues (2013) compared random systematic biopsies with targeted PHS lesions; 58% of lesions suspicious on PHS were positive for cancer. However, the TRUS biopsy detected only 13% of cancers, much lower than standard TRUS detection rates of 45% to 50%, which calls into question the biopsy technique used.

Javed and colleagues (2014) reported on the ability of PHS to detect and localize prostate cancer compared with TRUS biopsy and transperineal biopsy. Tumor volumes of PHS-predicted lesions were also analyzed on radical prostatectomy histopathologic analysis. PHS had a sensitivity and specificity of 100% and 5.9%, respectively, when compared with TRUS biopsy. Compared with transperineal biopsy, PHS had a sensitivity and specificity for cancer detection in the posterior gland of 100% and 13%, respectively, and for the anterior gland, 6% and 82%, respectively. There was no correlation between total tumor volume estimates from PHS and radical prostatectomy specimens. Sensitivity and specificity of PHS for detecting tumor foci 0.2 mL or greater in volume were 63% and 53%, respectively. The estimated sensitivity for PHS to detect tumor greater than 0.5 mL was 37%. Index lesions were also biopsied, although no definition was given for the features of the index lesion—that is, cancer score or Gleason grade. There were no differences in the definitions of clinically significant cancer between measured tumor volume of suspected index lesions detected by PHS and radical prostatectomy histopathologic examination. These findings suggest that PHS is poor at localizing prostate cancer; assessing tumor burden, and detecting small foci of disease.

Recent innovations in MRI are also a further attempt to accurately localize prostate cancer extent without the need for invasive procedures and associated morbidity.

Multiparametric Magnetic Resonance Imaging

Multiparametric magnetic resonance imaging (mpMRI) involves different imaging parameters including T2-weighted imaging (T2W), dynamic contrast-enhanced (DCE) imaging, diffusion-weighted imaging (DWI), and magnetic resonance spectroscopy (MRS). On T2W, water appears bright, fat appears dark, and prostate cancer appears as areas of low signal. DCE images are rapidly acquired after administration of intravenous contrast. Uptake and release of contrast is more rapid in prostate cancer owing to the increased vascularity; compare with surrounding normal tissues. DWI reflects the differential movement of water within tissues, according to their tissue architecture, cell density, cell membrane integrity, and presence of necrosis. Prostate cancer has restricted diffusion, appearing bright on longer b-value sequences and dark on an apparent diffusion coefficient map. MRS portrays the concentration of choline, citrate, and creatinine. The ratio of choline and creatinine to citrate is increased in prostate cancer (Kurth et al., 2011). The sensitivity and specificity of mpMRI have been reported to be 93% and 98%, respectively, in detecting and excluding high-grade cancers greater than 0.5 mL in volume (Ukimura et al., 2013). There are several ways to target based on the outputs of mpMRI—namely, in-bore MRI-guided biopsy, cognitive targeted biopsies, and magnetic resonance imaging-ultrasound (MRI-US) fusion-guided biopsy.

Several studies have reported on use of MRI-US fusion, which involves combining prebiopsy magnetic resonance imaging with a live ultrasound image at time of biopsy to guide more accurate biopsies. Puech and colleagues (2013) compared several biopsy strategies to see which was more accurate in detecting clinically significant prostate cancer, defined as maximum cancer core length of 3 mm or more and/or Gleason grade of 3 +4 or greater. Ninety-five patients with suspicious lesions on MRI underwent 12-core systematic biopsy and 4-core target biopsy (TB) with TRUS guidance, with two cognitive target cores aimed visually (TB-COG) and two target cores using MRI-TRUS fusion software (TB-FUS). Clinically significant prostate cancer was detected by systematic TRUS in 52% (n = 49) and by TB in 67% (n = 64). In 12 of 51 (24%) MRI targets with positive systematic TRUS and TB results, TB led to Gleason score upgrading. In 79 MRI targets, 47% (n = 37) were positive with TB-COG and 53% (n = 42) with TB-FUS (P = .16). Neither technique was superior for Gleason score assessment. Delongchamps and colleagues (2013) compared the accuracy of visual TBs and computer-aided automated MRI-US fusion system with 10- to 12-core systematic biopsy in 391 patients. Overall, the rigid and elastic system TB performed significantly better than random biopsy (P = .0065 and .0016, respectively) in detecting overall and higher Gleason score cancer. In this study a TB-only strategy would have avoided unnecessary biopsy in 45% while limiting the number of cores in the other 55%.
study also showed that MRI-US fusion–targeted biopsies resulted in 22% additional cases of Gleason 3+4 or higher prostate cancer and 67% additional cases of clinically significant prostate cancer (Gleason ≥4+3) compared with 12-core systematic biopsy (Siddiqui et al, 2013).

Pinto and colleagues (2011) compared MRI-US fusion–targeted biopsy under electromagnetic tracking with standard 12-core TRUS biopsy in 101 men; 54.4% of men had prostate cancer. Cancer was detected in 27.9%, 66.7%, and 89.5%, respectively, of patients with low, moderate, and high suspicion on MRI of having cancer. MRI-US fusion-guided biopsy performed better in the detection of cancer in MRIs with a low, moderate, and high suspicion of cancer compared with standard 12-core TRUS biopsy (4.8% vs. 3.8%, 20.7% vs. 12.3%, and 53.8% vs. 29.9%, respectively). Overall, MRI-US fusion–guided biopsy detected more cancer per core than standard 12-core TRUS biopsy alone for all levels of suspicion combined (20.6% vs. 11.7%, respectively). Electromagnetic tracking can also aid focal therapy because therapeutic instruments used in cryotherapy, high-intensity focused ultrasound (HIFU) ablation, or brachytherapy can be guided in real time.

The current drawbacks of MRI are its inability to differentiate between prostate cancer and prostatitis, inflammation, or prostatic intraepithelial neoplasia (PIN). MRI-guided biopsy is time-consuming, because patients have to have an initial MRI, which is then repeated at time of biopsy. MRI-US fusion also has some limitations. It relies on accurate prostate segmentation; the prostate needs to be outlined—manually or semiautomatically—on both MRI and ultrasound images (van de Ven and Barentsz, 2013). This segmentation is also a time-consuming task and is operator dependent. The fusion itself, however, is a relatively quick process, taking under 90 seconds in one study (Bubley et al, 2013), with error rates varying from 2.5 mm to 5 mm depending on whether nonrigid or rigid fusion is used.

We recently conducted a systematic review of the literature reporting on image-fusion devices used to guide and target biopsies in the detection of prostate cancer (Valerio et al, 2015) (Figs. 117-13 and 117-14). Fourteen studies used a paired cohort design. A total of 2293 men were included, with a sample size ranging from 13 to 582. Three studies were conducted in biopsy-naïve men, three were conducted in men with a previous negative TRUS biopsy, eight studies reported on a mixed cohort of men who were either biopsy naïve or had undergone a previous prostate biopsy, and one also included men with radiorecurrent disease.

Our systematic review showed that MRI-TRUS image fusion–targeted biopsies detect more clinically significant cancers using fewer cores compared with standard biopsy techniques. Most studies also showed a higher detection of clinically insignificant cancer, although four studies demonstrated a lower detection rate of clinically insignificant cancer by MRI-US image fusion biopsies. The detection of clinically significant disease was 4.8% to 52% for standard biopsy and 13.2% to 50% for MRI-US image fusion–targeted biopsy. Across all studies in which both rates were reported, the use of MRI-TRUS fusion allowed the detection of greater numbers of clinically significant cancers compared with standard biopsy. The absolute difference in detection rate between the two approaches was a median of 6.8% (range +0.9 to +41.4%) and always in favor of the MRI-TRUS software-based approach.

There was substantial discrepancy in the definition of clinically significant disease. Only one study did not report the criteria for defining this outcome. In all the remaining studies, the presence of Gleason pattern 4 was considered clinically significant disease. In eight studies, maximum cancer core length was also considered, although the threshold above which clinically significant disease was defined ranged from 3 mm to 10 mm.

The detection rate of any cancer was 14.3% to 59% and 23.7% to 82.1% in the standard biopsy strategy versus MRI-TRUS image fusion biopsy. The absolute difference in overall detection of prostate cancer between the two approaches was median +6.9% in favor of the MRI-US image fusion–targeted biopsy approach (range +8.8% to +53.2%). In four studies, standard biopsies detected more clinically insignificant disease than the software-based approach. MRI-TRUS image fusion biopsies detected 5% to 16.2% additional clinically significant cancers. Only in two studies did the use of MRI-TRUS fusion allow the detection of more clinically insignificant cases compared with standard biopsy.
clinically significant cancers that were missed by standard biopsy alone. On the other hand, standard biopsies detected 0% to 12.4% additional clinically significant cancers that were missed by MRI-TRUS fusion biopsies. However, if the study using transperineal mapping biopsies is removed so that the standard biopsy is only a TRUS biopsy approach, this figure stood at 0% to 7%.

In all series, an image fusion approach was more efficient in detecting clinically significant disease. The median number of cores needed to detect one man with clinically significant cancer was 37.1 (interquartile range [IQR], 32.6 to 82.8; range 23.2 to 252) and 9.2 (IQR 4.6 to 24.8; range 4 to 37.7) for standard and MRI-TRUS image fusion–targeted biopsy, respectively. The median difference in number of cores required across the series was 32.1 cores (IQR +28.3 to +57; range +21.4 to +84.8) in favor of the targeted approach. In other words, to detect the same number of clinically significant cancers with standard biopsy, one would need to use approximately four times the number of cores as compared with an image fusion–targeted approach.

Two studies evaluated the outcomes of MRI-TRUS image fusion biopsies versus visual registration–targeted biopsy. One study did not report sufficient information by which to determine the primary outcome measure and a number of the secondary outcome measures. In the only outcome reported—namely, detection of any cancer—MRI-TRUS image fusion biopsies had a higher rate (53% vs. 47%; no P value given). The other study evaluated the two targeting approaches in 125 men with 172 targets in total. In a per-target analysis, MRI-TRUS image software biopsies detected more clinically significant cancers (20.3% vs. 15.1%; P = .05) and more cancer overall (32% vs. 26.7%; P = .14). It also had better efficiency compared with visual registration, requiring 9.8 rather than 13.2 cores to detect 1 man with clinically significant cancer (Wysock et al, 2014). Furthermore, there was no additional usefulness in visual registration targeting, whereas the image fusion approach detected 7.6% additional clinically significant cancers that would have been missed by the visual registration approach. However, the study was underpowered to show the demonstrated absolute difference in detection rate of approximately 5%, as it was powered a priori to demonstrate a 15% difference in detection rate.

For delivery of tissue-preserving focal therapy, accurate localization and characterization of clinically significant prostate cancer must occur. TRUS biopsy is unable to provide such information accurately. Saturation biopsies seem to add only a small additional benefit unless carried out with a template transperineal mapping technique. A transperineal route has several advantages in that it allows systematic coverage of the gland, which provides accurate localization that can be reproduced when providing focal therapy. There have been imaging developments to help improve guidance of biopsies to allow for more accurate sampling. Studies have shown that MRI has a higher sensitivity and specificity compared with TRUS in detecting clinically significant cancer. Targeted biopsies have been shown to detect more clinically significant lesions than random TRUS biopsy with fewer cores taken, with reduced costs from shorter biopsy times and histopathology processing times.

At the heart of the arguments for and against each modality of localization is the need for precision in excluding disease from untreated areas. Greater accuracy up front will logically translate into lower recurrence or de novo disease rates in untreated areas in the long term. Some clinicians and patients may accept the inaccuracy and uncertainty of tools for determining unilaterality—for example, use of TRUS biopsy—to avoid further (expensive and/or morbid) interventions, with the understanding that a higher recurrent or residual cancer rate is found in the untreated side. Provided that the interval between treatment and detection of cancer in the contralateral side is not sufficient for disease progression, patients could then have that side treated.

Biopsy data are commonly used to determine cancer risk. A targeted approach to lesions found on imaging may have an impact on the risk that a particular man is assigned. Features widely used to indicate high risk include Gleason score of 7 or higher, as well as parameters to indicate the amount of cancer, such as maximum cancer core length, maximum percentage cancer, and the number of positive biopsy specimens (Epstein, 2011). However, if a tumor is exposed to a greater sampling density than the rest of the prostate, it is likely that the proportion of cores that are positive, and the maximum cancer core length, will be greater compared with a TRUS

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biopsy. In addition, higher Gleason patterns, if truly present, are more likely to be sampled (Fig. 117-15).

If the trend toward image-guided biopsy continues unchecked, it is likely that we will witness a systematic increase in risk attribution in the men subjected to biopsy if the standard criteria for attributing risk are applied (see Fig. 117-15). It is therefore likely that new risk prediction models based on targeted biopsies will be required. As a start to correct what could be regarded as an artificial increase in cancer risk derived from targeted biopsy, a risk stratification system that is independent of the number of positive cores could be considered.

Ablative Technology

There are a number of ablative technologies that could potentially deliver focal therapy (Ahmed et al, 2009b). HIPEC and cryosurgery conform closely to the desired attributes and are at present the only two modalities that have retrospective and prospective data demonstrating feasibility of focal ablation, low side effect rates, very high genitourinary preservation rates, and good early cancer control. Photodynamic and interstitial photothermal therapies have both shown promise in single-center studies and are at present demonstrating feasibility of focal ablation, low side effect rates, and good early cancer control. Photodynamic and interstitial photothermal therapies have both shown promise in single-center studies and are at present demonstrating feasibility of focal ablation, low side effect rates, and good early cancer control.

Cryotherapy

Cryotherapy is the ablation of tissue by extremely cold temperatures. The first written report of its use was in 19th-century London, where Arnott applied ice-salt mixtures to breasts and cervical cancers (Arnott, 1851). Cryotherapy exerts its effects via a number of pathways, namely:

1. Direct cytolysis through extracellular and intracellular ice crystal formation
2. Intracellular dehydration and pH changes
3. Ischemic necrosis via vascular injury
4. Cryoactivation of antimutator immune responses
5. Induction of apoptosis
6. Endothelial damage, which leads to platelet aggregation and microthrombosis

Figure 117-15. A Gleason 3+4 lesion in the left peripheral zone that through transrectal biopsies may be misclassified as very low risk and very high risk 4+4 through a true hit into the central pattern 4 using current risk stratification systems. In reality, the lesion is intermediate risk.

7. Injury that occurs during warming as a result of osmotic cellular swelling and vascular hyperpermeability

A number of factors affect the efficiency of tissue destruction, namely:
1. Velocity of cooling
2. Nadir temperature
3. Freezing duration
4. Velocity of thawing
5. Number of freeze-thaw cycles
6. Presence or absence of large blood vessels, which can act as heat sinks

Overall, a minimum freezing temperature of −40° C for a duration of 3 minutes is sufficient for tumor eradication (Hoffmann and Bischof, 2002). It has also been demonstrated that complete cell death is unlikely at temperatures greater than −20° C, although cells not destroyed by initial freezing to −20° C were destroyed with a second freeze cycle (Tsatsanis et al, 1996). Histopathologic changes after cryotherapy in the prostate are divided into an early degenerative phase caused by coagulative necrosis and a later phase of repair—fibrosis, calcification, and hyalinization (Grampsas et al, 1985; Borkowski et al, 1996).

Although this source of energy is known to be very effective against prostate cancer, it was not before significant technologic developments were made that this source of energy became very attractive in prostate cancer. Mainly, third-generation cryotherapy devices are able to use gas-based systems to provide rapid freeze and thaw cycles (Fig. 117-16). Also, manufacturers have been able to develop multiprobe systems while decreasing the size of each cryoprobe, so the precision of ablation could be enhanced (Fig. 117-17). Finally, the toxicity has significantly decreased because of the development of bladder and urethral warmers during the treatment, and the systematic use of thermocouples for verifying the temperature both in critical surrounding structures and in the treatment area.

Focal cryotherapy to an area of the prostate is delivered under transrectal ultrasound guidance using cryoneedles inserted via the perineum using a brachytherapy grid or in a freehand fashion. In addition, thermocouples are positioned in the same way, normally in the treatment area, in the Denonvilliers fascia, and in other key areas such as the rhabdosphincter and the neurovascular bundles at the discretion of the surgeon. A urethral cystoscopy is warranted before beginning the treatment, to verify the position of the needles; finally, a continuous urethral warmer to protect the urethra is inserted and maintained during the whole procedure (Figs. 117-18 and 117-25). In addition to the standardized technique introduced in 1995 by the American Urological Association released a Best Practice statement to underline the optimal procedural requirements to deliver effective cryotherapy. The panel recommended a double freeze-thaw cycle and the use of rapid freezing up to −40° C with a slow, almost passive, thaw.

High-Intensity Focused Ultrasound

Ultrasound refers to mechanical vibrations above the threshold of human hearing (16 kHz) and has the ability to interact with tissue to produce biologic changes. Applying an alternating voltage across a piezoelectric material such as lead zirconate titanate generates ultrasound (Figs. 117-26 and 117-27). These materials oscillate at the same frequency as the alternating current, causing ultrasound waves that can propagate through tissue. This in turn causes alternating cycles of increased and reduced pressure (compression and rarefaction, respectively). Diagnostic ultrasound usually uses frequencies in the range of 1 to 20 MHz, but therapeutic HIFU uses frequencies of 0.8 to 3.5 MHz with delivery of energy levels within the ultrasound beams that are several times greater than the energy levels within diagnostic ultrasound. Therapeutic ultrasound can be conveniently divided into two broad categories: low intensity (0.125 to 3 W/cm²) and high intensity (>5 W/cm²). The former can stimulate normal physiologic responses to injury and accelerate other processes such as the transport of drugs across the skin. High-intensity ultrasound can selectively destroy tissue...
PART XIV The Prostate

Figure 117-16. Diagram depicting the Joule-Thomson effect of cryotherapy.

Figure 117-17. Cryotherapy probes (17 G in size)—IceRod cryotherapy needles (Galil Medical, Arden Hills, MN).

Figure 117-18. Available cryoablation systems for operative planning and real-time monitoring of freezing process. A, Presice Cryoablation System (Galil Medical, Arden Hill, MN). B, Cryocare CS (Endocare/HealthTronics, Austin, TX). (B, Used with permission of Endocare, Inc., a wholly-owned subsidiary of HealthTronics, Inc. © 2015 HealthTronics, Inc. All rights reserved.)
Chapter 117  Focal Therapy for Prostate Cancer

Figure 117-19. Screenshot of the Presice Cryoablation System (Galil Medical, Arden Hill, MN) user interface for preoperative simulation and isothermal mapping.

Figure 117-20. Cryotherapy is delivered using transperineal needles into the prostate under ultrasound guidance. (Courtesy Galil Medical.)

Figure 117-21. The ice ball that forms can take temperatures down to ~40°C to ~60°C for cell kill. Two freeze-thaw cycles are delivered.

Figure 117-22. T2-weighted magnetic resonance imaging (MRI) scan of a 56-year-old man who had a prostate-specific antigen (PSA) level of 8.9 and a negative transrectal ultrasound (TRUS)-guided biopsy in 2008. Subsequently the PSA rose to 16 in 2009 and he underwent another TRUS biopsy, which showed Gleason 3+3 1-mm prostate cancer, so he underwent active surveillance. The PSA again rose to 18 in 2013, and another biopsy showed focal high-grade prostatic intraepithelial neoplasia. Finally, the PSA was 25 in 2014 and the MRI scan shown here was obtained, showing a right anterior lesion.
Figure 117-23. The lesion from the same patient as in Figure 117-22 was confirmed on the other sequences (diffusion-weighted and dynamic contrast). Here, the dynamic contrast-enhanced scan using gadolinium contrast is shown. Targeted transperineal biopsies of this lesion showed four of four cores positive, with Gleason 3+4 and maximum cancer length involvement of 9 mm.

Figure 117-24. The man from Figures 117-22 and 117-23 opted for focal cryotherapy after appropriate counseling. This was guided by image fusion so the needles could be placed accurately into lesion and ensure a margin was incorporated into the treatment. Red represents lesion contour from magnetic resonance imaging (MRI); green represents prostate contour from MRI.

Figure 117-25. Early 2-week contrast-enhanced magnetic resonance imaging after focal cryotherapy in the man from Figure 117-24 showed confluent lack of perfusion in the area of ablation. He had no urinary leakage, and erections were sufficient for penetrative sexual intercourse.
Chapter 117  Focal Therapy for Prostate Cancer

Figure 117-26. One of the transrectal high-intensity focused ultrasound devices. This is the Sonablate 3G system (SonaCare Medical, Indianapolis, IN).

Figure 117-27. The Sonablate high-intensity focused ultrasound transrectal probe has two focal lengths: 3 cm and 4 cm.

HIFU relies on the physical properties of ultrasound, which allow it to be brought into a tight focus with an acoustic lens, a bowl-shaped transducer, or an electronic phased array. As ultrasound propagates through a tissue, zones of high and low pressure are created. When the energy density at the focus is sufficiently high (during the high-pressure phase), tissue damage occurs. The volume of ablation (or lesion) after a single HIFU pulse or exposure is small and varies according to transducer characteristics. It is typically shaped like a grain of rice or cigar with dimensions on the order of 1 to 3 mm (transverse) × 8 to 15 mm (along beam axis). To ablate larger volumes of tissue for the treatment of solid cancers, these lesions are placed adjacent to one another. The two predominant mechanisms of tissue damage are the conversion of mechanical energy into heat, and inertial cavitation. If tissue temperatures are raised above 56° C, then immediate thermal toxicity can occur, provided the temperature is maintained for at least 1 second. This will lead to irreversible cell death from coagulative necrosis. In fact, during HIFU the temperatures achieved are much greater than this, typically above 80° C, so even short exposures can lead to effective cell death. Inertial cavitation occurs at the same time but is neither as controllable nor predictable. It occurs as a result of the alternating cycles of compression and rarefaction. At the time of rarefaction, gas can be drawn out of solution to form bubbles, which then collapse rapidly. The mechanical stress and a degree of thermal injury induce cell necrosis (Kennedy, 2005). Histologically, the tissue changes that occur are homogeneous coagulative necrosis, with an...
Photodynamic Therapy

Photodynamic therapy (PDT) uses a photosensitizing drug that is activated, after a given drug-light interval, by light of a specific wavelength. It requires tissue oxygen for the treatment effect, with the activated drug forming reactive oxygen species, which are directly responsible for damage to the treated volume. The photosensitizing drugs are activated either while in the tissue or in the vasculature. Tissue-activated drugs have long drug-light intervals (typically hours to days), which means that the drug and light are given in separate treatment sessions. These drugs usually take a long time to be cleared from the body and can accumulate in the skin, requiring patients to be covered from sunlight (which could activate the drug and cause a sunburn-like reaction) for a few weeks. Some of the tissue-activated photosensitizers accumulate preferentially in tumor tissue. These include aminolevulinic acid (ALA), which is used in the diagnosis of bladder tumors and has also been assessed for use in the treatment of prostate cancer. Vascular-activated drugs have the advantage of a short drug-light interval (i.e., minutes), which allows the whole treatment to be done in a single session. They are usually cleared rapidly from the circulation, without accumulation in the skin, such that light restrictions are not necessary after a few hours.

Light delivery for prostate cancer, along with other interstitial tumors, uses low-power laser light directed to the treatment site by optical fibers. These fibers can deliver light only at the end of the fiber (like a torch) or along a cylindrical diffuser (like a strip light). For prostate cancer, a transperineal approach is currently used, with hollow plastic needles placed in the prostate with use of transrectal ultrasound imaging. Cylindrical diffusers of the desired length are then placed within the hollow plastic needles, and low-power laser energy, at a wavelength determined by the individual photosensitizer, is delivered to the prostate. Other approaches that have been used are transurethral light delivery and open insertion of fibers at laparotomy.

Focal Photothermal Therapy

Photothermal therapy uses laser fibers with the objective to raise the temperature directly in the treatment area. No photosensitizing agent nor oxygen tissue supply are needed. The ablation effect is claimed to be predictable, accurate, and restricted within the target area. In photothermal therapy, the patient is under general anesthesia or sedated with a urethral catheter placed but removed after the procedure. With a transperineal approach, an open-ended catheter is introduced into the target lesion, and after the correct placement has been verified, an optical laser fiber is inserted to deliver the treatment. Early in the clinical experience, MRI was used for treatment planning, and the placement of the fibers and the treatments were carried out under TRUS guidance. Lately, the use of...
Focal Therapy for Prostate Cancer

**Figure 117-32.** Screenshot of the Sonablate high-intensity focused ultrasound (HIFU) device. Treatment is delivered in blocks *(red area)*. The lower two ultrasound images are pre-HIFU baseline images and allow a direct comparison. There are other safety features built into the device to prevent collateral damage. The power of each pulse can be controlled, giving fine control of the energy delivery into the prostate.

**Figure 117-33.** Post-treatment contrast magnetic resonance imaging in the man from Figures 117-30 to 117-32 shows confluent ablation and some extraprostatic damage, which are quite typical for high-intensity focused ultrasound and point to effect in microscopic extracapsular disease.

**Figure 117-34.** A 12-month scan from another man who underwent focal high-intensity focused ultrasound (HIFU) and was found to have a suspicious area of recurrence *(arrow)*. This was confirmed on targeted biopsies as Gleason 3+4 2 mm. He chose re-treatment with HIFU in a focal manner.

Magnetic resonance–compatible material has allowed in-gantry ablation under real-time MRI monitoring.

**Focal Irreversible Electroporation**

Irreversible electroporation causes tissue damage by permanently altering the cell homeostasis using low-energy direct current.

Indeed, the use of low voltage avoids local thermal effects and instead forms nanopores in the cellular membrane, which lead to cell death. The energy is delivered to the tissue from the generator to electrode needles inserted around the tumor. Irreversible electroporation has some key features that make it potentially very attractive. First, once the needles have been positioned, the treatment is very quick, usually less than 5 minutes. Second, it seems to
The Prostate

Figure 117-35. Early contrast magnetic resonance imaging after repeated focal high-intensity focused ultrasound shows excellent treatment effect. The patient was found to be cancer free on mapping template biopsies 2 years later.

Figure 117-36. A 66-year-old man with a prostate-specific antigen level of 7.5 and normal rectal examination findings underwent prebiopsy magnetic resonance imaging (MRI) as part of a validating cohort trial called the Prostate MRI Imaging Study (PROMIS). This involves prebiopsy MRI that remains blind to the physician and the patient. The patient then undergoes a transrectal biopsy and a template mapping transperineal biopsy at a sampling frame of 5 mm. This image shows a discrete lesion anteriorly on T2-weighted MRI.

Radiofrequency Ablation

RFA acts by converting radiofrequency waves to heat, resulting in thermal damage. High-frequency current flows from the needle electrode to target tissue with resultant ionic agitation and heat-producing molecular friction, denaturation of proteins, and cell membrane disintegration. The cellular and tissue effects of RFA vary with the duration of ablation and the local temperature achieved. This temperature-time dependence was demonstrated by in vitro studies in which irreversible cell injury of benign and malignant human cell lines were heated to 45°C for 60 minutes, 55°C for 5 minutes, and 70°C for 1 minute. These changes take 4 to 6 minutes at temperatures exceeding 50°C and occur almost immediately above 60°C. Temperatures greater than 105°C cause vaporization of tissue, resulting in gas formation and inefficient creation of radiofrequency lesions. The goal of RFA is to induce temperatures of 50°C to 100°C throughout the tumor. Histologic analysis after RFA demonstrates typical coagulative necrosis characterized by cell membrane disruption, protein denaturation, and vascular thrombosis. Exophytic tumors that are surrounded by perirenal fat are...
Figure 117-39. This demonstrates the scoring proforma used by the radiologist in the trial.

Figure 117-40. The template transperineal map confirms the index lesion is this right anterior tumor with Gleason 3+4=7 3 mm. There are low-volume Gleason 3+3=6 areas in the rest of the prostate that magnetic resonance imaging (MRI) could not detect, arguably a good trait for MRI to have.

better treated than central tumors in which vascular structures can act as a heat sink.

In practice, a grounding pad is placed on the patient, and the radiofrequency probe is inserted in the ablation zone. A computer-controlled generator provides an alternating current in the radio wave frequency of the electromagnetic spectrum. Bipolar RFA decreases the risk of accidental burns associated with monopolar RFA. The impedance of the tissue to this monopolar current leads to local tissue hyperthermia, which is the basis for the cell kill effect. The temperatures reached during RFA depend on the generator's power, tissue impedance, heat conductivity, and heat dissipation via the local circulation. Commercially available RFA units are classified into temperature-based or impedance-based systems. This means that the computer-controlled generator provides energy to the probe based on either the average temperature achieved or the measured impedance of the tissue monitored during ablation.
The Prostate Database Registry, an online database supported by a private manufacturer and independently managed by a research company (Watermark, Indianapolis, IN) and a medical advisory board. The registry has no restricted eligibility for patients, who are selected by their surgeon following local guidelines with the approval of the Institutional Review Board.

In a recent report from the COLD Registry, 1,160 men were treated with focal cryoablation (Ward and Jones, 2012). In terms of cancer control, the 3-year biochemical disease-free survival (BDFS) was at 75.7%; the positive biopsy rate was 26.3% when considering only the patients who underwent biopsy because of biochemical failure, or 3.7% if the whole cohort of patients is considered the denominator. In terms of functional outcomes, urinary Impedance rises toward infinity when tissues are desiccated during ablation or when there is charring. RFA technology can also be classified by dry and wet RFA. The latter allows constant infusion of saline during ablation to reduce the degree of charring and thus a premature rise in impedance. Currently, there is one device under evaluation in the prostate space (Figs. 117-44 and 117-45).

Outcomes

Focal Cryoablation

Most of the actual knowledge regarding the outcomes of focal cryoablation as first-line treatment comes from the COLD (Cryo On-Line Database) Registry, an online database supported by a private manufacturer and independently managed by a research company (Watermark, Indianapolis, IN) and a medical advisory board. The registry has no restricted eligibility for patients, who are selected by their surgeon following local guidelines with the approval of the Institutional Review Board.

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the functional outcomes refer to the whole study population, including patients having whole-gland treatment; also, no PROM specific for evaluating continence was used.

In summary, focal PDT has been assessed only in a stage Ila-b study with promising results in terms of toxicity and variable results in terms of efficacy. At the time of writing, a stage III (RCT) study comparing the oncologic outcome and the safety profile of PDT against active surveillance in men with very low-risk disease has achieved the recruitment target of 400 patients, with a randomization allocation of 1:1. Although many argue that these men do not represent the ideal population for an active treatment because active surveillance is a safe option for them, it needs to be acknowledged that this is the first stage III trial comparing focal therapy with a standard option.

Focal Photothermal Therapy

Photothermal therapy is a strict focal-based modality in which only small areas of cancer are treated. So far, two stage I and one stage Ila trials have been completed using focal photothermal therapy (Lindner et al., 2009, 2013; Otto et al., 2013). Overall, residual disease in the treated area was found in 22% to 33% of men who had a systematic biopsy after treatment. When reported, potency and full continence were preserved in 96% to 100% of men, respectively, although no specific PROM for continence assessment was used.

Although photothermal therapy is a promising new energy source with excellent genitourinary outcomes, the oncologic results are limited because only small areas of cancer have so far been targeted. Also, despite the small volume ablated, the operative time at the moment is still significant (around 2.5 to 4 hours). This technique would probably benefit from a larger multicenter stage IIB trial to explore the optimal parameters for successfully delivering energy and to explore reproducibility.

Focal Irreversible Electroporation

Only two case series including patients treated by focal irreversible electroporation have been reported (Brausi et al., 2011; Valerio et al., 2014). In the only study with protocol biopsy, residual disease was found in 27% of patients. Erectile function was preserved in 89% to 100%, whereas continence was maintained in 100%. This technology is very promising but is still in the early stage of assessment. A prospective development trial stage Ila using PROMs and targeted biopsy of the treated area will better clarify the short-term outcomes of this technology. We recently systematically reviewed these data.

OVERALL DATA

A number of series were identified evaluating focal therapy in the primary setting (Table 117-2) (Madersbacher et al., 1995; Zlotta et al., 1998; Beerlage et al., 1999; Souchon et al., 2003; Bahn et al., 2006; Moore et al., 2006; Ellis et al., 2007; Onik et al., 2007; Muto et al., 2008; Murat et al., 2009a; Lindner et al., 2010a; Raz et al., 2010; Truesdale et al., 2010; Ahmed et al., 2011a; El Fegoun et al., 2011; Tay et al., 2011; Ahmed et al., 2012d; Bahn et al., 2012; Chopra et al., 2012; Dickinson et al., 2012; Nguyen et al., 2012; Ward and Jones, 2012; Barrett et al., 2013; Napoli et al., 2013).

This equates to 2232 men treated with focal therapy and reported p0715 in the literature. Six series used cryosurgery, 12 HIFU, 1 PDT, 3 photothermal therapy, 1 radiofrequency interstitial tumor ablation (RITA), and 1 MRI-guided brachytherapy, and 1 incorporated various ablation techniques. Median follow-up periods for the reported focal therapy series are 0 to 10.6 years (overall range 0 to 11.1). In our systematic review, most of the studies used some form of preoperative MRI in combination with biopsy parameters as criteria to select patients for inclusion; some recent series use this modality for treatment planning (Table 117-3). The latest prospective trials combine mpMRI with template prostate mapping biopsy.
<table>
<thead>
<tr>
<th>SERIES</th>
<th>ABLATION TYPE</th>
<th>PSA (ng/mL)</th>
<th>GLEASON SCORE AT PREOPERATIVE BIOPSY</th>
<th>RISK CLASSIFICATION</th>
<th>FOLLOW-UP</th>
<th>PRESENCE OF ANY CANCER</th>
<th>PRESENCE OF CLINICALLY SIGNIFICANT CANCER</th>
<th>BDFS</th>
<th>PSA KINETICS (AT LAST FOLLOW-UP UNLESS OTHERWISE STATED)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madersbacher et al, 1995</td>
<td>HIFU</td>
<td>24 mean (range 2-82.8)</td>
<td>NR</td>
<td>NR</td>
<td>Few hours (mean/median NR)</td>
<td>29/29 (100%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>Zlotta et al, 1998</td>
<td>RITA</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Mean/median NR (range 0 days-3 mo)</td>
<td>14/14 (100%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Beerlage et al, 1999</td>
<td>HIFU</td>
<td>10.8 mean (range 3.5-20)</td>
<td>NR</td>
<td>NR</td>
<td>8.5 days median (range 7-12)</td>
<td>13/14 (93%)</td>
<td>4/14 (29%)</td>
<td>had residual tumor in the treated area</td>
<td>NR</td>
</tr>
<tr>
<td>Souchon et al, 2003</td>
<td>HIFU</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Moore et al, 2006</td>
<td>PDT</td>
<td>6.95 median (range 1.9-15)</td>
<td>3+3: 6 (100%)</td>
<td>NR</td>
<td>NR</td>
<td>6/6 (100%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bahn et al, 2006</td>
<td>Cryoablation</td>
<td>4.95 mean (range 0.2-25.1)</td>
<td>≤6: 23 (74%) 7: 8 (26%)</td>
<td>NR</td>
<td>70 mo mean (range 2-107)</td>
<td>1/25 (4%)</td>
<td>NR</td>
<td>92.9%</td>
<td>NR</td>
</tr>
<tr>
<td>Onik et al, 2007</td>
<td>Cryoablation</td>
<td>8.3 mean (range 0.2-25.1)</td>
<td>NR</td>
<td>Low: 26 (48%) Intermediate: 20 (36%) High: 9 (16%)</td>
<td>3.6 yr mean (range 1-10)</td>
<td>Only patients having biopsy: 4/30 (13%) All patients: 4/55 (7%)</td>
<td>NR</td>
<td>3-yr: 95%</td>
<td>Mean 2.4 (SD NR)</td>
</tr>
<tr>
<td>Ellis et al, 2007</td>
<td>Cryoablation</td>
<td>7.2 mean (SD 4.7)</td>
<td>≤6: NR (78.3%) 7: NR (20%) ≥8: NR (1.7%)</td>
<td>Low: 40 (66.7%) Intermediate: 14 (23.3%) High: 6 (10%)</td>
<td>12 mo median (range 3-36)</td>
<td>Only patients having biopsy: 14/35 (40%); 1/35 (3%) in the treated side All patients: 14/60 (23%); 1/60 (1.7%) in the treated side</td>
<td>NR</td>
<td>80.4%</td>
<td>Median 1.7 (IQR NR)</td>
</tr>
<tr>
<td>Muto et al, 2008</td>
<td>HIFU</td>
<td>5.4 median (range 0.2-25.1)</td>
<td>Unknown: 2 (6.9%) ≤6: 16 (55.2%) 7: 6 (20.7%) ≥8: 5 (17.2%)</td>
<td>NR</td>
<td>34 mo median (range 8-45)</td>
<td>At 6 mo: 3/28 (10.7%) At 12 mo: 4/17 (23.5%)</td>
<td>NR</td>
<td>2-yr Low risk: 83.3% Intermediate risk: 53.6%</td>
<td>At 36 mo: mean 1.89 (SD 1.51)</td>
</tr>
<tr>
<td>Murat et al, 2009a</td>
<td>HIFU</td>
<td>NR</td>
<td>NR</td>
<td>Low: 33 (59%) Intermediate: 23 (41%)</td>
<td>42 mo median (NR)</td>
<td>NR</td>
<td>NR</td>
<td>3-yr: 76% 5-yr: 60%</td>
<td>Nadir after first HIFU: 0.5 mean (NR) Nadir after secondary redo HIFU: 0.47 mean (SD NR)</td>
</tr>
<tr>
<td>------------------</td>
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<td>----------------</td>
</tr>
<tr>
<td>Lindner et al, 2009</td>
<td>Photothermal laser</td>
<td>5.7 mean (SD 1.1)</td>
<td>3+3: 12 (100%)</td>
<td>Low risk: 12 (100%)</td>
<td>6 mo</td>
<td>6/12 (50%) 4/12 (33%) in the treated area</td>
<td>2/12 (17%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lindner et al, 2010a</td>
<td>Photothermal laser</td>
<td>4.2 median (range 2.9-14.8)</td>
<td>3+3: 2 (50%) 4+3: 2 (50%)</td>
<td>NR</td>
<td>1 wk</td>
<td>4/4 (100%) with no residual tumor in the treated area</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Raz et al, 2010</td>
<td>Photothermal laser</td>
<td>3.76 median (range 2.74-4.79)</td>
<td>3+3: 2 (100%)</td>
<td>Low: 2 (100%)</td>
<td>≤1 mo</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Truesdale et al, 2010</td>
<td>Cryoablation</td>
<td>6.54 mean (SD 4.87)</td>
<td>≤6: 50 (65%) 7: 25 (32%) 8: 2 (3%)</td>
<td>Low: 44 (57%) Intermediate: 31 (40%) High: 2 (3%)</td>
<td>24 mo median (0-87)</td>
<td>Only patients having biopsy: 10/22 (45.5%); 3/22 (14%) in the treated area All patients: 10/77 (13%); 3/77 (3.9%) in the treated area</td>
<td>NR</td>
<td>72.7% Mean 1.23 (SD 1.38)</td>
<td></td>
</tr>
<tr>
<td>El Fegoun et al, 2011</td>
<td>HIFU</td>
<td>7.3 mean (range 2.6-10)</td>
<td>≤3+3: 10 (83%) 3+4: 2 (17%)</td>
<td>NR</td>
<td>10.6 yr median (range 7.5-11.1)</td>
<td>1/12 (8%)</td>
<td>0/12</td>
<td>5-yr: 90% 10-yr: 38% Median 1.5 (range 0.1-6.8)</td>
<td></td>
</tr>
<tr>
<td>Ahmed et al, 2011a</td>
<td>HIFU</td>
<td>7.3 median (range 3.4-11.8)</td>
<td>NR</td>
<td>Low: 5 (25%) Intermediate: 15 (75%)</td>
<td>12 mo</td>
<td>2/19 (11%)</td>
<td>0/19</td>
<td>NR</td>
<td>At 12 mo: mean 1.5 (SD 1.3)</td>
</tr>
<tr>
<td>Ward and Jones, 2012</td>
<td>Cryoablation</td>
<td>1149 (99%) available &lt;6: 211 (18%) 4 to &lt;10: 782 (68%) 10 to &lt;20: 126 (11%) ≥20: 30 (3%)</td>
<td>1148 (99%) available ≤6: 844 (74%) 7: 240 (21%) ≥8: 64 (5%)</td>
<td>1157 (99%) available Low: 541 (47%) Intermediate: 473 (41%) High: 143 (12%)</td>
<td>21.1 mo mean (SD 19.7)</td>
<td>Only patients having biopsy: 43/163 (26.4%) All patients: 43/1160 (3.7%)</td>
<td>NR</td>
<td>3-yr: 75.7% NR</td>
<td></td>
</tr>
<tr>
<td>Tay et al, 2011</td>
<td>MRI-guided HIFU</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0/1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Chopra et al, 2012</td>
<td>MRI-guided HIFU</td>
<td>6.2 mean (range 2.7-13.1)</td>
<td>3+3: 2 (25%) 3+4: 4 (50%) 4+3: 2 (25%)</td>
<td>NR</td>
<td>&lt;2 hr</td>
<td>8/8 (100%) 6/8 (75%)</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>SERIES</th>
<th>ABLATION TYPE</th>
<th>PSA (ng/mL)</th>
<th>Gleason Score at Preoperative Biopsy</th>
<th>Risk Classification</th>
<th>Follow-Up</th>
<th>Presence of Any Cancer</th>
<th>Presence of Clinically Significant Cancer</th>
<th>BDFS</th>
<th>PSA Kinetics (At Last Follow-Up Unless Otherwise Stated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bahn et al, 2012*</td>
<td>Cryoablation</td>
<td>5.4 median</td>
<td>3+3: 30 (41%) 3+4: 25 (34%) 4+3: 18 (25%)</td>
<td>Low: 24 (33%)</td>
<td>3.7 yr median (range 1-8.5)</td>
<td>12/48 (25%) including the patient having positive biopsy of the untreated side; 1 of the treated side</td>
<td>5/48 (10%)</td>
<td>NR</td>
<td>At 36 mo: mean 2.1 (SD 3.8)</td>
</tr>
<tr>
<td>Ahmed et al, 2012d</td>
<td>HIFU</td>
<td>6.6 median</td>
<td>3+3: 13 (32%) 3+4: 24 (59%) 4+3: 4 (10%)</td>
<td>Low: 11 (27%)</td>
<td>12 mo</td>
<td>9/39 (23%)</td>
<td>3/39 (8%)</td>
<td>NR</td>
<td>Median 1.9 (IQR 0.8-3.3)</td>
</tr>
<tr>
<td>Dickinson et al, 2012*</td>
<td>HIFU</td>
<td>NR</td>
<td>3+3: 31 (35%) 3+4: 50 (57%) 4+3: 7 (8%)</td>
<td>NR</td>
<td>32 mo median (range 24-69)</td>
<td>20/72 (28%)</td>
<td>10/2 (14%)</td>
<td>Phoenix 71/87 (82%) Stuttgart 57/87 (86%)</td>
<td>NR</td>
</tr>
<tr>
<td>Nguyen et al, 2012</td>
<td>MRI-guided brachytherapy</td>
<td>5.0 median</td>
<td>3+3: 280 (88%) 3+4: 38 (12%)</td>
<td>Low: 265 (83%)</td>
<td>5.1 yr (IQR 2.8-7.3)</td>
<td>Only patients having biopsy: 17/24 (71%) All patients: 17/318 (5.3%)</td>
<td>NR</td>
<td>Phoenix: 5-yr: 91.5% 8-yr: 78.1% Phoenix and PSAV &gt;0.75/yr 5-yr: 91.9% 8-yr: 86.2%</td>
<td>NR</td>
</tr>
<tr>
<td>Napoli et al, 2013</td>
<td>MRI-guided HIFU</td>
<td>8.8 median</td>
<td>3+3: 3 (60%) 3+4: 2 (40%)</td>
<td>NR</td>
<td>9 mo median (range 7-14)</td>
<td>5/5 (100%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Barret et al, 2013*</td>
<td>HIFU 21 (20%) Brachytherapy 12 (11%) Cryoablation 50 (47%) PDT 23 (22%)</td>
<td>6.1 mean (IQR 5-8.1)</td>
<td>3+3: 106 (100%)</td>
<td>Low: 106 (100%)</td>
<td>9 mo median (range 6-15)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>12-mo: median 2.7 (IQR 1-4.4)</td>
</tr>
</tbody>
</table>

*This series partially overlaps with one previously reported.

BDFS, biochemical disease-free survival; HIFU, high-intensity focused ultrasound; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PSA, prostate-specific antigen; PSAV, PSA velocity; PDT, photodynamic therapy; RITA, radiofrequency interstitial tumor ablation; SD, standard deviation.
**Chapter 117  Focal Therapy for Prostate Cancer**

**TABLE 117-3  Case Series of Focal Therapy Showing Toxicity and Functional Outcomes**

<table>
<thead>
<tr>
<th>SERIES</th>
<th>COMPLICATIONS</th>
<th>URINARY CONTINENCE</th>
<th>ERECTILE FUNCTION (ABILITY TO HAVE PENETRATIVE INTERCOURSE)</th>
<th>RECTAL TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madersbacher et al, 1995</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Zlotta et al, 1998</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
| Beerlage et al, 1999          | NR                | NR                 | NR                                                          | Rectourethral fistula: 0/14 (0%)  
Perineal pain: 14/14 (100%)  
Rectal bleeding: NR  
Diarrhea: NR  
PROM: NR |
| Souchon et al, 2003           | NR                | NR                 | 1/3 (33%)  
PROM: Brief Sexual Function Inventory | NR                   |
| Moore et al, 2006             | Urinary retention: 1/6 (17%)  
Urethral stricture: NR  
UTI: 1/6 (17%)  
Outcome measure: NR | NR                 | Pad-free: NR  
Leak-free: 5/6 (83%)  
PROM: AUA-7 | Rectourethral fistula: 0/3 (0%)  
Perineal pain: NR  
Rectal bleeding: 2/6 (33%)  
Diarrhea: NR  
PROM: NR |
| Bahn et al, 2006              | NR                | Pad-free: 28/28 (100%)  
Leak-free: NR  
PROM: NR | 24/27 (88.8%)  
PROM: Brief Male Sexual Function Index | NR                   |
| Onik et al, 2007              | NR                | Pad-free: 24/25 (96%)  
Leak-free: NR  
PROM: NR | 44/51 (86%)  
PROM: NR | NR                   |
| Ellis et al, 2007             | NR                | Pad-free: 55/55 (100%)  
Leak-free: 53/55 (96.4%)  
PROM: NR | 24/34 (70.6%)  
PROM: NR  
(vacuum therapy and oral therapy for erectile dysfunction offered preoperatively) | Rectourethral fistula: 0/34 (0%)  
Perineal pain: NR  
Rectal bleeding: NR  
Diarrhea: NR  
PROM: NR |
| Muto et al, 2008              | Urinary retention: NR  
Urethral stricture 1/25 (4%)  
UTI 1/25 (4%)  
Outcome measure: NR | Pad-free: NR  
Leak-free: NR  
PROM: UCLA-EPIC, IPSS | NR | NR |
| Murat et al, 2009a            | NR                | 28/52 (54%)  
PROM: IIEF-5 | NR | NR |
| Lindner et al, 2009           | Urinary retention: No  
Urethral stricture: No  
UTI: No  
Outcome measure: NR | Pad-free: 12/12 (100%)  
Leak-free: 12/12 (100%)  
PROM: IPSS | NR (100%)  
PROM: IIEF-5 | Rectourethral fistula: 0/12 (0%)  
Perineal pain: 3/12 (25%)  
Rectal bleeding: No  
Diarrhea: No  
PROM: NR |
| Lindner et al, 2010a          | NR                | NR                 | NR | NR |
| Raz et al, 2010               | NR                | NR                 | NR | NR |
| Truesdale et al, 2013         | NR                | Pad-free: 77/77 (100%)  
Leak-free: NR  
PROM: IPSS | NR | PROM: IIEF | NR |
| El Fegoun et al, 2011         | Urinary retention: 1/12 (8%)  
Urethral stricture: No  
UTI: 2/12 (16%)  
Outcome measure: NR | Pad-free: 12/12 (100%)  
Leak-free: NR  
PROM: IPSS | NR | NR |

*Continued*
### PART XIV  The Prostate

#### TABLE 117-3  Case Series of Focal Therapy Showing Toxicity and Functional Outcomes—cont’d

<table>
<thead>
<tr>
<th>SERIES</th>
<th>URINARY CONTINENCE</th>
<th>ERECTILE FUNCTION (ABILITY TO HAVE PENETRATIVE INTERCOURSE)</th>
<th>RECTAL TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmed et al, 2011a</td>
<td>Pad-free: 19/20 (95%) Leak-free: 18/20 (90%) PROM: UCLA-EPIC, IPSS</td>
<td>19/20 (95%) PROM: IIEF-15</td>
<td>Rectourethral fistula: 0/20 (0%) Perineal pain: NR Rectal bleeding: NR Diarrhea: NR PROM: FACT-P</td>
</tr>
<tr>
<td>Ward and Jones, 2012</td>
<td>Pad-free: 499/507 (98.4%) Leak-free: NR PROM: NR</td>
<td>169/291 (58.1%) PROM: NR</td>
<td>Rectourethral fistula: 1/507 (0.2%) Perineal pain: NR Rectal bleeding: NR Diarrhea: NR PROM: NR</td>
</tr>
<tr>
<td>Barret et al, 2013</td>
<td>Pad-free: 106/106 (100%) Leak-free: NR PROM: IPSS</td>
<td>NR PROM: IIEF-5</td>
<td>Rectourethral fistula: 1/106 (1%) Perineal pain: 1/106 (1%) Rectal bleeding: 0 Diarrhea: NR PROM: NR</td>
</tr>
</tbody>
</table>

*This series partially overlaps with one previously reported.

AUA, American Urological Association; FACT-P, Functional Assessment of Cancer Therapy-Prostate; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; NR, not reported; PROM, patient-reported outcome measure; UCLA-EPIC, University of California, Los Angeles Expanded Prostate Index Composite; UTI, urinary tract infection.

To minimize the possibility of leaving significant areas of cancer untreated. Other tools of preoperative assessment that have been used include transrectal Doppler ultrasound. In summary, among the primary selected studies, 2 series used only TRUS biopsy, 2 used TRUS biopsy and Doppler ultrasound, 6 used TRUS biopsy and MRI, and 4 used template prostate mapping and mpMRI. The preoperative assessment was not reported in 11 studies. Furthermore, all reported series have treated all known areas of cancer, but no reported series have explicitly stated that therapy was aimed at the index lesion and deliberately left low-volume, low-grade lesions untreated. Of ongoing trials, most are aiming to treat all known areas of cancer, and 3 trials explicitly aim treatment at the index or clinically significant lesions with surveillance of untreated low-volume, low-grade lesions.

In the largest series of 1160 men using cryoablation, and in another series using HIFU with multiple strategies (n = 88), it was not possible to determine the extent of tissue ablation per patient. Either hemiablation or focal ablation was used in the remaining cases.

studies, with 12 using a hemiablation or extended “dog-leg” or “hockey-stick” approach (number of patients, 537; relative percentage of data available, 49%); 16 used focal or zonal ablation (562, 51%), and 3 used unilateral focal ablation when multifocal disease was present (65, 6%). Our systematic review of focal therapy series demonstrated the summary outcomes shown in Table 117-3.

**Side Effects, Complications, and Quality of Life**

Fourteen series reported hospital stay, with median length of hospital stay of 1 day. Other perioperative outcomes are poorly reported, with only one study using a standardized classification of these outcomes (Dindo-Clavien classification). The most frequent complications, namely urinary retention, urinary stricture, and urinary tract infection, occurred in 0% to 17%, 0% to 5%, and 0% to 17%, respectively. Only five studies actually reported all of these. Urinary functional outcomes were reported using validated questionnaires in nine studies; physician reported rates were used in five studies. Using validated questionnaires, the pad-free continence rate varies between 95% and 100%, and leak-free rates are reported at 83% to 100%.

Erectile function is reported using validated questionnaires in 10 and physician reported rates in 3 studies. Considering only trials evaluating focal therapy with “intention to treat,” when validated questionnaires were used, erectile function sufficient for penetration was reported in 54% to 100% of patients (with or without phosphodiesterase type 5 inhibitor [PDE5I] medication). Physician-reported rates were 58.1% to 85%. One study evaluated the systematic use of a vacuum device and oral therapy (penile rehabilitation) after focal cryoablation. The results, based on nonvalidated outcome measures, found an ability to have penetrative sex in 70.6% (24 of 34) potent men. Historical rates of potency preservation after whole-gland cryotherapy have been 10% to 25%.

Rectal toxicity was often poorly reported. Presence or absence of rectourethral fistula, for instance, was explicitly reported in only 10% of the reported series. When reported, rates of fistula formation were 0% to 1% of these series that reported that 1 of 41 men had grade 3 rectal toxicity conservatively managed as a possible rectourethral fistula. Finally, PROs evaluating overall quality of life are uncommonly used in these studies, with only 3 publications reporting them; in 1 study using hemiablation HI/UF, the patients reported stable quality-of-life scores measured using the Functional Assessment of Cancer Therapy–Prostate (FACT-P) instrument, whereas another demonstrated a slight deterioration after focal HI/UF using the same instrument.

**Cancer Control**

Apart from six early feasibility trials that verified the effect of tissue ablation by analysis of radical whole-mount prostatectomy specimens, nine series incorporated routine mandatory post-focal therapy biopsies in their protocol. In the early six series, the ablative technique was delivered to test the safety and pilot the efficacy of the treatment without the specific aim to completely ablate the whole tumor present. In all, 74 men had radical prostatectomy, and residual disease was found in 73 of them.

Of the remaining nine series, in three series only the treated side underwent biopsy, whereas in six series the contralateral side underwent biopsy, too. When post-therapy biopsies were routinely offered, clinically significant cancer was present in 0% to 17% (total number of men, 202). When also clinically insignificant cancer was taken into account, and excluding one feasibility trial aiming to evaluate safety rather than ablation, 4% to 50% of men had positive biopsies after treatment (total number of men, 235). When biopsies were offered only “for cause,” overall positive biopsy rates of 13% to 71% were demonstrated for all types of cancer; when considering all patients enrolled in these series, this percentage was 3.7% to 23%. None of these series reported the percentage of significant cancer among patients having biopsy. Two series evaluated the presence of residual tumor in the treated area; this amounted to 3% to 14% when considering all patients having biopsy and 1.7% to 3.9% when the denominator was all treated patients.

Biochemical control using Phoenix criteria was reported in 5 series. Other definitions used were American Society for Therapeutic Radiology and Oncology (ASTRO) (5 series), Stuttgart (1 series), and Phoenix plus PSA velocity over 0.75 ng/mL/yr (1 series). The results ranged from 86.2% at 8 years’ follow-up (318 men) to 60% at 5 years (56 men). PSA tended to decrease by 66% to 80% from baseline to 12 months. With respect to the need for secondary focal treatments, only 12 series reported this at 0% to 34%. Salvage local treatments—in which a different modality was used or if whole-gland therapy was eventually delivered—was reported in 14 series with rates of 0% to 33%. One feasibility trial had higher secondary focal (67%) and salvage treatment (63%); these afterprospects were not considered in the overall range because the intent to treat was not to destroy all tumor. The progression to metastatic disease was not reported in most of the studies, because the follow-up is too short to have a significant percentage of patients developing metastasis. Nevertheless, when it is indicated, it is extremely low (0% to 0.3%). When considering CSS, it is extremely high, as expected with the small numbers and short follow-up inherent in almost all reported series. No man died of prostate cancer after focal treatment in the defined follow-up period. Four men died of other causes in the follow-up period. Trifecta outcome was reported in 3 studies, and ranged from 50% to 89% (no incontinence of urine; erections sufficient for penetrative sexual intercourse; cancer control at 12 months or more).

**Follow-up After Focal Therapy**

Early feasibility studies demonstrated an absence of rectal toxicity and preservation of genitourinary function in up to 90% to 95% of men (Ahmed et al, 2011a, 2011d). They demonstrated impotence rates of approximately 15% with little to no incontinence. The studies used a variety of methods to identify unilateral disease including Doppler TRUS biopsies, TRUS alone, and template biopsies and in a few cases, MRI and other imaging that confirmed clinical suspicion. Finally, complete PSA normalization was reported rates were 58.1% to 85%. One study evaluated the systematics of using validated questionnaires, the pad-free continence rate varies between 95% and 100%, and leak-free rates are reported at 83% to 100%.

Using validated questionnaires, the pad-free continence rate varies between 95% and 100%, and leak-free rates are reported at 83% to 100%.
of radical surgery or radiotherapy (ASTRO Consensus Panel, 1997; D’Amico et al. 1998). Radiotherapy definitions tend to overestimate biochemical disease-free survival, in general with a 5-year lag in deeming a treatment failed compared with surgery. Even within these long-established therapies there can be wide variation in definitions used for failure, with over 166 definitions reported in the literature (Cookson et al. 2007). The definition of success for ablative technologies delivered in a whole-gland manner has not reached consensus (Aus, 2006; Ahmed et al. 2009a). Some have adopted ASTRO criteria or modified the acceptable increase above nadir to 1.2 ng/mL (deemed the Stuttgart definition) (Blana et al. 2009). Others, on the other hand, have determined that a PSA nadir upper threshold should be used, although there is no agreement on whether this should be 0.2, 0.4, or 0.5 ng/mL.

With untreated tissue remaining after focal therapy, it would seem unwise to use absolute biochemical parameters or even PSA kinetics alone without a form of standardization against a particular patient’s volume of untreated tissue and volume of cancer ablated. PSA will vary according to the ablative technology, whether a particular device was used, the amount of tissue ablated, and any residual tissue that remains. With the last, the untreated tissue may be benign in its entirety or have clinically insignificant areas of low-volume, low-grade cancer that have been deliberately untreated to deliver tissue preservation. The parameters that may prove to be of greater use are discussed in the following sections.

**Prostate-Specific Antigen Density**

Stamey and colleagues (1987) were the first to correlate PSA serum values and volume of prostatic tissue, showing that the contribution from benign prostatic hyperplastic tissue was 0.30 ng/mL per gram of tissue and 3.5 ng/mL per cm² of cancer tissue. PSA density may therefore be a good measure because it will allow for adjustment for residual tissue volume after focal therapy.

**Nadir Prostate-Specific Antigen**

Setting the PSA decrease relative to the percent of tissue ablated may be more pragmatic. The nadir could be defined by the amount of ablated tissue, with 5% ablation leading to 5% or greater decrease in PSA. Any increase from the nadir would need to be defined within the context of phase II 3- to 5-year trials that take into account the natural tendency for benign prostatic tissue growth and therefore PSA to increase with age (Vesely et al. 2003). The nadir could also be defined in a more intuitive manner by taking into account the proportion of pretreatment PSA that was likely to be accounted for the ablated tumor and the proportion secreted by ablated normal tissue. An accurate determination of cancer volume on MRI or ultrasound can aid in this calculation, whereas derived cancer volumes can be obtained from template TPM biopsies. This is likely to lead to a more robust PSA nadir so that 50% total tissue ablation is likely to lead to a PSA nadir less than 50% of pretreatment PSA, as the contribution to the total PSA is disproportionately higher from cancer tissue. This is borne out by early data from hemiablative strategies, which show a mean decrease of 80% in PSA occurring.

**Prostate-Specific Antigen Kinetics**

PSA kinetics (velocity [e.g., 1 ng/mL/yr] and doubling time [e.g., 2 years]) has been shown to be of some value in determining failure in evaluating progression in active surveillance (Dall’Era et al. 2008). Future trials will need to evaluate the PSA velocity and PSA doubling times that are predictive of failure, as well as velocity and doubling time adjusted for degree of prostate tissue remaining (PSA density kinetics).

**Histologic Outcomes**

Biopsies should be used to determine absence of disease within treated areas to verify short-term focal ablative success as well...
as untreated areas to detect recurrent and de novo disease, respectively, in the medium to long term. However, TRUS-guided biopsies, if used for the latter objective, will be subject to the same systematic and random errors inherent in this test when applied in diagnosis of prostate cancer. So, a degree of targeting using non-invasive imaging to identify clinically significant lesions may be necessary. TRUS-guided biopsies used in this setting are also prone to detect clinically insignificant cancers (low volume, low grade), which are unlikely to influence disease progression; such foci may indeed have been missed on initial localization strategies (Ahmed, 2009). Therefore, their subsequent detection many years after focal therapy need not necessarily equate to the verdict of recurrent, or de novo cancer. Definitions related to clinical significance would need to take account of grade and cancer core length involvement as in diagnostic strategies—2 to 3 mm of cancer in any one core with absence of Gleason pattern 4 may be a starting point (O’Donnell and Parker, 2008), but such criteria will need careful validation. In addition, more accurate volume assessments of cancer foci, if present on surveillance imaging, will be needed. If they are not visualized on surveillance imaging, a post-treatment template transrectal ultrasound (TRUS) mapping biopsy may be required to determine the disease burden of any cancer found on surveillance biopsies (Onik et al, 2009).

Biopsies will need to also take into account the therapeutic strategy used at baseline. Was the strategy one of ablating all measurable disease with absence of any cancer in untreated areas, or was some element of cancer accepted in untreated areas, for example, absence of any clinically significant areas (up to 3-mm low-volume, low-grade foci accepted)? In addition, were template mapping biopsies or TRUS-guided biopsies used to localize disease? If the latter, then disease found on surveillance biopsies may simply represent the sampling error of the initial localization tool used.

In summary, biopsies of the prostate for surveillance after focal therapy must be used in a more refined and accurate manner, taking into account the localization and therapeutic strategy used in the pretreatment selection of focal therapy candidates (Turkbey et al, 2009). Early gadolinium contrast-enhanced MRI, within 1 to 2 weeks of treatment, has been shown to accurately predict areas of necrosis after whole-gland and focal HIFU, as well as other modalities such as PET, thus having a role in early verification of treatment effect (Kirkham et al, 2008). In addition, a number of authors have stated that multifunctional MRI (T2-weighted, dynamic contrast enhancement, diffusion, spectroscopy) seems to meet the ideal attributes for detection of clinically significant cancer, thus potentially being used to drive the delivery of focal therapy. A number of groups have demonstrated accuracy of over 85% to 90% for lesions that measure 0.2 mL or 0.5 mL in volume. The exclusion of significant lesions may be more important than T2 weighting alone to enhance the negative predictive value; negative predictive values for 0.5-mL lesions have been demonstrated to be as high as 95% if multifunctional MRI is used before TRUS-guided biopsy (Villers et al, 2006; Puech et al, 2009). Because 0.5 mL is commonly used as the threshold at which prostate cancer lesions become clinically significant, the inherent ability of multifunctional MRI to be able to detect large lesions and not detect small lesions may be its greatest attribute and may serve to justify its use not only in disease localization for focal therapy but also as a triage test before TRUS-guided biopsy (Ahmed et al, 2009a). These results, which used radical prostatectomy reference standard validation, need verification in other centers as part of multicenter trials. In addition, it was stated that multifunctional MRI is key to also validate against template mapping biopsies, a reference standard that would have less inherent selection bias owing to its applicability to all men.

It therefore seems logical that, in the medium to long term, surveillance of untreated areas of the prostate could be undertaken by mpMRI to detect recurrence, especially if clinically significant cancer. A negative MRI would imply absence of clinically significant disease that requires no treatment. This would avoid any potential overtreatment after focal therapy. Other ultrasound imaging modalities (elastography, ultrasound tissue characterization [e.g., FImS], CEUS) that are starting to demonstrate promise in the detection of prostate cancer before treatment could also be applied after focal therapy (Hoyt et al, 2008; Atri et al, 2009; Gravas et al, 2009).

**SAVAGE THERAPY AFTER RADIOTHERAPY**

Over 400,000 men are diagnosed with prostate cancer every year in Europe (Ferlay et al, 2013). Many—estimated at 50,000—undergo primary radiotherapy (Cross and McPhail, 2008). Radiotherapy is an effective treatment in the majority of patients, but approximately 1 in 4 will experience biochemical failure indicated by a rising serum PSA level. Of those men with biochemical failure, half to three quarters have localized recurrence (an estimated 10% to 15,000) (Lee et al, 1999; Kuban et al, 2003; Rannuru et al, 2011). These men might be suitable for further local treatment (Cross and McPhail, 2008). Men with recurrent prostate cancer usually have failure after the age of 65 years and thus have additional comorbidities and problems that have led to a number of quite varied treatment options being available, ranging from watchful waiting with delayed systemic androgen deprivation therapy (ADT) to local salvage therapies such as surgery or ablative therapy. In over 90% of men with recurrent prostate cancer, the strategy used is watchful waiting with delayed systemic ADT (Crossfeld et al, 2002; Agarwal et al, 2008; Boulkaram et al, 2010) when indicated. Estimates for eventual ADT use within 5 years vary (50% to 90%) (Lukka et al, 2005; Kuban et al, 2008; Bolla et al, 2009; Kuban et al, 2011; Warde et al, 2011; Arcangeli et al, 2012).

**Determination of Failure Using Prostate-Specific Antigen Criteria and Imaging**

Serum PSA criteria for failure have a sensitivity and specificity of 60% to 70% (Roach et al, 2006). We and others have shown that mpMRI has high sensitivity (70% to 90%) for the presence of clinically significant disease at the time of biochemical PSA relapse, but the role of mpMRI as a surveillance tool alongside PSA testing is not yet known. Imaging is used to monitor treatments in many other solid-organ cancers, but the paradigm has not yet been accepted in management of prostate cancer until now. Kara and colleagues (2011) compared the role of DCE MRI (1.5T MRI) with TRUS in the follow-up (18 months from radiotherapy) of 172 patients who were treated with external beam radiotherapy (EBRT). The sensitivity and specificity of TRUS and T2-weighted MRI differed significantly—53.3% and 60% versus 86% and 100%—although the sensitivity of DCE MRI was greatest at 93% with a specificity of 100%. Haider and colleagues (2008) evaluated the role of mpMRI compared with standard surveillance (33 men). On a sextant basis, DCE MRI had significantly better sensitivity (72% vs. 38%), positive predictive value (46% vs. 24%), and negative predictive value (95% vs. 88%) than T2-weighted MRI. Specificities were high for both DCE MRI and T2-weighted MRI (85% vs. 80%). TRUS biopsy, however, was the reference standard in these studies. MRI-targeted biopsies as well as whole-gland TBM biopsy studies from the UCL...
group have shown promising accuracy rates in identifying radiorecurrent disease (Anumalaiyan et al, 2010). One study looking at 26 men with biochemical failure after radiotherapy found that there was a similar rate of detection between MRI-targeted biopsies and TPM for clinically significant cancer: 85% (22 of 26 patients) compared with 92% (24 of 26 patients), respectively (unpublished data). These data indicate that a comparative effectiveness study is necessary.

Watchful Waiting with Androgen Deprivation Therapy

Watchful waiting with ADT is quite common (Berge et al, 2007). ADT provides symptomatic control but has limitations. First, it is palliative in intent (Pagliarulo et al, 2012; Payne et al, 2013; Heidenreich et al, 2014b). Second, there are common side effects. These include hot flushes (50% to 80%); breast tenderness or enlargement (up to 60%); lethargy (most); erectile dysfunction or decreased libido (10% to 17%) (Potosky et al, 2001); osteopenia or osteoporosis with consequent fracture (19%) (Shahinian et al, 2005); variable cognitive impairment (Jannada et al, 2012); symptomatic anemia (13%) (Strum et al, 1997); metabolic syndrome (>50%) (Braga-Basaria et al, 2006); obesity, hyperglycemia, or diabetes (11%) (Derweesh et al, 2007); and cardiovascular disease (5%) (Saigal et al, 2007; Thomas and Neal, 2013).

Third, ADT is expensive, costing thousands per patient over his lifetime. In fact, because ADT does not cure the cancer, after an average of 2 years the cancer cells change and become resistant to ADT (so-called castration resistance). When this happens, new drugs are prescribed that can improve survival by a few months. However, these drugs carry a risk of more side effects and are very costly (tens of thousands of dollars every year). For instance, an incremental cost-effectiveness ratio (ICER) of many thousands of dollars per QALY is required compared with nonhormonal palliation (Bayoumi et al, 2000; National Institute for Health and Care Excellence [NICE], 2008; Lu et al, 2012) (approximately €8000 to €30,000 per year).

Detecting Distant Disease

Bone Scan

After primary treatment of prostate cancer, bone is the first site of relapse in more than 80% of patients. Plain film and bone scans form the mainstay of detection. Bone scans are able to detect metastases up to 18 months before plain film. There needs to be only a 10% change in bone mineral turnover to be detected by bone scans, whereas the bone must demineralize by 50% before a lesion is detected by plain film (Taoka et al, 2001). Bone scans and plain film have been shown to underestimate the true incidence of metastatic disease. Rubendorf and colleagues (2000) performed autopsies on 1589 men with prostate cancer (47% were unsuspected), and the incidence of metastatic bone disease was 90%. Bone scans are also well known for their high rate of false positives resulting from degenerative changes, inflammation, Paget disease, and trauma.

Choline Positron Emission Tomography/Computed Tomography Scan

A significant development in positron emission tomography (PET) radiopharmaceuticals has occurred. Several radiotracers able to visualize different tumor metabolisms are currently available, including fluorine-18 (18F) fluorodeoxyglucose (FDG) for glucose metabolism; carbon-11 (11C)11C-labeled choline and 11C-acetate for lipid metabolism; 13C-methionine for amino acid metabolism; and deoxy-18F-fluoromethylcholine for imaging cell proliferation (Picchio et al, 2011).

Among the different PET tracers evaluated for prostate cancer imaging, 11C/choline has been particularly investigated. Choline is an essential component of phospholipids of the cell membrane. Cell proliferation and upregulation of choline kinase are two mechanisms suggested for the increased uptake of this tracer in prostate cancer (Richter et al, 2010). The presence of choline transporters also seems to be involved in the process of its uptake in cancer cells (Muller et al, 2009). 18F-choline has been shown to have a greater sensitivity and accuracy than 18F-FDG PET/CT to detect prostate malignancy: sensitivity 73% versus 31% and accuracy 67% versus 53%, respectively (Hodolcic et al, 2013). A high Gleason score and rising PSA level have been shown to increase rates of detection of [18]-fluoromethylcholine (18F-FCH) PET/CT. One study found that 18F-FCH PET/CT detected prostate cancer recurrence in 97% of patients with Gleason score above 7, 82% of patients with Gleason score of 7, and 63% of patients with Gleason score below 7. Forty-three percent of patients in this study had recurrence in the prostate bed, and 57% of patients had local metastasis. Currently, it is not recommended to perform choline/PET in patients with a PSA value below 1 ng/mL. Also, choline PET/CT has a low spatial resolution and is limited in the identification of small lymph node deposits (Fig. 117-49).

Whole-Body Magnetic Resonance Imaging

Recent advances in MRI have made it possible to image the whole body (WB-MRI) within a reasonable time of 50 to 60 minutes. DCE MRI and DWI complement conventional anatomic MRI techniques and provide a combined approach for assessing cancer anatomy, microstructure, and function. This enables the study of extraskeletal involvement, including lymph nodes and other soft-tissue metastases (Koh et al, 2007; Komori et al, 2007). Also WB-MRI is conducted without irradiation; therefore patients are not exposed to the cumulative radiation exposure of bone scans, plain films, and CT, which is more than several years of natural background radiation (Heliou et al, 2012; Lecouvet et al, 2012).

A few studies have reported good sensitivity and specificity of WB-MRI compared with current imaging tools. Lecouvet and colleagues (2012) compared DWI–WB-MRI with bone scanning, plain films, and CT in 100 patients; 68 were felt to have metastases. The sensitivities of CT and WB-MRI for detecting enlarged lymph nodes were similar, at 77% to 82% for both; specificities were 95% to 96% and 96% to 98%, respectively. Sensitivities of the combination of bone scan and plain films plus CT versus WB-MRI for detecting bone metastases and/or enlarged lymph nodes were 84% and 91% to 94%, respectively (P = 0.03 to 0.10); specificities were 94% to 97% and 91% to 96%, respectively.
Biopsy cores are taken every 5 to 10 mm, with two biopsy cores taken in the same grid coordinate to cover grid gaps to base. If the full length of the gland is not covered by one biopsy core, in a treatment-naive prostate gland, 5-mm TPM has been shown to be a more accurate diagnostic method when compared with current standard TRUS biopsy.

Magnetic Resonance Imaging for Diagnosing Local Recurrence

Kara and colleagues (2011) compared the role of DCE MRI with TRUS in the follow-up (18 months from radiotherapy) of 172 patients who were treated with EBRT. The sensitivity and specificity of TRUS and T2-weighted MRI differed significantly—53.3% and 60% versus 86% and 100%—although the sensitivity of DCE MRI was greatest at 93% with a specificity of 100%. Haider and coworkers (2008) evaluated the role of mpMRI against sextant biopsy in 33 men. On a sextant basis, DCE MRI had significantly better sensitivity (72% vs. 38%), positive predictive value (46% vs. 24%), and negative predictive value (95% vs. 88%) than T2-weighted MR. Specificities were high for both DCE MRI and T2-weighted MRI: 85% versus 80%. TRUS biopsy, however, was the reference standard in these studies. This is a poor reference standard compared with whole-mount histology and whole-transperineal template prostate mapping biopsies, so these results must be interpreted with some caution.

MRR-targeted biopsies as well as whole-gland TPM biopsies have shown promising accuracy rates in identifying radiorecurrent disease (Duddridge et al., 2007). Whole-gland salvage surgery (radical prostatectomy or cryoablation) may be potentially curative but carries a high risk of side effects. These are rectal injury (5% to 10%) (requiring further major open reconstructive surgery) and incontinence necessitating use of pads (>50%), as well as poor quality of life (Bianco et al., 2005; Touma et al., 2005; Sanderson et al., 2006; Boukaram et al., 2010; Kimura et al., 2010).

An alternative approach is further local treatment, so-called salvage therapy (Dudridge et al., 2007). Whole-gland salvage surgery (radical prostatectomy or cryoablation) may be potentially curative but carries a high risk of side effects. These are rectal injury (5% to 10%) (requiring further major open reconstructive surgery) and incontinence necessitating use of pads (>50%), as well as poor quality of life (Bianco et al., 2005; Touma et al., 2005; Sanderson et al., 2006; Boukaram et al., 2010; Kimura et al., 2010; Chade et al., 2012; Yuh et al., 2014; Zugor et al., 2014). These occur because of the close proximity of nerves, muscle, and other organs, which inevitably have collateral damage because even keyhole surgery is not precise enough to overcome the fibrosis and scarring that result from the previous radiation. As a result, there is very poor uptake of this technique even if minimally invasive therapies such as cryoablation (Table 117-4) (Ahmed et al., 2005; Galosi et al., 2004; Sanderson et al., 2005; Galosi et al., 2006; Boukaram et al., 2010; Kimura et al., 2010; Chade et al., 2012; Yuh et al., 2014; Zugor et al., 2014). These occur because of the close proximity of nerves, muscle, and other organs, which inevitably have collateral damage because even keyhole surgery is not precise enough to overcome the fibrosis and scarring that result from the previous radiation. As a result, there is very poor uptake of this technique even if minimally invasive therapies such as cryoablation are used (Table 117-4) (Ahmed et al., 2005; Galosi et al., 2004; Sanderson et al., 2005; Galosi et al., 2006; Boukaram et al., 2010; Kimura et al., 2010; Chade et al., 2012; Yuh et al., 2014; Zugor et al., 2014).

Salvage Radical Prostatectomy

Salvage radical prostatectomy offers satisfactory oncologic control with BDFS of 31% to 69% at 5 years and at 30% to 43% at 10 years (Bianco et al., 2005; Touma et al., 2005). However, this salvage method is not often performed owing to the high risks of morbidity. Complications such as incontinence (10% to 80%), anastomotic stricture (17% to 32%), and rectal injuries (3.3% to 50%) stem from fibrosis, merging of tissue planes used for dissection, and poor wound healing caused by radiotherapy. Studies reporting these outcomes have all emphasized the importance of an experienced surgeon because of the high technical demand.

A number of studies have shown good CSS with salvage brachytherapy for radio-recurrent disease. Grado and colleagues (1999)
showed actuarial BDFS at 3 and 5 years for 49 patients to be 48% (95% CI 32% to 63%) and 34% (95% CI 17% to 51%), respectively. Aaronson and colleagues showed rates of 89.5% BDFS over 3 years in a small group of only 24 after exclusion of 14 (Aaronson et al., 2009). Brachytherapy appears to be a potentially useful salvage therapy that needs further evaluation. Common complications include lower urinary tract symptoms, hesitancy, nocturia, rectal bleeding, and frequent bowel movements. A serious complication is a prostatic-rectal fistula, which in one study occurred in 12% of patients. These complications were found to be higher than those of salvage cryotherapy (Isma'il et al., 2007; Pisters et al., 2008).

Whole-Gland Salvage Cryotherapy

Salvage cryotherapy has shown good 5-year BDFS (40% to 58%), which can be up to 73% in patients who had low-risk disease before radiotherapy. It must be noted that these studies vary in their definition of biochemical failure (PSA ≥0.5 ng/mL vs. ASTRO vs. Phoenix definition) (Ahmed et al., 2005; Galosi et al., 2007). With improvements in technique and development of cryotechnology such as thermocouples that monitor the temperature at important sites within the prostate, and a urethral warming device used to prevent tissue sloughing, complication rates have improved, although they can still be high: incontinence 4% to 73%, rectourethral fistula 0% to 3.4%, perineal pain 5.6% to 39.5%, and urinary retention 0% to 67% (Ng et al., 2007; Nguyen et al., 2007). Sloughing and urethral stricture rates have been reduced from 10% to 15% to as low as zero. Erectile dysfunction has not improved (72% to 86%).

Whole-Gland Salvage High-Intensity Focused Ultrasound

A number of studies have looked at HIFU as a potential salvage therapy for radiotherapy failure cases. Murat and colleagues (2007b) treated 167 patients who had radiocurrent disease with salvage HIFU. Patients were separated into low-, intermediate- and high-risk groups based on pradiotherapy disease risk; progression-free survival rates at 3 years were reported as 53%, 42%, and 25%, respectively. Ahmed and colleagues had 1- and 2-year progression-free survival rates of 62% and 48%, respectively, in patients who achieved a PSA nadir below 0.5 ng/mL (Ahmed et al., 2012b), in men in whom very few selection criteria were applied. Overall, common complications include incontinence (10% to 50%), bladder neck stenosis (17%), retention from urethral stricture (17%), erectile dysfunction (66.2% to 100%), and rectourethral fistula (3% to 16%) (Gellet et al., 2004; Rebillard et al., 2008; Chalasani et al., 2009).

Focal Salvage Therapy

Prior radiotherapy results in decreased vascularity and poor wound healing in tissues surrounding the prostate, so the relative inability of ablative therapies to sharply predict and demarcate boundaries of treatment results in a significantly greater risk of complications than with their primary counterparts. For instance, the treatment of apical lesions that are in close proximity to the urethra could lead to significant urethral and external sphincter damage. Despite good oncologic control, salvage radical prostatectomy is not widely performed owing to high morbidity. Brachytherapy, cryotherapy, and HIFU are also used as salvage therapies, but their long-term oncologic outcome is still unknown and the morbidity is still high. In primary therapy, these latter treatments are currently undergoing evaluation as part of tissue-preserving focal therapy strategies in which they target cancerous lesions in the prostate. Some early data suggest that a similar strategy could be adopted for radiocurrent disease.

The goal of these ablative therapies is the same: maximum destruction of cancerous tissue with minimal damage to critical surrounding structures such as the urethra, the urinary sphincter, bladder neck, and rectum (Huang et al., 2007). However, potential problems of focal therapy in radiocurrent disease include accurately localizing recurrent disease within the prostate, the margins of safe treatment that preserve oncologic efficacy while minimizing harm, and strategies of follow-up. These problems are common to the focal therapy story in treatment-naive disease (Ahmed et al., 2012a) (Figs. 117-50 to 117-54).

Location of Recurrent Disease

There has been some debate regarding the multifocality and localization of radiocurrent disease. Two studies, conducted by Lebovici and colleagues (2012) and Huang and colleagues (2007), examined radiocurrent prostatectomy specimens in radiocurrent disease. They showed that radiocurrent disease is often bulky, high volume, bilateral (74%), and close to (67% to 74%) or involving the urethra (7%). They concluded that because biopsies were not able to accurately detect radiocurrent disease, focal therapies might miss important areas of cancers that could lead to progression and metastatic spread.

<table>
<thead>
<tr>
<th>WHOLE-GLAND MODALITY</th>
<th>BIOCHEMICAL DISEASE-FREE SURVIVAL RATES</th>
<th>INCONTINENCE</th>
<th>RECTOURETHRAL FISTULA</th>
<th>FURTHER ENDOSCOPIC INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radical prostatectomy</td>
<td>28%-87%</td>
<td>68%</td>
<td>0%-15%</td>
<td>10.9%-23.9%</td>
</tr>
<tr>
<td>High-intensity focused ultrasound (HIFU)</td>
<td>25%-62%</td>
<td>38%-50%</td>
<td>2%-4%</td>
<td>1.3%-36%</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>11%-86%</td>
<td>4.4%-13%</td>
<td>1%-4%</td>
<td>Not available</td>
</tr>
</tbody>
</table>
Chapter 117  Focal Therapy for Prostate Cancer

Huang and coworkers (2007) found that of 46 radical prostatectomy specimens, 90% had cancer foci at the apex. Furthermore, 28% of specimens in this study also had multifocal disease. However, other studies have shown that recurrence occurs at the initial cancer index lesion site (Cellini et al. 2002; Pucar et al. 2007). Cellini and colleagues (2002) found that in 118 patients, areas not initially affected by tumor had no evidence of disease recurrence at a median of 45 months of follow-up. There is a possibility that if only one focus is treated and multifocal disease is present, these areas can develop and metastasize; however, it may be more probable that the index lesion hypothesis may also be relevant in this setting.

We previously discussed the role of TPM biopsies and mpMRI in detection of localized recurrence. These modalities would in theory have the ability to provide 3D data to drive the focal delivery of ablative modalities for focal salvage.

**Focal Salvage Brachytherapy**

Kaplan and colleagues (2013) looked at the role of MRI fusion imaging to guide focal salvage brachytherapy. Twelve patients with pathologically confirmed recurrence of prostate cancer had MRI-US fusion image-guided intraoperative dosimetry. A median of 42 (range, 30 to 71) seeds containing iodine-125 (125I) or palladium-103 (103Pd) were placed, and isodose distributions were concentrated on the biopsy-proven abnormalities on MRI only. Total prescribed dose was 8000 cGy. Biochemical failure was defined using the previous ASTRO consensus definition. Toxicity was graded according to the Radiation Therapy Oncology Group (RTOG) and Late Effects Normal Tissue (LENT) criteria. Median follow-up after salvage brachytherapy was 48 months (range, 19 to 111). Three of 12 patients had biochemical failure; 4 of 12 patients had grade 2 or 3 RTOG toxicities including subacute grade 3 urinary retention and had grade 3 urinary incontinence after TURP was performed 5 years after salvage brachytherapy. This is a small study that used TRUS biopsy to confirm recurrence as well as the old ASTRO definition to determine biochemical failure. Another study by van Vulpen and colleagues (2012) delivered focal salvage 125I brachytherapy to 16 patients with DCE MRI and biopsy-proven recurrence. Prescription dose to the recurrence was 144 Gy. After 6 months only 1 patient was found to have grade 3 toxicity according to the National Cancer Institute Common Toxicity Criteria.
Focal Salvage Cryotherapy

Eisenberg and colleagues (2008) performed a retrospective study on 19 patients. These patients were selected on the basis that they fulfilled Phoenix definition for biochemical failure, they had TRUS biopsy–confirmed recurrence, the recurrence was unilateral, and their glands were only partially treated with cryotherapy. Fifteen men had longer than 6 months’ follow-up, which included tri-monthly PSA and TRUS biopsy. The complication rates in this study were low; 1 patient developed mild stress urinary incontinence, 1 developed a prostatic urethral stricture that required dilation, and 1 developed a prostatic urethral ulcer managed with suprapubic catheter drainage with resolution after 6 months. Whether this represented a fistula was difficult to determine from the study report. Only 5 patients had available potency data, with 2 men maintaining potency and 3 impotent after treatment. According to the Phoenix definition of failure, 89%, 79%, and 79% of men were free of biochemical recurrence at 1, 2, and 3 years, respectively. Although 19 men were included, only 10 men were rebiopsied, with 90% (9 of 10) having no recurrence at 1-year overall. Overall, this was a small study with limited and poor follow-up. Although BDFS rates appeared to be good, not all patients were followed, and only half of these men had a biopsy after salvage treatment.

Focal Salvage High-Intensity Focused Ultrasound

Ahmed and colleagues (2012c) performed focal salvage HIFU in 39 patients. Disease recurrence was confirmed by mpMRI and either TPM (20 men) or TRUS biopsies targeted to the area of recurrence (19 men). Focal HIFU was either hemiablation (ablation of the lobe to urethra) or quadrant ablation (ablation of one half of the lobe anterior or posterior). Patients with recurrence confirmed by TRUS biopsies underwent hemiablation. If there was multifocal cancer, then the patient underwent index lesion ablation if the untreated areas had 1 core or less with 3 cores (A and Baco et al., 2014). After hemisalvage HIFU, the mean (standard deviation [SD]) PSA nadir was 0.69 (0.83) ng/mL at a median (interquartile range) of 0.7 (2.0) to 2.3 (4.5) months to detectable disease (A and Baco et al., 2014). For men who did not achieve PSA nadir less than 0.5 ng/mL and the 1-year, 2-year, and 3-year BDFS rates were 86%, 75%, and 63%, respectively, using Phoenix criteria. However, when biopsy postsalvage was positive and requirement for ADT was included in the definition of failure, these rates decreased to 79%, 67%, and 45%, respectively. For men who did not achieve PSA nadir less than 0.5 ng/mL (56%), the 1-year, 2-year, and 3-year BDFS rates were much lower at 55%, 24%, and 0%, respectively.

Another recent study has shown that 48 patients were prospectively enrolled in two European centers wherein inclusion criteria were biochemical recurrence after primary radiotherapy, positive MRI, and one or more positive biopsies in only one lobe (Baco et al., 2014). Biochemical failure was defined using Phoenix criteria. Patients with obstructive voiding symptoms at the time of treatment underwent an endoscopic bladder neck resection or incision during the same anesthesia to prevent the risk of postoperative obstruction. After hemisalvage HIFU, the mean (standard deviation [SD]) PSA nadir was 0.69 (0.83) ng/mL at a median (interquartile range) follow-up of 16.3 (10.5 to 24.5) months. Disease progression occurred in 16 of 48 (33%). Of these, 4 had local recurrence in the untreated lobe and 4 bilaterally, 6 developed metastases, and 2 had rising PSA levels without local recurrence or radiologically confirmed metastasis. Progression-free survival rates at 12, 18, and 24 months were 83%, 64%, and 52%, respectively. Severe incontinence occurred in 4 of the 48 patients (8%), 8 (17%) required one pad a day, and 36 of 48 (75%) were pad free. The International Continence Society questionnaire showed a mean (SD) deterioration from 0.7 only partially treated with cryotherapy, and focal salvage treatments to robustly evaluate harms and benefits of whole-gland and focal salvage therapy with medium- and long-term outcomes. At present there are few studies (and those lack robust data), although early signs are that toxicity may be significantly lower than with whole-gland salvage approaches. There is an urgent need for further large prospective studies involving targeted ablative treatments to robustly evaluate harms and benefits of whole-gland and focal salvage therapy with medium- and long-term outcomes.

CONCLUSION


REFERENCES


SUGGESTED READINGS


The complete reference list is available online at www.expertconsult.com.
REFERENCES


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PART XIV The Prostate


Chapter 117 Focal Therapy for Prostate Cancer


Kanthabalan A, Abi-Azezzer M, Arya M, et al. Transperineal MRI-targeted biopsy versus transperineal template prostate mapping biopsy in the...
Chapter 17 Focal Therapy for Prostate Cancer


