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ORIGINAL ARTICLE

Re-evaluating the concept of "dominant/index tumor nodule" in multifocal prostate cancer

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Abstract Prostate cancer (PCa) often presents as a multifocal disease with heterogeneity in Gleason score (GS) and genetic alterations. Dominant/index tumor nodule (DN), the largest nodule in a multifocal disease, is presumed to harbor the most aggressive biological behavior and therefore dictate the overall clinical behavior of PCa. In this study, we examined the pathological features of DN and re-evaluated the validity of the "DN" concept in multifocal PCa. A total of 201 consecutive radical prostatectomy specimens were totally submitted and examined. All independent cancer foci were recorded with prognostically important pathological parameters. Unifocal and multifocal disease was present in 25 (12.4 %) and 176 (87.6 %) cases, respectively. In 20 (11.3 %) multifocal cases, the highest GS, the largest tumor volume (TV), and extraprostatic extension (EPE) did not concur in the same tumor nodules. Non-DNs had a higher GS and EPE in 13 cases each and had both the highest GS and EPE in 5 cases. In the majority of multifocal prostate cancer (88.7 %), DNs have the highest GS and EPE. In these cases, DN is still a valid concept and can be used for assigning overall GS and procuring tissue for research. However, in a significant number of cases (11.3 %), the largest TV, the highest GS, and EPE did not concur in the same tumor nodules. In these cases, pathologists should de-emphasize the concept of DN. Instead, they should place the emphasis on the multifocal nature of the disease and document the pathological features of all independent tumor foci that have the largest TV, the highest GS, and EPE.

Keywords Prostate cancer · Radical prostatectomy · Dominant tumor · Index tumor

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Introduction

It is well documented that prostate cancer (PCa) presents as a multifocal disease in majority of cases with two or more tumor nodules within the prostate gland [1–7]. PCa also demonstrates heterogeneity among different tumor nodules in the same prostate gland. Histologically, different tumor nodules in the same prostatectomy specimen often show different Gleason scores (GS) [4–8]. Arora et al. showed that multifocal cancer was present in 87 % of radical prostatectomy (RP) specimens; only 9 % of those multifocal cancer cases had all tumor nodules with primary and secondary Gleason grades the same as the overall Gleason scores assigned to the RP specimen [4]. At molecular and genetic levels, Cheng et al. studied the pattern of allelic loss in prostate cancer from patients who had two or more separate cancer foci and found that the pattern of allelic loss was distinct between different foci in 15 of 18 cases, supporting the independent clonal origin [9]. A recent study on *TMPRSS2* gene rearrangements in multifocal PCa demonstrated differing gene arrangement status and class between different tumor foci, providing further molecular evidence of independent clonal origin of the multifocal cancer foci [10]. The morphological and genetic heterogeneities of multifocal PCa suggest that different cancer foci may be biologically distinct with the presumption that some tumor foci are more aggressive than others within the same prostate gland.

The multifocal and heterogeneous nature of PCa poses significant challenges to PCa grading and research. First, how do pathologists assign an overall GS to a RP with multiple cancer foci exhibiting different GS? Second, how do researchers procure multifocal PCa so that the sampled tumor tissue actually represents the overall biological behavior of the disease?

To circumvent these issues, the concept of "dominant/index tumor nodule" (DN) was first introduced by McNeal et al. to refer to a tumor nodule that most likely harbors the most aggressive biological behavior among the multifocal tumor nodules within a prostate gland and therefore may dictate the overall biological behavior of the disease [11]. In 2005, an International Society for Urological Pathology (ISUP) consensus recommended the use of DN for tumor grading and tissue banking for research in RP specimens [12]. DN has also garnered considerable interest recently in the focal therapy for PCa as it is naturally an ideal target for therapeutic intervention. However, the definition of DN is ambiguous in terms of which of the pathological parameters (tumor size, GS, or staging parameter) should be used. At the 2009 ISUP consensus meeting, the urological pathology experts did not reach a consensus on the pathological parameters that defined DN in RP specimens [13]. At present, DN refers to the tumor nodule of the largest size in a multifocal disease [4, 6, 7, 11, 12].

However, the largest tumor volume (TV), the highest GS, and staging parameters (extraprostatic extension (EPE)) do not always concur in the same tumor nodule, as demonstrated by a few studies in the literature [4, 7]. Data on the pathological features of DN in multifocal PCa is, however, quite limited. In the current study, we examined the pathological features of multifocal prostate cancer lesions in 201 RP specimens with emphasis on three most commonly used pathological parameters, including GS, TV, and EPE. The aim of our study is to examine how often the largest TV, the highest GS, and EPE concur in the same tumor nodule; therefore, a DN can be definitively assigned. We also re-evaluated the validity of the concept of DN in multifocal PCa for Gleason grading and procuring tissue for research.

Materials and methods

Case selection and histology preparation

A total of 201 consecutive RP specimens collected between 2011 and 2012 at the authors' institution were included in this study. Patients with preoperative radiation or androgen deprivation therapy were excluded from this study.

Each RP specimen was totally embedded and submitted. Briefly, after fixation in 10 % neutral buffered formalin, the apex and base of the prostate were coned and perpendicularly sectioned and entirely submitted. Each prostate was then serially sliced perpendicular to the posterior surface of the prostate at approximately 3-mm intervals from the apex to the base. The sections from the junctions between the seminal vesicles and prostate were also submitted for evaluation. All submitted specimens were stained with hematoxylin and eosin (H&E) for histologic evaluation. For those cases with a portion of the specimen procured for research, the frozen sections of the procured tissue were obtained and examined together with routinely processed tissue.

Histopathological evaluation

H&E slides of each RP specimen were examined. All cancer foci were traced on the glass slides. The TV of each cancer focus was calculated using a grid method [4, 14]. Briefly, a transparent film with 2×2 mm grid was overlaid on the slides. Each grid represents a TV of 0.013 cm^3 (area [0.04 cm^2]× thickness of the tissue section [3 mm]×correction factor for fixation-induced tissue shrinkage) [1, 12] [15]. The TV of a traced focus is obtained by multiplying the total number of grids within the traced lesion by 0.013. Pathological data including primary and secondary Gleason grades, dimension and TV of each traced cancer focus, GS and linear extent of EPE and positive surgical margins, and seminal vesicle invasion (SVI) were then recoded in a "prostate map" (Fig. 1). Tumor foci were considered to represent the same tumor nodule if they were ≤3 mm from each other [6, 8, 16] or in

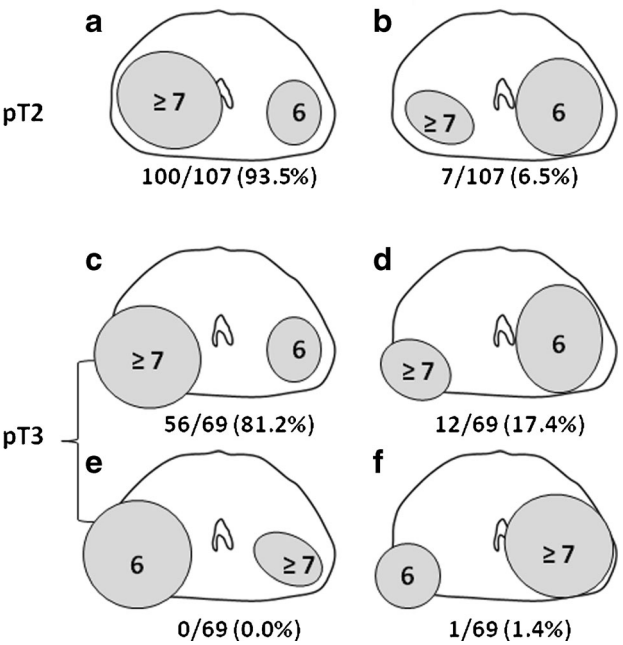

Fig. 1 Schematic representation of multifocal prostate carcinoma staged as T2 or T3 disease. *Shaded circles* represent cancer nodules. If they are within the contour of the prostate gland, they are T2 disease (**a**, **b**). If they extend beyond the prostate contour, they are T3 disease (**c**–**f**). The *size of the circles* approximates the size of the tumor nodule, and the *numbers inside the circles* represent Gleason scores of the tumor nodules

similar anatomic locations on consecutive slices. The largest tumor nodules were designated as DNs. Once the distribution of PCa foci was constructed, GS (using the 2004 ISUP modified Gleason grading system), dimension, and TV were then determined for all the separate cancer foci. The GS, EPE, SVI, surgical margin status, and pathological staging of RP specimens were evaluated according to the latest ISUP consensus recommendations [12, 13, 17, 18].

Statistical analysis

Patients' age, serum PSA level, prostate weight, TV, and size of the largest tumor nodule were analyzed using Student's *t* test. The χ^2 or Fisher's exact test was used for analysis of categorical variables. The *p* values of <0.05 were considered statistically significant. All the statistical analysis was performed using GraphPad Prism 5 (GraphPad Software, La Jolla, CA, USA).

Results

The clinical and pathological characteristics of 201 patients and their RP specimens are summarized in Table 1. Cases with higher GS and pathological stages and positive surgical margins had larger total TV. The mean total TV was 0.71, 1.21, and 2.79 cm^3 in GS 6, 7, and ≥8 diseases, respectively ($p<0.001$); 0.75 and 2.01 cm^3 in T2 and T3 diseases, respectively ($p<0.0001$); and 1.12 and 1.79 cm^3 in cases with negative and positive surgical margins, respectively ($p=0.0223$).

Unifocal and multifocal disease was present in 25 (12.4 %) and 176 (87.6 %) cases, respectively. There was no significant difference in GS, total TV, incidence of EPE, SVI, and positive surgical margin between unifocal and multifocal cases (Table 2). However, the mean size of the largest tumor nodule in multifocal cases was significantly greater than that in unifocal cases (22.1 vs. 16.2 mm, $p=0.006$; Table 2). Thirty-two (15.9 %) cases, 5 cases in unifocal and 27 cases in multifocal disease, met the criteria for pathologically insignificant tumor, defined as GS ≤6, organ-confined PCa with a total TV ≤0.5 cm [3, 16–20]. The incidence of insignificant tumor was not different between the unifocal and multifocal cases ($p=0.5612$).

In 176 cases with multifocal PCa, the mean number of tumor foci was 3.1 (range 2 to 8) per prostate. The tumor was located primarily in the peripheral zone (PZ) in 70.1 %, in the transition zone (TZ) in 14.9 %, in PZ and TZ in 15.5 %, and in the central zone (CZ) in 0.5 % of the cases. The mean total TV was 1.22 cm^3 (range 0.026 to 10.31 cm^3). The mean size and TV of the largest tumor nodule were 16 mm (range 1 to 42 mm) and 0.97 cm^3 (range 0.013 to 9.69 cm^3), respectively. The size of the largest tumor nodule correlated with the total TV (Spearman $r=0.7749$, $p<0.0001$). In 176 multifocal cases, 74 had the same GS in all tumor nodules, while 102 showed heterogeneous GS in different tumor nodules within a prostate gland. The difference between the highest and the lowest GS was 1 in 87 cases, 2 in 9 cases, and 3 in 6 cases.

Tumor nodules of the largest volume were considered DNs. In 157 (88.6 %) cases, the highest GS, the largest TV, and EPE concur in the same tumor nodules, i.e., dominant nodules (DNs). However, in 20 (11.4 %) cases, these pathological features did not concur in the same tumor nodules.

In 107 multifocal pT2 cases, DNs had the highest GS in 100 (93.5 %) cases (Fig. 1a). However, DNs did not have the highest GS in 7/107 (6.5 %) cases (Fig. 1b). In 69 multifocal pT3 cases,

Table 1 Clinical and pathological characteristics of 201 patients undergoing RP for prostate cancer

Clinical characteristics		
Age: mean (range)		62 (44–78) years
Preoperative serum PSA: mean (range)		8.3 (0.5–19) ng/mL
Pathological findings in RP		
Prostate weight: mean (range)		47.2 (26–148) g
Gleason score	6	64 (31.8 %)
	7	115 (57.2 %)
	≥8	22 (10.9 %)
Pathological stage	T2	125 (62.2 %)
	T3a	63 (31.3 %)
	T3b	13 (6.5 %)
Positive surgical margins	Apex only	8 (4.0 %)
	Base only	1 (0.5 %)
	Posterolateral only	10 (5.0 %)
	Multiple	3 (1.5 %)
Total TV: mean (range)		1.23 (0.03–10.64) cm^3

Table 2 Comparison of pathological parameters in RP specimens with unifocal and multifocal disease

Tumor focality		Unifocal ($n=25$)	Multifocal ($n=176$)
Gleason score*	6	8 (32 %)	56 (31.8 %)
	7	14 (56 %)	101 (57.4 %)
	≥8	3 (12 %)	19 (10.8 %)
Total TV (cm^3)*		1.17	1.23
Size of the largest tumor nodule (mean, mm)**		16.2	22.1
EPE: case number (%)*		7 (28)	69 (39.2)
SVI: case number (%)*		1 (4)	12 (6.8)
Pathological stage*	T2	18 (72)	107 (60.8 %)
	T3	7 (28)	69 (39.2 %)
Positive margin: case number (%)*		4 (16)	18 (10.2)
Insignificant tumor: case number (%)*		5 (20)	27 (15.3)

*$p>0.05$; **$p=0.0060$

DNs also had the highest GS and EPE in 56 (81.2 %) cases (Fig. 1c). In 12 (17.4 %) cases, tumor nodules with EPE had the highest GS but not the largest TV (Fig. 1d). In no case, the tumor nodule with EPE had the largest TV but not the highest GS (Fig. 1e). In 1 (1.4 %) case, the tumor nodule with EPE had neither the highest GS nor the largest TV (Fig. 1f).

Of the 20 cases with the largest tumor size, the highest GS and EPE did not concur in the same tumor nodules (Table 3); the second or third largest nodules had a higher GS than DNs in 13 cases, including 7 cases with GS 6 in DNs and GS 7 (n=6) and GS 9 (n=1) in the second or third largest nodules and 6 cases with GS 7 in DNs and GS ≥8 in the second or third largest nodules. In 13 cases, DNs were organ-confined, but EPE was present in non-DNs. In five cases, the highest GS and EPE were present in non-DNs. In seven cases with GS 6 in DNs, a higher GS (six cases with GS 7 and one case with GS 9) was found on the contralateral side of the prostate gland (Table 4).

Table 3 Twenty cases with discordant pathological parameters in dominant nodules

Case no.	Dominant nodule			Second largest nodule			Third largest nodule		
	EPE	GS	TV	EPE	GS	TV	EPE	GS	TV
1	−	6	0.30	−	7	0.10	−	6	0.02
2	−	6	0.22	−	6	0.14	−	7	0.04
3	−	7	0.46	−	9	0.25	−	7	0.13
4	−	6	0.33	−	7	0.14	−	6	0.07
5	−	6	0.36	−	7	0.16	−	7	0.12
6	−	7	0.57	−	8	0.40	−	6	0.23
7	−	7	0.38	−	7	0.26	−	8	0.16
8	−	7	0.91	+	7	0.12			
9	−	6	0.42	+	9	0.16	−	6	0.04
10	−	6	1.51	−	6	0.40	+	7	0.22
11	−	7	0.75	+	7	0.10	−	6	0.07
12	−	7	0.40	−	9	0.23	+	8	0.05
13	−	7	0.69	+	7	0.47	−	7	0.43
14	−	7	0.26	+	6	0.16	+	7	0.14
15	−	7	0.87	+	7	0.10	−	6	0.04
16	−	7	0.46	+	7	0.26	+	6	0.17
17	−	7	0.36	+	8	0.23	−	6	0.18
18	−	7	0.53	+	7	0.27	−	6	0.14
19	−	6	0.36	+	7	0.20	+	7	0.16
20	−	7	0.29	+	8	0.22	−	7	0.14

EPE extraprostatic extension, *GS* Gleason score, *TV* tumor volume

Table 4 Pathological features of non-dominant nodules contralateral to Gleason score 6 dominant nodules

Case no.	Dominant nodule		Non-dominant nodule(s) on the contralateral side			
			Nodule 1		Nodule 2	
	GS	TV (cm^3)	GS	TV (cm^3)	GS	TV (cm^3)
1	3+3=6	0.30	3+4=7	0.10		
2	3+3=6	0.22	3+4=7	0.04	3+3=6	0.14
3	3+3=6	0.33	4+3=7	0.14		
4	3+3=6	0.36	3+4=7	0.16	3+4=7	0.12
5	3+3=6	0.42	5+4=9	0.16	3+3=6	0.04
6	3+3=6	1.51	4+3=7	0.22	3+3=6	0.40
7	3+3=6	0.36	3+4=7	0.20		

GS Gleason score, *TV* tumor volume

Discussion

Pathological features of multifocal prostate cancer are well documented [1–5, 9, 19–27]. However, only a few studies addressed the discordant pathological features in DNs in RPs [4, 8]. The aim of our study was therefore to further examine the pathological features, including tumor size, TV, GS, and EPE in DNs in 201 totally submitted RP specimens. We addressed the following two issues: (1) How often do DNs have discordant histological features, i.e., the largest tumor size, the highest GS, and EPE do not concur in the same tumor nodule? (2) The validity of the "DN" concept in the grading, prognosis, and tissue banking of multifocal prostate cancer.

Multifocal PCa is seen in 60–90 % of RP specimens [1–5, 9, 19–27]. In this study, we found multifocal disease in 87.6 % of 201 consecutive cases. Both unifocal and multifocal diseases have similar GS distribution, total TV, incidence of EPE, SVI, and positive surgical margins. Pathological stage distribution is also similar in the two. The frequency of pathologically insignificant disease using the Epstein criteria [28] is not different in unifocal and multifocal diseases. However, the size of the largest tumor nodule is significantly greater in the multifocal disease than in the unifocal disease (22.1 vs. 16.2 mm). Our finding is similar to that of Noguchi et al., who, in studying 222 RP specimens, found no difference in the frequency of adverse pathological features such as EPE, SVI, positive surgical margins, and lymph node metastasis between unifocal and multifocal diseases [29]. These findings suggest that multifocal prostate cancer is no more likely than the unifocal disease to have adverse pathological features such as higher GS, EPE, and SVI.

The concept of DN bore out of necessity and convenience for evaluating RP specimens with multifocal PCa with the assumption that DNs most likely harbor the most aggressive biological behavior among multifocal tumor nodules and therefore dictate the overall biological behavior of the disease. All published studies used tumor size as the criterion for assigning DNs [4, 6, 7, 11, 12]. However, a few studies have shown that prognostically important pathological features

(largest tumor size, highest GS, and staging parameters) do not always concur in the same tumor nodules. Ruijter et al. found in their study of 61 RP specimens that 18 % of index tumors had GS lower than adjacent non-index tumors and in two cases EPE was found in non-index tumors [8]. Arora et al. reported that index tumors had the same GS as the overall GS in only 68 % of cases [4]. Since data on the discordant pathological features in DNs are quite limited in the literature, we did a detailed analysis of pathological features of DNs in the current study. In the majority of multifocal cases (156/176, 88.7 %), the highest GS, the largest TV, and EPE are found in DNs. Therefore, there is no issue identifying the DNs and subsequently assigning an overall GS and procuring tissue for research in these cases. However, in 11.3 % (20/176) cases, DNs did not have the highest GS and/or EPE. In 13 cases, non-NDs had a higher GS than DNs, including 7 cases with GS 6 in DNs and GS ≥7 in non-DNs and 6 cases with GS 7 in DNs and GS ≥8 in non-DNs. In 13 cases, DNs were organ-confined, but EPE was present in non-DNs. In 5 cases, the highest GS and EPE were present in non-DNs. In these 20 cases, assigning DNs is problematic.

Studies have suggested that defining DNs based on the tumor size may be flawed for several reasons. First, prognostically important pathological parameters including the largest TV, the highest GS, and EPE do not always concur in the same tumor nodule (in 12 % of cases in this study). Second, although the tumor volume is a critical pathological parameter in most cancer types as an adverse prognostic indicator, its clinical significance in PCa progression after RP is inconclusive and controversial. In almost all studies, tumor size/volume correlates very well with cancer progression in univariate analysis. However, this correlation is not consistently found in multivariable analysis [30]. Several molecular studies also found that the largest tumor foci do not always contribute to the development of metastasis as the molecular changes seen in the metastatic deposits and circulating tumor cells do not consistently match those in DNs [31, 32]. Third, GS seems to be a more significant prognostic predictor with the percentage of Gleason grade 4 and 5 cancer considered to be the most powerful predictor of patient outcomes [33–35]. These high-grade components, even when present in non-DNs, are likely the driver of patients' clinical outcomes. High-grade components (GS ≥8) should therefore be included in the prognostic estimation with other pathological parameters such as TV and staging parameters regardless of whether they are present in DNs or non-DNs.

Even though GS is a very important pathological parameter, evidence so far has, however, suggested that GS 6 PCa is considered to have an indolent biological behavior. The incidence of pelvic lymph node metastasis in PCa with GS ≤6 in RP is well below 1 % [36–38]. A recent study by Ross et al. found that GS ≤6 PCa does not appear to be capable of metastasizing to lymph nodes if strict criteria are used to grade PCa [39]. Therefore, if a DN has GS 6 (as illustrated in Fig. 1b, c), it can be considered to have an indolent biological behavior and have no likelihood to metastasize to pelvic lymph nodes. In these cases, attention should be directed at PCa with GS ≥7 in other non-DN tumor foci.

It is therefore important for pathologists to carefully examine the pathological features of all independent tumor foci in multifocal PCa. If adverse pathological features (largest TV, highest GS, and staging parameters) concur in a single tumor nodule, the DN concept is still valid. DNs can be used for assigning the overall GS and procuring tissues for research, as recommended by several consensuses [10, 11, 40]. However, if adverse pathological features (largest TV, highest GS, and EPE) do not concur in a single tumor nodule, pathologists should de-emphasize the DN concept. Assigning DNs based on any single pathological parameter currently is not supported by scientific evidence. Pathologists should report the multifocality and the pathological features of all independent foci. In such cases, pathologists should describe the presence of separate tumor nodules with the largest TV, the highest GS, and staging parameters and their respective pathological features. Similarly, all the independent nodules with the largest size, the highest GS, and staging parameters should be sampled when procuring tissue for research. Re-evaluation of the significance of the dominant nodule (index lesion) is particularly relevant to determine the optimal biopsy sampling strategy in the emerging technique of targeted biopsy based on MRI. The dominant nodule if chosen as the single target for biopsy will miss potentially more important disease in a subset of patients. Based on the findings of this study, more accurate determination of biology of a cancer in patients with multifocal PCa may be better determined through a wider systematic biopsy rather than targeted biopsy focused only on the dominant lesion.

Conclusions

Prognostically important pathological parameters (largest tumor volume, highest GS, and staging parameters) concur in the same tumor nodule in the majority of multifocal prostate cancer (88.7 %), and therefore, the concept of DN is valid in these patients. In these cases, DNs can be used to assign an overall GS and procure tissue for research. However, adverse pathological parameters (largest tumor volume, highest GS, and staging parameters) do not concur in the same tumor nodule in a significant number of cases (11.3 %). In these cases, pathologists should de-emphasize the DN concept, especially when the DN has a GS 6, and report the multifocality and the pathological features of all independent tumor foci.

Conflict of interest The authors declare that they have no conflict of interest.

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