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FOCAL THERAPY IN PROSTATE CANCER: FUTURE TRENDS

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INTRODUCTION

As the most frequently diagnosed male malignancy, second only to lung cancer as a cause of cancer mortality, prostate cancer represents a major health problem in the USA. In the past decade there has been an increase in the detection rate of prostate cancer and a significant increase in the proportion of men with early confined disease. This trend toward early detection has resulted in a proportionally significant increase in the diagnosis of prostate cancer in many men with clinically insignificant disease, based on cancer volume (<1 mL) and slower growth rate [1]. According to one report, 30–40% of men aged >50 years have prostate cancer, but only 8% of cancers become clinically significant [2]. The current emphasis on curative treatment includes early detection and radical primary local treatment of the prostate and adjunct tissue with surgery or radiation. However, it is well recognized that such radical treatment is associated with significant morbidity and can be 'over-treatment', greatly affecting the quality of life in a subset of patients with localized disease. Patients frequently ask why the urologist cannot treat just the diseased part of their prostate. Few other malignancies share such a dilemma. The management of breast cancer has developed from radical treatment, with extensive disfiguring dissection of the anterior thoracic wall, to localized treatment with wide excision or 'lumpectomy' with or without axillary clearance.

DETERMINING THE LOCATION OF CANCER

The prostate is arbitrarily divided into anatomical zones describing the ductal drainage systems. The posterior peripheral zone comprises 70% of the prostate volume and is the location of 60–70% of prostate cancers. Another 10–20% of prostate cancers are in the transition zone. The central zone, which accounts for 25% of prostate volume, is the site of 5–10% of prostate cancers. Prostate cancer is a multifocal disease that involves both lobes of the prostate in two-thirds of cases [3]. The rate of cancer detection is higher in saturation-biopsy series than with the standard extended-core biopsy practised in most urological clinics. Furthermore, the recent development of three-dimensional (3-D) computer modelling of the prostate both provides biopsy sampling accuracy and assists in localizing significant cancer foci [4].

Clearly, a vital requisite for the successful focal treatment of a confined prostate cancer involves the development of intraprostatic imaging models with high sensitivity for detecting significant cancer foci. Promising steps toward that end include new advances in endorectal MRI coupled with MR spectroscopic imaging (MRSI), radioisotope tracer techniques, dual imaging with CT and ProstaScint® monoclonal antibody scanning, among others.

CURRENT STATUS AND FUTURE TRENDS

Attempts to treat one side of the prostate with target cryotherapy are currently underway. Although promising, such an approach appears to limit treatment to a few patients with unilateral disease. In addition, this technique requires the exclusion of cancer on the contralateral side. Studies have shown that sextant TRUS-guided biopsies cannot predict unilateral disease, and it is vital that a TRUS saturation biopsy be used to achieve an accurate diagnosis. At our institution we are in the process of conducting a phase II trial to study the feasibility of focal target ablation of prostatic foci based on a saturation biopsy, using patented 17 G cryoneedles. A computerized 3-D real-time topographical reconstruction of the prostate has been developed to aid in identifying clinically significant cancerous (≥1 mL) islands using zonal mapping of the prostate. Although the development of this model is still in its early stages, it will aid in the focal ablation of prostate cancer with minimally invasive techniques, thereby achieving curative treatment in men with localized disease.

POTENTIAL ADVANTAGES AND DISADVANTAGES OF THE FOCAL TARGET THERAPY APPROACH

Potential advantages of focal therapy in treating localized prostate cancer include maintaining curative and survival rates comparable with those of conventional primary surgical and radiation therapy, with no increase in complications, e.g. erectile dysfunction, urinary incontinence and rectal injury. This approach is cost-effective, based on a shorter time required for the procedure and a briefer inpatient hospital stay. In addition, focal therapy will improve patient satisfaction and quality of life.

Potential drawbacks to this approach include the risk of incomplete treatment, which may be a result of missed cancer foci and inadequate ablation to the target tissue. However, these possible disadvantages can be overcome with current technical advances in target-ablation probes using cryoneedles, high-frequency ultrasound, thermal and laser machines to achieve confined and complete target destruction. The National Cancer Institute is currently recruiting patients for a

study to evaluate the role of MRI and MRSI in diagnosing the extent of disease in patients with prostate cancer.

It is important to acknowledge that this approach is not universally applicable to all patients, e.g. those who have periurethral and extracapsular extension of the tumour may not benefit from focal treatment. Other circumstances that limit the usefulness of focal therapy include: (i) the inability to use current postoperative guidelines for PSA to monitor efficacy and recurrence, as prostatic tissue will remain; and (ii) the inability to have a final pathological report depicting the Gleason score and the extent of extracapsular invasion (margin status), which may delay further treatment for these patients.

CONCLUSIONS

The use of focal target therapy for prostate cancer based on a real-time 3-D model of the prostate may potentially achieve complete destruction of all significant cancer foci within the prostate in an effective and cost-effective manner. The recent emergence of high-resolution imaging tools coupled with advances in computerized modelling software should be used in the near future to give alternative treatment options to men with localized, early-stage cancer. This approach is an important step in our quest for better ways to treat the disease while maintaining a good quality of life for our patients.

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THE URGENCY OF THE PROBLEM AND THE PROBLEM OF URGENCY IN THE OVERACTIVE BLADDER

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INTRODUCTION

The importance and relevance of urgency as the cardinal syndrome of the overactive bladder syndrome (OAB) has been clearly recognized by the ICS. Urgency is now considered by many to be the pivotal clinical symptom in OAB, as it is the symptom which leads to frequency, nocturia and incontinence; furthermore, it is a surrogate endpoint for patients having better 'control', as shown by what patients say when they report a successful outcome on therapy. Nevertheless, the problems associated with the use of the term urgency are many and include terminology and the definition of urgency, the communication of this concept to both clinicians and patients alike, and ultimately the measurement of urgency, which is the subject of a review and a paper in this issue of the *BJU International*.

In addition to the term OAB, which is defined as 'urgency with or without incontinence, usually with frequency and nocturia' in the absence of infection or other obvious pathology, the ICS standardization committee suggested synonymous terms to be the 'urgency/frequency syndrome' or 'urge syndrome' [1]. Therein lies a problem, as whilst the terms 'urgency' and 'urge' can be suggested to be subtly different, with urge as a normal sensation and urgency an abnormal sensation, i.e. as defined by the ICS as 'the complaint of a sudden compelling desire to pass urine which is difficult to defer'. This implies that there is a continuum between the normal desire to void and urgency, a hypothesis for which there is no evidence at present. A strong case can be made for suggesting that the definition of urgency should be further qualified by adding the phrase '*for fear of leakage*', which was previously in the definition but abandoned at the time of the last revision of terminology. It is clear that from discussions with European and Asian colleagues that the nuance of the difference between urgency and urge does not translate into other languages, and indeed a cursory review of the current situation clearly emphasizes the problem even in English. Whilst in the standardization report both the term 'urge syndrome' is clearly suggested to be synonymous with the urgency/frequency syndrome, and incontinence associated with OAB is identified as 'urge incontinence', such descriptions should, according to the ICS standardization committee's own description, be the *urgency syndrome* and *urgency incontinence*. This confusion in terminology in current publications is also clear from a review by Chapple *et al.* published in this issue [2].

TERMINOLOGY

How can we communicate this term to colleagues and assess the outcome of therapy in patients? It is clear from the present discussion that the terms 'urge' and 'urge incontinence' should be abandoned, in favour of the terms '*urgency*' and '*urgency incontinence*', and a strong case can be made for suggesting that the definition of urgency should be further qualified by adding the phrase *for fear of leakage*. Cardozo *et al.* [3] address the important issue of measuring urgency in their interesting paper in the next issue of *BJU International*, where they carried out a detailed psychometric evaluation of their Urgency Perception Scale (UPS). They state that 'physician reviewers' felt that the conceptualization of the UPS was 'valid and rational', but acknowledge in the discussion that 'the UPS is not a diagnostic tool and cannot distinguish 'urge' incontinence from stress incontinence'. They correlated the UPS in detail against voiding diaries and state-of-the-art patient assessments, including the generic Medical Outcomes Study Short-Form

36 (SF-36) and the incontinence-specific King's Health Questionnaire (KHQ) and the disease-specific Overactive Bladder Questionnaire (OABq). These were combined with a patient self-assessment question on the severity of the bladder condition, a question on perception of treatment benefit and on an overall treatment-effect scale. The authors acknowledge that scales such as this have uncertain responsiveness, although there are moderate correlations between diary variables and changes in symptoms attributable to therapy. They suggest that this is a result of the sensitivity of the UPS in measuring a tendency to incontinence, which is related to the focus of the scale on 'the ability to hold urine when 'the urge' to urinate occurs'. This is evidenced by diary-card data, where the correlation with the UPS was best with incontinence episodes per day and pad usage. Furthermore, as a summation of all voids is measured using scales, therefore scales do not quantify and differentiate between both normal and abnormal voids, which leads to variability, and is likely to result in a limited sensitivity and specificity. Nevertheless, the UPS was statistically significantly correlated with many domains in the disease-specific questionnaires and these were more marked than those seen with the SF-36, where they were only small to moderate. One explanation is that in two of the three studies encompassing 1417 patients out of from 2586, urgency incontinence was not a recruitment criterion, although interestingly the data from the UPS (discussed in [3]) identify that whilst ≈12% of patients in the studies where urgency incontinence was a prerequisite selected question 3, i.e. 'I am usually able to finish what I am doing before going to the toilet', this was not markedly dissimilar to the value of ≈8% in the other two studies. When considering scales such as the UPS from a methodological perspective, it should be noted that they aim to measure the intensity of the desire to void rather than urgency as such. Therefore, only the last one or two gradations in these scales measure what we and others would consider to be urgency, the remainder of the options only measuring aspects of the desire to void. Furthermore, it is a leap of faith to infer that there is an automatic progression from normal desire to void through to urgency.

The review in this issue [2] criticises that by Cardozo *et al.* [3] by stating that 'The UPS was found to be conceptually valid but to have uncertain responsiveness based on the few response options available to the patients'. In particular, a patient who says that he/she is usually able to finish a task before going to the toilet is given no room to improve despite still having OAB. The UPS also lacks temporal characteristics that would enhance its ability to be understood by patients. For example, 'I am not able to hold urine' is not a clear statement in the absence of a specified period. Not being able to hold urine for 30 min is certainly different from not being able to hold urine for 3 h. The UPS, quite correctly, purports to measure the perception of urgency rather than urgency per se. However, it has at least one category (response #3) that appears to be inconsistent with the compelling nature of urgency as defined by the ICS [1]. Similarly, response #1 ('I am usually not able to hold urine') would appear to be applicable to urgency with incontinence only. In this context it is important to consider that only a third of patients with OAB have urgency incontinence.

Clearly urgency is a symptom and as such is difficult to define, to communicate to both patients and colleagues alike, and to measure and quantify, notwithstanding the additional variable introduced by inter-individual variation. Aspects such as how the symptom of urgency differs from 'urge' or 'the normal desire to void' (the latter in our view being a preferable term), remain unresolved. Once these terminological issues have been resolved then it will be possible to investigate the other important characteristics of the symptom of urgency. For instance, where the sensation is located; in the suprapubic area or the perineum?; are there in fact differences in the symptom of urgency and its clinical features in men as contrasted to women? Certainly this would be expected to be the case with a greater likelihood of an association with urgency incontinence and a shorter 'warning or postponement time' in women rather than men; is there a difference in the sensation of urgency in people with a neurological cause rather than those with idiopathic detrusor overactivity?

It is evident that we are now reaching a clearer understanding of 'both the problem of urgency and the urgency of the problem', and agreeing on standardized unambiguous terms and clear definitions are essential steps if we are to advance our knowledge in this field.

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IS PELVIC LYMPHADENECTOMY REALLY NECESSARY IN PATIENTS WITH A SERUM PROSTATE-SPECIFIC ANTIGEN LEVEL OF <10 ng/mL UNDERGOING RADICAL PROSTATECTOMY FOR PROSTATE CANCER?

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INTRODUCTION

The necessity and extent of pelvic lymph node dissection (LND), particularly in patients with a PSA level of <10 ng/mL remains a subject of intense debate. Overall, in our series of 463 patients with localized prostate cancer and without previous therapy (radio- or hormonal

therapy), who all had an extended LND, lymph-node metastasis was detected in 24% [1]. Extended lymphadenectomy in this series included the nodes along the external iliac vein, the obturator fossa and along the internal iliac artery, and a median (range) of 21 (6–75) nodes were removed per patient. Stone *et al.* [2] compared 150 patients with modified and 39 with extended LND; not only did they find, as was to be expected, a significant difference in the number of nodes removed, 9.3 vs 17.8 ($P < 0.05$), but also three times as many patients with lymph-node metastasis, 7.3% vs 23.1% ($P = 0.02$). This was confirmed by Heidenreich *et al.* [3] in a study comparing a historical control group with standard (external iliac vein and obturator fossa) and a contemporary group with extended lymphadenectomy (external iliac vein, obturator fossa, internal iliac artery, common iliac vessels and presacral). A median of 11 (6–19) and 28 (21–46) nodes were removed for standard and extended LND, respectively. At the same time the number of patients with lymph-node metastasis increased from 12/100 to 27/103. Heidenreich *et al.* further concluded, that as of all nodes removed only three were found to be positive along the common iliac vessels and in the presacral area, removing lymphatic tissue from these regions could be neglected.

In contrast, the importance of removing the nodes along the internal iliac artery is becoming increasingly clear. In our series 17% of patients had positive nodes exclusively in this area, and in [4] and [5], 29% and 19%, respectively. The proportion of patients with nodes either exclusively in this area or in combination with another location was 59% in our and 67% in the series by Tenaglia and Iannucci [5]. Without removing the tissue along the internal iliac artery a significant number of patients would be left with diseased nodes.

It is often stated that once patients have node-positive disease this should be considered systemic and treated accordingly, and that removing further nodes shows no benefit. However, in our series the number of positive nodes removed correlated inversely with the chance of remaining biochemically disease-free. The rate of biochemical progression, symptomatic tumour progression and death was significantly lower in patients with only one lymph node involved, so that there may be a potential cure for patients with low metastatic load if all diseased nodes are removed. In accordance, Stein and Skinner (unpublished data, courtesy of Stein and Skinner, University of Southern California, December 2003) reported an ≈40% chance of PSA recurrence-free survival after 10 years in patients with stage D1 prostate cancer, again implying a potential chance of cure even in these patients.

Variable	PSA, ng/mL <10	PSA, ng/mL ≥10
N	287	312
Median (range):		
age, years	63 (44–76)	64 (45–76)
PSA, ng/mL	6.2 (0–9.92)	17.9 (10.1–192)
Lymph nodes removed	19 (1–72)	20 (1–75)
Incidence of +ve nodes, n/N (%)	31/287 (11)	102/312 (33)
% incidence in one region:		
external iliac vein	10	11
obturator fossa	32	18
internal iliac artery	20	22
along internal iliac artery + another region	55	66

TABLE 1
Demographics and incidence of lymph node metastasis in patients with a PSA of <10 or ≥10 ng/mL, from our updated series, and the incidence of lymph node metastasis (exclusively in one region) according to location after extended LND for clinically localized prostate cancer

In contrast, Dimarco *et al.* [6] detected no survival advantage after extended lymphadenectomy for prostate cancer. In that study the median number of nodes removed decreased from 14 between 1987 and 1989, to five between 1999 and 2000. Interestingly, removing more nodes in the earlier period led to similar results for disease progression and survival as removing fewer nodes in the later period. As T-stage migration over time is an accepted phenomenon this may imply that, thanks to a more extended lymphadenectomy, patients with higher-stage disease had comparable survival chances to a recent population with earlier stage disease.

The need for extended lymphadenectomy is further enhanced by the analysis of Di Blasio *et al.* [7] showing that the number of nodes removed is associated with progression ($P = 0.044$). Removing ≈13 nodes had the lowest risk of disease progression, regardless of nodal disease status. Bader *et al.* [8] reported similar findings, with 16%, 12%, 8% and 8% of patients showing disease progression after removing 0–4, 5–9, 10–14 and >14 nodes for pT1/pT2N0 prostate cancer, respectively.

Our reported series has been criticised for not representing the actual current situation; the series included many patients with locally advanced disease and a high median PSA level of 11.4 ng/mL. This may not reflect the current situation, where mainly patients with a PSA of <10 ng/mL are treated. Thus we discriminated between patients with a PSA of <10 and ≥10 ng/mL. Not unexpectedly, the incidence of positive nodes increased to 33% for the patients with a PSA of >10 g/mL (Table 1). What was more surprising was that 11% of patients in the low-PSA group had positive nodes. The distribution of the positive nodes was similar in both groups, with ≈20% found exclusively along the internal iliac artery (Table 1). Another interesting finding was that in patients with positive nodes, despite a PSA level of <10 ng/mL, two-thirds had organ-confined disease. Thus, neither PSA or local T-stage appear to be valid factors to determine the need for LND. When assessing the Gleason score we found that, as expected, with increasing pathological Gleason score more patients had metastatic disease. Only 3% with a Gleason score of <6, vs 17% with a score of ≥6 (Table 2). Can we therefore restrict LND to patients with a Gleason score ≥6 and a PSA level of <10 ng/mL in the prostate biopsies? Probably not, as ≈30% of biopsies are understaged.

Many surgeons tend to base their decision on nomograms based on limited or standard LND; these nomograms should help to determine the stage of disease based on clinical staging, the serum PSA value and the preoperative Gleason score. Table 3 shows the predicted values (Partin nomogram) and the results of the Heidenreich *et al.* [4] and our series, where all patients underwent extended LND. Both groups find a much higher

TABLE 2 The Gleason score of the prostatectomy specimen in patients with positive lymph nodes and a serum PSA of <10 ng/mL

Gleason score	No. patients with +ve nodes/ N patients (%)
2	0/12
3	0/11
4	1/39 (2)
5	3/62 (5)
6	6/75 (8)
7	6/52 (12)
8	9/14 (38)
9	6/12 (50)
Totals	31/287 (11)
<6	4/124 (3)
≥6	27/163 (17)

TABLE 3 The predicted incidence of lymph node metastasis according to the Partin Tables, and the incidence in patients with extended lymphadenectomy

	Partin	[3,4]	[1]
N	–	321	596
pN +ve (%) at Gleason score:			
PSA < 10 ng/mL			(287)
2–4	0	0	1.4
5–7	2–8	10	8
8–10	8	57	42
PSA 10–20 ng/mL			(178)
2–4	0	0	7
5–7	12	10	25
8–10	27	57	50

incidence of nodal disease than predicted; this should be considered when relying on such tables.

The impact on disease progression and survival remains unconfirmed because of the relatively benign course of disease in prostate cancer, necessitating a follow-up of 10–15 years. However, there are findings indicating an improved course of disease after extended LND with removal of all diseased nodes, especially in patients with low-volume metastatic disease. Of patients with only one positive node, 75% remained free of tumour progression and only 14% have so far died from prostate cancer in the series by Bader *et al.* [8] (Table 4). In other forms of cancer, e.g. stomach, oesophagus, pancreas and lung, a positive effect on survival was reported as a result of extended lymphadenectomy (Table 5) [9–12]. Why should prostate cancer be an exception?

Number of	+ve lymph nodes, n (%) 1	2	>2
patients	116	45	82
with tumour progression	29 (25)	14 (31)	32 (39)
dead from prostate cancer	16 (14)	7 (16)	20 (24)

TABLE 4 Tumour progression in patients with pN+ve prostate cancer

Cancer	LND limited	extended	P
Stomach [9]			
5-year survival, %	36	54	<0.05
Oesophagus [10]			
5-year survival, %	43	61	<0.01
Pancreas [11]			
2-year survival, %	0	23	–
Lung (pN1 only) [12]			
18-month survival, %	42	62	0.03

TABLE 5 Impact of extended LND on survival in other types of cancer

In summary, an extended lymphadenectomy should be used in all patients having LND and radical prostatectomy for prostate cancer, even those with a PSA level of <10 ng/mL. Special attention should be placed on removing the lymphatic tissue along the internal iliac artery, as a significant number of positive nodes are found in this area, which is often neglected. Because of the higher probability of detecting positive nodes during lymphadenectomy, nomograms based on standard LND should be applied with caution. The impact of extended lymphadenectomy on disease progression and survival remains to be confirmed. However, there are certain indications, that as in other forms of cancer, removing all diseased nodes may have a positive effect on the course of the disease.

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Abbreviations: **LND**, lymph node dissection.