Review

Pathology of Prostate Cancer and Focal Therapy ('Male Lumpectomy')

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Abstract. *Focal therapy of the prostate is defined as prostate gland ablation aiming at eradication of unifocal low-risk prostate cancer, and preserving uninvolved (peri-) prostatic tissue and therefore quality of life. The major arguments against focal therapy can be classified under the headings of understaging and multifocality. The argument of understaging highlights the importance of the occasional, but troublesome, finding of a large, extraprostatic or high-grade tumor (Gleason score ≥7) in about a quarter of radical prostatectomy specimens removed from men initially classified as having a low-risk tumor. Indeed, 85% of all prostate cancer cases are multifocal. These concerns can be offset by additional testing: another biopsy, especially a transperineal mapping biopsy, and magnetic resonance imaging (MRI) of the prostate. The technology needed to ablate small regions or sectors of the prostate harboring a known cancer is rapidly becoming available. Cryotherapy is already being used and the preliminary data are encouraging, Ultrasound-guided high-intensity focused ultrasound (HIFU), photodynamic therapy using newly developed light-sensitizing agents, and MRI-guided HIFU are all promising new tools.*

The traditional approach to the treatment of prostate cancer is radical, whole-gland treatment, such as radical prostatectomy, radiation therapy, cryotherapy, or high-intensity focused ultrasound (HIFU) (1, 2). Improvements in screening and detection have meant that many men with prostate cancer now present with low-risk disease, potentially amenable to organ-sparing ablative procedures or focal therapy, *i.e.* individualized treatment that selectively ablates known disease and preserves existing functions, with the overall objective of minimizing lifetime morbidity without compromising life expectancy (1, 2).

Despite the fact that 20-30% of patients might be candidates for parenchyma-preserving approaches (3-5), analysis of the Cancer of the Prostate Strategic Urologic Research Endeavor database found that 94% of men with low-risk prostate cancer receive radical, whole-gland therapy (6). A study of 24,405 men with low-risk prostate cancer found that if initial expectant management is deemed appropriate for all low-risk cancer cases, 11% (2,564) of patients who underwent radical prostatectomy and 45% (10,973) of patients who received radiation therapy were overtreated (7). Traditionally, the issues of understaging and multifocality of prostate cancer have hampered efforts to select appropriate candidates for focal therapy.

This review will discuss pathological issues related to focal therapy in prostate cancer, *i.e.* 'male lumpectomy'.

Definition of and Candidates for Focal Therapy

Focal therapy, or subtotal ablation, is a technique that allows the urologist to ablate a known focus or region of prostate cancer while maintaining the nonmalignant parenchyma (2). As such, focal therapy includes any treatment that selectively targets a portion of the gland that is determined to be malignant, which can be as much as 95% of the gland (near-total ablation), as long as a segment of normal tissue is intentionally preserved. The area of intentionally preserved

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parenchyma is typically non-malignant tissue adjacent to the neurovascular bundles, which allows preservation of erectile function and urinary continence (1).

Candidates for focal therapy are patients with unifocal low-risk prostate cancer (defined as tumor stage cT1c or cT2a, Gleason grade 3+3 or lower, and serum prostate specific antigen (PSA) level <10 ng/ml), aged ≤75 years and with at least 10 years of life expectancy. Some authors are less strict in the selection, and would also consider as candidates for focal therapy patients with low-to-intermediate risk prostate cancer and Gleason score 3+4=7, the size of the tumor being not an inclusion/exclusion criterion (8-11).

Prostate Cancer Prognosis and Implementaton of Focal Therapy

Over the past few decades, both the use of serum PSA screening and public awareness of prostate cancer have increased dramatically. All this has led to a subsequent early detection of prostate cancer. Changes in stage, tumor volume, unilaterality and unifocality have increased the feasibility of implementing focal therapy.

Stage. Over the past two decades, the incidence of palpable disease identified on digital rectal examination has diminished in the Europe and US, with nonpalpable T1c prostate cancer being the most common clinical stage in 2009 (12, 13). The widespread utilization of PSA testing has increased the proportion of PSA-detected cancer cases, as more biopsies are now carried out on the basis of either an abnormal level or rate of change in serum PSA.

Polascik *et al*. (14) analyzed pathological data from 3,676 men with localized prostate cancer who were treated with RP between 1988 and 2006. The prevalence of stage pT2a disease (tumor in ≤50% of one lobe) increased from 2.8% of patients during the period 1988-1995 to 13.0% during 2001-2006. Of all pT2a tumors, 69.4% were identified in men who underwent RP during 2001-2006, compared with just 10% during 1988-1995. Overall, patients with pT2a tumors had minimal percentage tumor involvement (PTI; ≤5%) or small-volume (PTI 5-10%) disease in 65% and 14% of cases, respectively, and the cancer was low-grade (Gleason score ≤6) in 59% of cases. Cox proportional hazard analysis demonstrated that pT2a disease (*versus* pT2b disease) was an independent predictor of improved biochemical recurrence-free survival during 2001-2006. These results indicate that a growing proportion of contemporary men who elect to undergo RP have pT2a tumors, associated with low PTI and Gleason score.

Tumor volume. Stamey *et al*. (15) found that tumor volume was associated with biochemical progression, which occurred in 14% of men with tumor volumes of 0.5-2.0 ml compared with 97% of men with tumor volumes >12 ml. Renshaw *et al*. (16) also showed that patients with tumor volume <1 ml did not experience biochemical recurrence, while all patients with tumor volume >2 ml did. Wheeler *et al*. (17) revealed that increasing levels of prostate capsular invasion were significantly associated with increasing tumor volume in their RP series.

Prostate tumor volume has decreased over time, from a mean volume of 4.7-6.1 ml in 1995-1999 (15) to 2.1-2.6 ml in 2001-2005 (18). Cheng *et al*. (18) noticed histologically defined small-volume cancer (<0.5 ml) in 55 (16%) out of 336 patients in their RP series. In contemporary RP series, the median tumor volume has been less than 1 ml (19, 20). Smaller, more localized tumors are theoretically easier to focally ablate as they occupy less of the prostate. In addition, larger tumors are believed to have an increased propensity for local invasion (extraprostatic extension or seminal vesicle invasion) and dissemination. Thus, from a conceptual point of view, focal therapy would be best applied when the tumor is small, localized and contained within a limited zone of the prostate.

Gleason grade. In contemporary series of patients who were selected for curative local therapy, most (85%) had a low to intermediate grade (Gleason score 5-7) tumor (21). Epstein *et al*. (22) found in a large RP series of 488 men with Gleason score 7 tumors that more than 50% of patients were cured at long-term follow-up, when those with extraprostatic extension (EPE) and positive margins were excluded. Some studies found that a Gleason grade of 4 was associated with increased EPE, seminal vesicle invasion, positive surgical margins and lymph node involvement (23). Other studies suggest that among Gleason score 7 tumors, a primary Gleason grade of 4 is associated with less-favorable clinical behavior than a primary Gleason grade of 3 (24, 25). Tollefson *et al*. (26) evaluated 1,688 men 10 years after RP and demonstrated that a Gleason score of 7 with a primary Gleason grade of 3, *versus* a primary Gleason grade of 4, was associated with increased biochemical disease-free survival (48% *versus* 38%), a lower rate of systemic recurrence (8% *versus* 15%) and greater cancer-specific survival (97% *versus* 83%). However, other studies did not reveal a prognostic significance of the primary Gleason pattern for biochemical disease-free survival and cancer-specific survival (25, 27). Such data suggest that as the Gleason score increases, so does the likelihood of adverse pathologic features, such as EPE, seminal vesicle invasion and metastasis, which can result in treatment failure.

Unilaterality and unifocality. Radical, whole-gland therapy has traditionally been used for the treatment of prostate cancer on the basis of the observed multifocality and heterogeneity of disease, reported in 50-87% of cases (Figure 1A and 1B) (4). In the pre-PSA and early PSA era, the mean number of lesions per prostate was found to be 7.3 (range 1-60), with multifocal

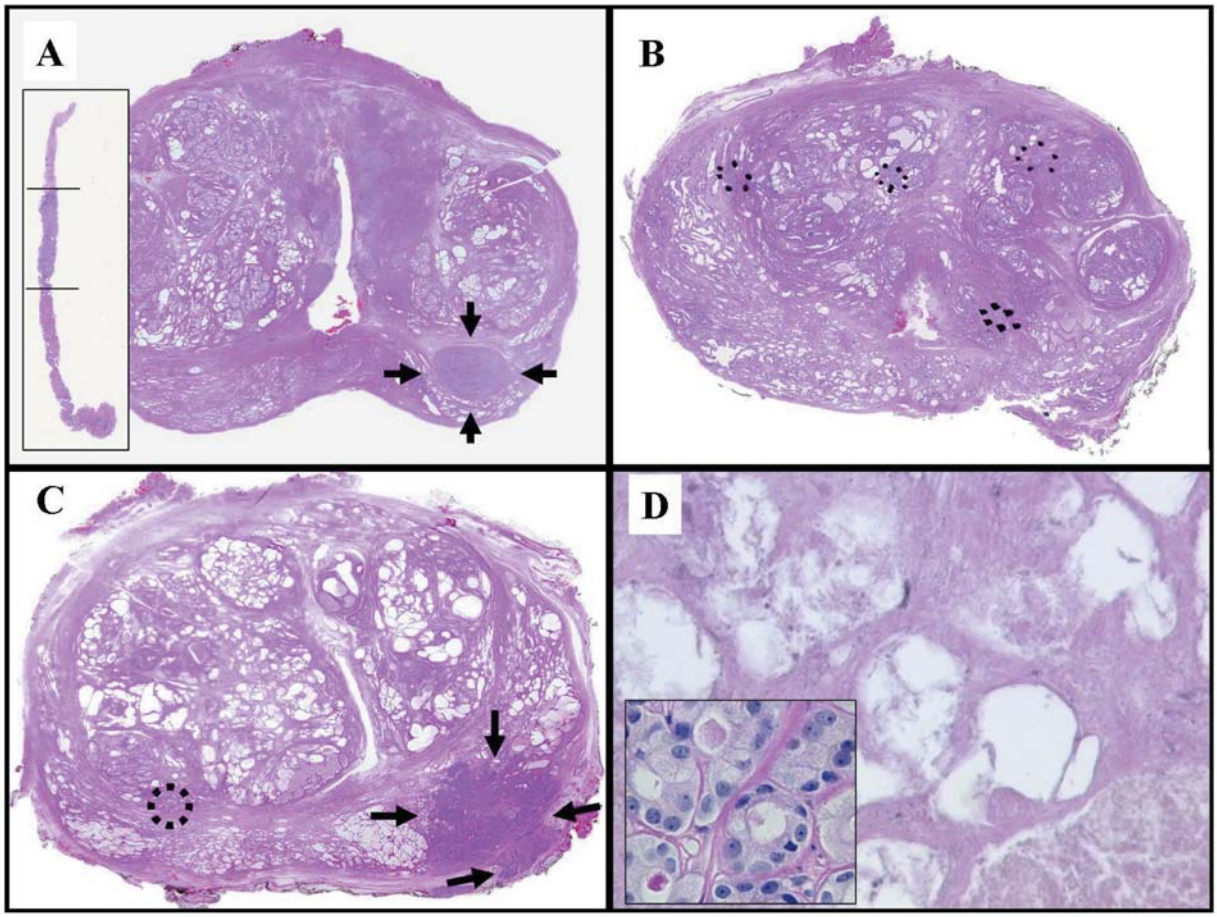

Figure 1. *Whole-mount section of radical prostatectomy specimen; A, Unifocal and unilateral prostatic adenocarcinoma of the peripheral zone (arrows). The preoperative positive biopsy is shown in the inset (the two black bars indicated the limits of cancer). B, Multifocal and bilateral prostatic adenocarcinoma (dotted areas). C, Bifocal and bilateral prostatic adenocarcinoma of the peripheral zone. The index tumor is indicated by the arrows. The contralateral tumor is highlighted by the dotted circle. D, Adenocarcinoma showing complete necrosis following cryoablation (an untreated tumor is shown in the insert).*

prostate cancer demonstrated in more than 85% of all RP specimens (28). Since the widespread introduction of PSA screening, however, and with the increasingly early detection of prostate cancer, authors have reported a substantial proportion of unifocal and unilateral disease. In their study of 100 RP specimens from patients with low-risk disease and unilateral cancer on prostate biopsy Yoon *et al*. (19) found, that bilateral disease was present in 63% of cases, with a mean of 2.9 lesions per prostate (range 1-9). Mouraviev *et al*. (5) analyzed 1,186 paraffin-embedded RP specimens from patients with clinically localized prostate cancer. Unilateral tumors were identified in 227 (19.2%) patients and suggested that almost one in five candidates (20%) treated with RP would be amenable to focal therapy targeting one lobe of the prostate (hemiablation). Certain geographic locations have demonstrated a much higher frequency of unifocal lesions than the U.S., including Austria (33-35%) (18), Greece (40%) (29) and South Korea (67%) (30).

Contentious Issues in Patient Selection

Gleason score 7 tumors. One contentious issue in the selection of candidates for focal therapy has been whether to include men with Gleason score 7 tumors, which do carry an increased risk of adverse pathology compared with those with a Gleason score ≤6. Nevertheless, Gleason score 3+4 =7 cancer can potentially be considered as an indication for targeted ablation, as it has been treated in several clinical studies with excellent short-term cancer control (31, 32). Although some studies of focal cryoablation suggest reasonable oncological outcomes when treating patients with Gleason score >7 tumors, these data are limited by small patient numbers and short duration of follow-up (33, 34).

Index tumor. Pathologists have noted that many RP specimens contain a large tumor (the 'index lesion') and smaller, satellite tumors (Figure 1C). While the natural history of different prostate cancer foci remains unknown,

some evidence exists that the index tumor is the biological driving force behind the malignant potential of prostate cancer. Wise *et al*. (35) evaluated the effect of small, independent, non-index prostate tumors on biochemical disease-free survival in 486 men treated with RP. The mean index tumor volume was 4.16 ml, while smaller tumors volumes averaged 0.63 ml. The biochemical disease-free survival rates were predicted equally well by the index and total tumor volumes, demonstrating that only the largest carcinoma needs to be measured for risk prediction. These data give support to the notion that the index tumor itself drives the overall aggressiveness of prostate cancer; therefore, if the index tumor can be identified and localized, therapies targeting that index tumor can be considered as being likely to offer good overall tumor control. Noguchi *et al*. (36) evaluated the prognostic value of secondary tumors in multifocal, localized prostate tumor. In their study, 222 men with T1c prostate cancer treated with RP were divided into three groups according to tumor focality and secondary cancer volumes: a single tumor (n=54; 24%); an index (largest) tumor with secondary tumor less than 0.5 ml (n=86; 39%); and an index tumor with secondary cancers greater than 0.5 ml (n=82; 37%). The authors found no difference between the three groups in terms of preoperative PSA levels, number of positive biopsy cores, proportion of Gleason grade 4-5 cancer on needle biopsy, or histological features in RP specimens. Surprisingly, when comparing biochemical failure rates among the three groups, the multifocal group with smaller secondary tumors had a better prognosis than the group with a single tumor. Thus, small secondary tumors might be clinically irrelevant if the index tumor can be focally ablated and controlled.

In the series from Stanford University, only index tumor volume and not total tumor volume was found to be an independent predictor of progression (15, 36, 37). This discrepancy might result from the minimal effect of small, low-grade satellite lesions, which nevertheless contribute to total tumor volume, on disease progression.

Inadvertently missed small-volume tumors. The question is whether small-volume tumor that is inadvertently missed by focal therapy should be considered clinically significant. Cheng *et al*. (38) found that the majority of small-volume prostate tumors are multifocal (69%), but remain unilateral in 63% of cases. Tumors were located predominantly in the peripheral zone (79%) and the posterior aspect (84%) of the prostate. The fact that patients develop multifocal tumors even with a very low total tumor volume suggests that additional lesions can arise if small tumors are left untreated. Of these small-volume tumors, 16% had Gleason score (8-9) that might be considered clinically significant and aggressive. This study suggests that a minority of untreated small-volume tumors would continue to develop and would later require treatment. Polascik *et al*. (39), in a study of 538 patients with biopsy-proven unilateral disease, identified clinically significant prostate cancer contralateral to a unilaterally positive prostate biopsy (6-16 cores) in fewer than 20% of RP specimens. Some of these tumors had adverse pathological features, such as EPE (14.9%), Gleason score >7 (4.7%), and seminal vesicle invasion (2.5%).

Evaluation of a Patient for Focal Therapy

The major concerns regarding focal therapy, *i.e*. understaging and multifocality, can be offset by additional testing: another biopsy, especially a transperineal mapping biopsy (40), and magnetic resonance imaging (MRI) of the prostate (41).

Biopsy. Prostate biopsy remains the single crucial factor for treatment planning. Most of the literature analyzing various biopsy schemes has focused on the detection of prostate cancer without regard to laterality or focality, as this type of detailed information is not necessary for whole-gland therapy. Similarly, retrospective analysis of various biopsy techniques performed to diagnose rather than to map prostate cancer foci will have limited applicability for focal therapy planning.

The current literature suggests that the identification of only a single or unilateral focus on traditional sextant or extended 12-core biopsy is not sufficient to exclude contralateral disease. Even the identification of only a single positive core in a patient at low risk for prostate cancer might not exclude bilateral disease in all instances. Barber (42) investigated the data of 129 men with a single positive core (on 6- to 12-core biopsy), 46 (36%) of whom were subsequently treated with RP. Final pathological assessment showed that almost 90% of treated tumors with Gleason score ≤6 had disease contralateral to the positive biopsy core, and 22% had evidence of high-grade disease (Gleason grade >4) in the contralateral lobe.

Routine sextant prostate biopsy cannot provide reliable, accurate information about the prognostic features of tumor lesions. Johnstone *et al*. (43) found that conventional prostate biopsy (6-12 cores) was unreliable in nine reported series, comprising almost 800 patients with minimal unilateral disease on prostate biopsy. Final pathological assessment of prostatectomy specimens revealed a maximum tumor volume greater than 10 ml in three series, EPE in 10.5% of cases, a median positive surgical margin rate of 10.5%, subsequent discovery of Gleason grade 4 disease in 14% of patients, and bilateral disease in around 80% of cases.

Biopsy techniques that map prostate cancer foci in three dimensions are likely to be required for focal therapy. Template transperineal prostate mapping biopsies might provide more exact information about spatial tumor distribution of cancer inside the prostate and might accurately identify unilateral cancer for the purpose of focal therapy.

Barzell and Melamed introduced template-guided transperineal three-dimensional pathological mapping (3DPM) to detect clinically significant tumors before focal therapy with a median of 69 cores (or 1.88 biopsies per ml of prostate) per patient (40). A total of 80 patients underwent extensive template-guided 3DPM of the prostate. Of these, 43 (54%) who had unilateral disease on transrectal ultrasound (TRUS)-guided biopsy actually had bilateral disease, that is they were "unsuitable for focal unilateral cryoablation". Compared with 3DPM, repeat TRUS-guided biopsy yielded a 47% false-negative rate for focal disease, 54% sensitivity and a 49% negative predictive value. These results indicate that 3DPM provides superior localization data compared with TRUS-guided biopsy. Crawford and Barqawi modified the transperineal TRUS-guided biopsy using a superimposed three-dimensional grid in real time to achieve a relatively accurate localization of cancer foci (44).

Barqawi *et al*. (45) performed three-dimensional systematic mapping biopsy (3DSMB) of the prostate in selected patients who had been diagnosed with low-risk disease and were contemplating an expectant management protocol. For this purpose, three-dimensional rendering software was developed and transperineal three-dimensional mapping biopsies were performed using 5 mm increments on a grid. A mean of 61.7 cores were taken; in 20% of cases, the Gleason score was upgraded to ≥8, and in 37% of patients a positive core was found on the contralateral side. In total, 25 out of 67 patients (37%) had their tumor upstaged after undergoing 3DSMB.

Two studies from Japan have also suggested some advantage of an extended transperineal biopsy protocol. Numao *et al*. (46) used a combined three dimensional 26-core (3D26) prostate biopsy. They demonstrated that the combined 3D26 biopsy accurately predicted the presence of Gleason pattern 4-5 cancer on RP specimens with a higher concordance rate (92.3%) than that between extended transrectal 12 biopsy and RP specimens. Furuno *et al*. (47) compared a routine transrectal sextant biopsy with an extensive transperineal ultrasound-guided template prostate biopsy (mean of 18 cores) in 113 men. Transrectal sextant biopsies missed more tumors in the anterior than in the posterior region of the gland. By contrast, the transperineal template technique detected cancer equally well in the anterior and posterior regions.

Imaging. The value of advanced MRI techniques in mapping prostate cancer remains investigational. Villers *et al*. (48) demonstrated the feasibility and efficacy of dynamic contrast-enhanced (DCE) MRI in 24 patients with localized prostate cancer who later underwent RP. MRI results were compared with analysis of RP whole-mount step sections. DCE-MRI identified 30 out of the 39 tumor foci greater than 0.2 ml and 27 out of the 30 tumor foci greater than 0.5 ml. The same group of authors found a further relationship between DCE-MRI and histopathology in terms of localization, morphological description, and volume assessment of cancer in the anterior prostate, *i.e*. the most-common site of tumors missed by conventional TRUS-guided biopsy. Ahmed *et al*. (49) criticized these studies, however, on the basis of their limitations, which included insufficient consideration of whether imaging identified tumors that were clinically significant, taking into account important pathologic variables such as tumor size and grade. If validated, DCE-MRI might become essential to the selection of patients for focal therapy.

Treatment Modalities and Outcome Evaluation

Focal therapy can be performed using any of a number of devices or techniques, including thermoablative methods, such as cryotherapy or HIFU, radiation techniques, such as brachytherapy, or chemical methods, such as regional alcohol injection.

An image-guided approach to identifying, targeting and focally destroying a specific tumor has yet to be realized, and is dependent upon the development of a reliable imaging modality capable of visualizing the tumor with high sensitivity and specificity. Short of this ideal, physicians are performing hemiablation in highly selected patients in whom the prostate cancer can be reasonably determined to be localized on one side of the prostate, based on high-volume, transperineal prostate mapping biopsy techniques.

Post-treatment follow-up procedures still have to be clearly defined. However, these should include serum PSA testing, prostate biopsies and imaging studies. The role of novel biomarkers, needs to be explored. Concerning prostate biopsies, these should be taken shortly after treatment to evaluate the efficacy of the therapeutic procedure, targeting the ablated (Figure 1D) and non-ablated tissues. Subsequently, biopsy mapping of the whole gland should be performed at long term intervals to detect either recurrences or development of additional neoplastic lesions. Imaging studies, such as those based on MRI, should be carried out immediately after treatment to evaluate the efficacy of ablation and then at regular intervals in association with prostate biopsy mapping.

Focal cryoablation has gained the most experience to date, with preliminary data demonstrating that potency is preserved in 71-89% of men, while continence is preserved in nearly 100% (28, 29). Biochemical disease-free survival, according to the American Society for Therapeutic Radiation and Oncology definition, has been reported to be in the range of 80-96%, with follow-up of 15-70 months (31, 32). Quality of life outcomes are impressive, achieved with very low morbidity, and have been reproducible across several centers. As additional data are amassed, long-term oncological efficacy and preservation of quality of life after focal therapy should become apparent.

Conclusion

The goals of focal therapy are, firstly, to destroy known areas of cancer (oncological goal) and, secondly, to preserve non-malignant tissue in an effort to maintain physiological function, such as urinary continence and potency (quality-of-life goal). At this time, focal therapy is offered for select candidates at certain centers in the U.S. and Europe. Focal therapy demands a better understanding of tumor biology, so that we can identify which foci require ablation and which more indolent foci can be actively followed up or treated with pharmacological or chemopreventative strategies. Improvement of biopsy techniques and imaging can greatly contribute to selecting the patients and their follow-up.

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