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Anatomically *versus* biologically unifocal prostate cancer: a pathological evaluation in the context of focal therapy

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Abstract:

Objectives: Since tumor focality in prostate cancer continues to be considered a major limitation for focal prostate therapy, in this study we attempted to compare the pathological features and the proportion of patients with anatomically unifocal *versus* biologically unifocal tumors (i.e. multifocal prostate cancer in which the secondary nonindex elements are small, low grade and clinically insignificant) who were suitable for focal therapy.

Methods: Ninety-five consecutive whole mount laparoscopic radical prostatectomy samples underwent pathological assessment (from January 2007 to November 2009). Tumor focality, laterality, Gleason score and volume of individual foci, total tumor volume, pathological stage and surgical margin status were assessed. The index lesion was defined as the largest by volume. Patients suitable for focal ablation were defined as having tumors that were unifocal, organ confined, with a Gleason score (GS) up to 7 prostate cancer, or multifocal, organ confined, GS up to 7 prostate cancer, with one large index lesion and the remaining foci demonstrating features of clinically insignificant disease (total tumor volume of all secondary foci ≤ 0.5 cm^3 with GS ≤ 6).

Results: Patients with biologically unifocal cancer had significantly lower total tumor volume (3.26 *versus* 7.28 cm^3; $p < 0.001$), index lesion volume (2.9 *versus* 7.16 cm^3; $p < 0.001$), rates of seminal vesicle invasion (4% *versus* 34%; $p < 0.001$), rates of positive surgical margins (22.4% *versus* 52.1%; $p < 0.001$) and rates of 4+3 GS tumors (10.2% *versus* 29.1%; $p = 0.018$). The proportion of patients suitable for focal therapy was higher in the biologically unifocal *versus* anatomically unifocal cancer group, although without reaching statistical significance (65.3% *versus* 45.8%; $p = 0.11$).

Conclusions: Patients with biologically unifocal tumors have better pathological outcome than those with anatomically unifocal disease. At present the assumption that multifocality should *a priori* exclude patients from any organ-preserving prostate cancer treatment is only theoretical and needs to be validated by future clinical trials since there are a large proportion of patients with multifocal disease apparently suitable for focal prostate therapy.

Keywords: focal therapy, index lesion ablation, prostate cancer

Introduction

In recent years, growing demand for minimally invasive treatment modalities offering oncologically safe and functionally rewarding outcomes has prompted researchers to explore the application of focal therapy in prostate cancer [Ahmed *et al.* 2007, 2011]. Conceptually, focal therapy implies selective targeting of the tumor area rather than treating the whole gland [Bostwick *et al.* 2007]. However, in prostate cancer, islands of tumor areas dispersed throughout the entire gland rather than a densely clustered tumor in a single anatomic location are usually seen, giving rise to multifocal tumors. Therefore, reasonable concerns have been raised regarding the implementation of focal prostate therapy for a predominantly multifocal malignancy.

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One fairly consistent morphologic feature of multifocal prostate cancer is the presence of a dominant (as measured by tumor volume) focus – the so-called index lesion – and one or more separate, secondary tumor foci of smaller volume [Villers *et al.* 1992]. These secondary tumors are usually small and well differentiated and it is suggested they are unlikely to contribute to disease outcome [Wise *et al.* 2002]. The term biologically unifocal tumor has been coined to describe multifocal tumors with clinically insignificant secondary tumor foci [Bostwick *et al.* 2007]. An emerging hypothesis is focal therapy, which could be implemented by targeting the index lesion only with surveillance of secondary tumor foci [Bostwick *et al.* 2007]. Such a concept has generated much debate [Ahmed 2009]. The key question still remains whether unifocal disease is the *sine qua non* for focal prostate therapy. Since the argument is somewhat complex and is mainly based on theoretical rationalization, there is increasing need for clinicopathological evidence. In this study, we attempt to evaluate and compare the pathological features of biologically unifocal tumors to those of anatomically unifocal tumors.

Methods

Between 13 January 2007 and 18 November 2009, 95 consecutive men with clinically localized prostate cancer underwent a laparoscopic radical prostatectomy at a single tertiary referral centre. Prostatectomy specimens were processed and examined according to a standardized previously described protocol which includes a thorough grading and volumetric assessment of all tumor foci within the gland [Karavitakis *et al.* 2010].

When multifocal disease was observed, the index lesion was considered the largest focus as measured by volume [Haggman *et al.* 1997]. Biologically unifocal cancers were considered to be cases with multifocal tumors in which the secondary (satellite) lesions were clinically insignificant – defined as total tumor volume of secondary tumor foci less than 0.5 ml with no Gleason pattern 4. Cases theoretically suitable for focal ablation were defined as having tumors that were anatomically unifocal, organ confined, with a Gleason score (GS) up to 7 prostate cancer, or multifocal, organ confined, GS up to 7 cancer, with an index lesion and the remaining foci demonstrating features of clinically insignificant disease [Ahmed *et al.* 2007].

Statistical analysis

A two-tail Mann–Whitney U test was performed for comparison of means between groups whereas analysis of categorical variables was based on Pearson's χ^2 test. All statistical analyses were performed using SPSS version 17 (SPSS Inc., Chicago, IL, USA) statistical software. Two-sided $p \leq 0.05$ was used to indicate statistical significance.

Results

Table 1 shows the baseline characteristics of the study cohort which are similar to those obtained from the analysis of the British Association of Urological Surgeons Complex Operations Database [Vesey *et al.* 2012].

Comparative analysis of clinicopathological outcome between anatomically unifocal *versus* biologically unifocal cases is presented in Table 2. A number of parameters were significantly higher in the anatomically unifocal group compared with the biologically unifocal group, including total tumor volume (3.26 *versus* 7.28 cm^3; $p < 0.001$), index lesion volume (2.9 *versus* 7.16 cm^3; $p < 0.001$), rates of Gleason score at least 7 (4+3) (10.2 *versus* 29.1%; $p = 0.01$), seminal vesicle invasion (4% *versus* 34%; $p < 0.001$) and positive surgical margin status (22.4% *versus* 52.1%; $p < 0.001$).

The proportion of patients suitable for focal therapy was higher in the biologically unifocal *versus* anatomically unifocal cancer group, although without reaching statistical significance (65.3% *versus* 45.8%; $p = 0.11$).

Discussion

We demonstrate in this UK series of unscreened and predominantly high-risk prostate cancers that biologically unifocal cancers seem to have better pathological features compared with anatomically unifocal tumors. In particular, biologically unifocal tumors had significantly lower tumor volume and index lesion volume as well as lower rates of surgical margin invasion and seminal vesicle invasion than unifocal tumors in a series of consecutive presenting patients. Since these features correlate with disease progression and survival of patients with prostate cancer, patients with biologically unifocal tumors appear to be a suitable target population for focal prostate therapy compared with those with unifocal disease.

Table 1. Baseline characteristics of the 95 patients with prostate cancer.

	Study cohort	BAUS Complex Operation Database
PSA (ng/dl), mean	11.9	*8.3*
Biopsy Gleason score (94 cases)		
≤6	56 (60%)	63%
7	36 (38%)	32%
≥8	2 (2%)	6%
D' Amico risk groups		
Low	37 (38.9%)	
Intermediate	34 (35.7%)	
High	24 (25.2%)	
Clinical stage (94 cases)		
T1	45 (48%)	52%
T2	34 (36%)	45%
T3	15 (16%)	3.6%
T4	0 (0%)	0.03%
Tumor focality		
Anatomically unifocal tumors	24 (25%)	
Multifocal tumors	71 (75%)	
Biologically unifocal tumors	49 (52%)	
Bilateral tumors	85 (90%)	
Positive surgical margins		
pT2	14 (23.7%)	22%
pT3	16 (47.2%)	56%
pT4	1 (100%)	100%
Total	31 (33%)	33%
Total tumor volume (cm^3), mean (range)	4.6 (0.02–30.5)	
Focus tumor volume (cm^3), mean (range)	1.6 (0.002–26.9)	
Pathological stage		
T2	59 (62%)	69%
≥T3	36 (38%)	31%
Specimen Gleason score		
≤6	29 (31%)	45%
7	61 (64%)	47%
≥8	5 (5%)	8%

BAUS, British Association of Urological Surgeons; PSA, prostate-specific antigen.

Table 2. Comparative analysis between biological unifocal (BU) and anatomically unifocal (AU) tumors.

	BU	AU	*p* value
Age (years), mean	62.04	61.38	0.4
PSA (ng/dl), mean	11.18	14.39	0.08
Total tumor volume (cm^3), mean	3.26	7.28	<0.001
Index lesion volume (cm^3), mean	2.9	7.16	<0.001
Seminal vesicle invasion, %	4	34	<0.001
Extracapsular extension, %	32.6	45.8	0.2
Positive surgical margins, %	22.4	52.1	<0.001
Specimen Gleason score ≥7 (4+3), %	10.2	29.1	0.01
Pathological stage ≥T3, %	32.6	50	0.15

A hypothetical explanation for this observation is based on the pathobiological phenomena characterizing prostate cancer progression. Two main theories have been postulated to explain the intimate mechanism of prostate cancer multifocality, the uniclonal and the multiclonal theory. The former suggests that multiple tumor foci are the consequence of intraglandular dissemination of a primary cancer [Ruijter *et al.* 1999]. By contrast the latter considers each tumor focus to have evolved via random, field carcinogenic events leading to autonomous growth of colonies of cancer cells within the same organ [Kallioniemi and Visakorpi, 1996]. Simultaneous growth and volumetric expansion of multiple tumor foci in a spatially limited organ such as the prostate gland may lead to the formation of a large tumor focus by fusion of several previously independent, smaller tumor foci. Consequently, we could hypothesize that large, unifocal prostate cancers are the culmination of a process of fusion of multiple foci. Based on this hypothesis within the natural history of prostate cancer, biologically unifocal cancer is midway between two extremes: The small potentially clinically insignificant unifocal cancer lesion at one extreme and the large, poorly differentiated, locally advanced unifocal cancer at the other. This model of the natural history of prostate cancer also suggests that there might be an emerging bias in favor of the unifocal tumor with regard to the proportion of cases suitable for focal ablation. Indeed, a considerable proportion of unifocal tumors are bulky and probably unsuitable for focal therapy if tumor volume was included in the eligibility criteria. Therefore, the difference in the proportion of patients suitable for focal therapy between the two groups might be even greater, offering further support to our hypothesis that patients with biologically unifocal tumors appear to be a suitable target population for focal prostate therapy.

Our pathology observation provides evidence that unifocal disease is not the *sine qua non* for focal prostate cancer therapy. Studies by Mouraviev and colleagues and Tareen and colleagues suggest that among men undergoing a radical prostatectomy for clinically localized prostate cancer, between 10% and 20% may have been suitable to receive ablation of the entire one half of the prostate (hemiablation) with preservation of the contralateral lobe [Mouraviev *et al.* 2007; Tareen *et al.* 2009]. However, the investigators exclude men with a single dominant lesion and contralateral insignificant disease. Indeed, we have previously shown that when these patients were also considered for hemiablation, nearly half the radical prostatectomy population could have been suitable for hemiablation of the prostate with conservation of the contralateral lobe [Karavitakis *et al.* 2010]. In another retrospective study, Bott and colleagues demonstrated that between 58.5% and 67.5% could have been suitable for focal therapy intended as ablation of all clinically significant lesions with untreated areas harboring either no cancer or clinically insignificant disease [Bott et al 2010].

Possibly inclusion of patients with biologically unifocal prostate cancer in a focal therapy protocol aiming to ablate only the index lesion requires an in-depth understanding of the natural history of the satellite lesions. Until now, most of the arguments originate from retrospective clinical and pathological analysis of radical prostatectomy specimens. Several studies have demonstrated the index lesion to be the most important determinant of cancer progression [Wise *et al.* 2002; Rashid *et al.* 1999]. This conclusion relies heavily on the volume-based tumor progression hypothesis initially elaborated by Stamey and colleagues [Stamey *et al.* 1993]. However, Stamey's hypothesis might be questioned in the light of other studies demonstrating that tumor aggressiveness might not always be a function of tumor volume [Miller and Cygan, 1994; Schmidt *et al.* 2006; Gburek *et al.* 1997]. Furthermore, it still remains to be seen whether each tumor focus in multifocal cancer should be considered an autonomous component or an indistinguishable part of the malignant disease. For example, several studies indicated that multifocal disease might be a more aggressive variant of prostate cancer [Magi-Galluzzi *et al.* 2006; Djavan *et al.* 1999], although others have disputed this point [Rice *et al.* 2009; Stamatiou *et al.* 2009]. In either case, because of the uncertainty, index-lesion ablation should be considered investigational and only be offered within clinical trials. Such trials are currently ongoing (MD Anderson Cancer Centre [ClinicalTrials.gov identifier: NCT00877682] and University College London [ClinicalTrials.gov identifiers: NCT01194648 and NCT00988130]). The results of these studies should clarify these points and provide answers to other questions relating to this highly contentious issue.

There are important concerns about whether focal therapy offers similar oncological outcomes

to conventional radical approaches for prostate cancer. Critics point out that in a man with low to intermediate risk prostate cancer without comorbidities and life expectancy more than 10 years, there might be increased risk of tumor progression and significant disease may be missed. Also, there remains an important limitation regarding optimal disease characterization in terms of tumor focality. Currently, transrectal ultrasound (TRUS) biopsy protocols appear inadequate for the selection of patients for focal therapy. In that respect, promising results derive from the implementation of brachytherapy template-guided transperineal saturation biopsy and of multifunctional or multiparametric magnetic resonance imaging modalities including spectroscopy, dynamic contrast enhancement and diffusion weighting [Ahmed *et al.* 2007]. Their application offers promising results with regard to tumor characterization in terms of tumor focality. However, these modalities might also be disadvantageous, with possible increased risk of complications (i.e hemorrhage, acute urinary retention), requirement of anesthesia and increased cost.

Another aspect deserving further scrutiny is post-focal-therapy surveillance. Because residual prostate tissue remains intact after focal therapy, prostate-specific antigen (PSA) continues to be produced from viable prostate luminal epithelial cells. Therefore absolute values of PSA appear to be inadequate for monitoring such patients. Additionally, positive follow-up biopsy results may not be synonymous with treatment failure but rather indicate detection of previously undetected insignificant disease or *de novo* carcinoma. In that case, post-treatment PSA kinetics such as PSA doubling time, PSA velocity and PSA density, and follow-up multiparametric MRI might play a key role in evaluation of treatment failure [Ahmed *et al.* 2007; Rouviere *et al.* 2010].

Given all these issues, the emerging concept of a biologically unifocal tumor might not be so relevant in today's practice. However, it might become critical in the future. Since research is the only way of gaining a greater understanding of tumor focality, in this study we aimed to provide relevant information from a histopathological perspective. Therefore, we appreciate that although absence of immediate clinical feedback might be an important limitation, we anticipate that our data will provide important histopathological evidence for future clinical investigation in this area.

Conclusion

Men with biologically unifocal tumors who have undergone radical prostatectomy seem to have better pathological outcomes than those with anatomically unifocal disease. At present, the assumption that multifocality should *a priori* exclude patients from any organ-preserving prostate cancer treatment is only theoretical and needs to be validated in future clinical trials. Such trials will allow us to determine the natural history of untreated low-volume low-risk prostate cancer lesions after the dominant index lesion alone is treated selectively.

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Conflict of interest statement

HUA receives research funding for other clinical trials in imaging and therapy of prostate from USHIFU (USA). HUA is a paid medical consultant for Steba Biotech and Oncura. HUA has received payments to attend medical conferences from the above companies.

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