Review Article

On cribriform prostate cancer

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Abstract: The management of newly diagnosed prostate cancer is challenging because of its heterogeneity in histology, genetics and clinical outcome. The clinical outcome of patients with Gleason score 7 prostate cancer varies greatly. Improving risk assessment in this group is of particular interest, as Gleason score 7 prostate cancer on biopsy is an important clinical threshold for active treatment. Architecturally, four Gleason grade 4 growth patterns are recognized: ill-formed, fused, glomeruloid and cribriform. The aim of this review is to describe the role of cribriform growth in prostate cancer with respect to diagnosis, prognosis and molecular pathology. Secondly, we will discuss clinical applications for cribriform prostate cancer and give recommendations for future research.

Keywords: Prostate; cancer; cribriform; pathology

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Introduction

The management of newly diagnosed prostate cancer is challenging because of its heterogeneity in histology, genetics and clinical outcome. Today, clinical-decision making mostly depends upon serum prostate specific antigen (PSA) level, clinical tumor stage, and pathologic biopsy Gleason score—a grading system based on architectural tumor patterns. While patients with the lowest Gleason scores ≤6 have an excellent outcome, those with the highest Gleason scores [9–10] have the worst (1).

The clinical outcome of patients with Gleason score 7 prostate cancer varies greatly. Improving risk assessment in this group is of particular interest, as Gleason score 7 prostate cancer on biopsy is an important clinical threshold for active treatment. The current broad definition of the Gleason grade 4 pattern may be one of the explanations for the variable outcomes of patients with Gleason score 7 prostate cancer. Architecturally, four Gleason grade 4 growth patterns are recognized: ill-formed, fused, glomeruloid and cribriform. The aim of this review is to describe the role of cribriform growth in prostate cancer with respect to diagnosis, prognosis and molecular pathology. Secondly, we will discuss clinical applications for cribriform prostate cancer and give recommendations for future research.

Prostate cancer grading by the pathologist: past and present

In 1966, Dr. Donald Gleason developed a histological classification of prostate cancer, which was solely based on its architectural pattern rather than cytological features (2). He distinguished five basic architectural patterns, numbered grade 1–5. Higher grades were considered to reflect more aggressive behavior. Because the majority of the prostate cancers showed more than one type of growth pattern, he suggested assigning two patterns to each case in the order of predominance. This grading system of Dr. Gleason was validated in 1974 and, after some modification

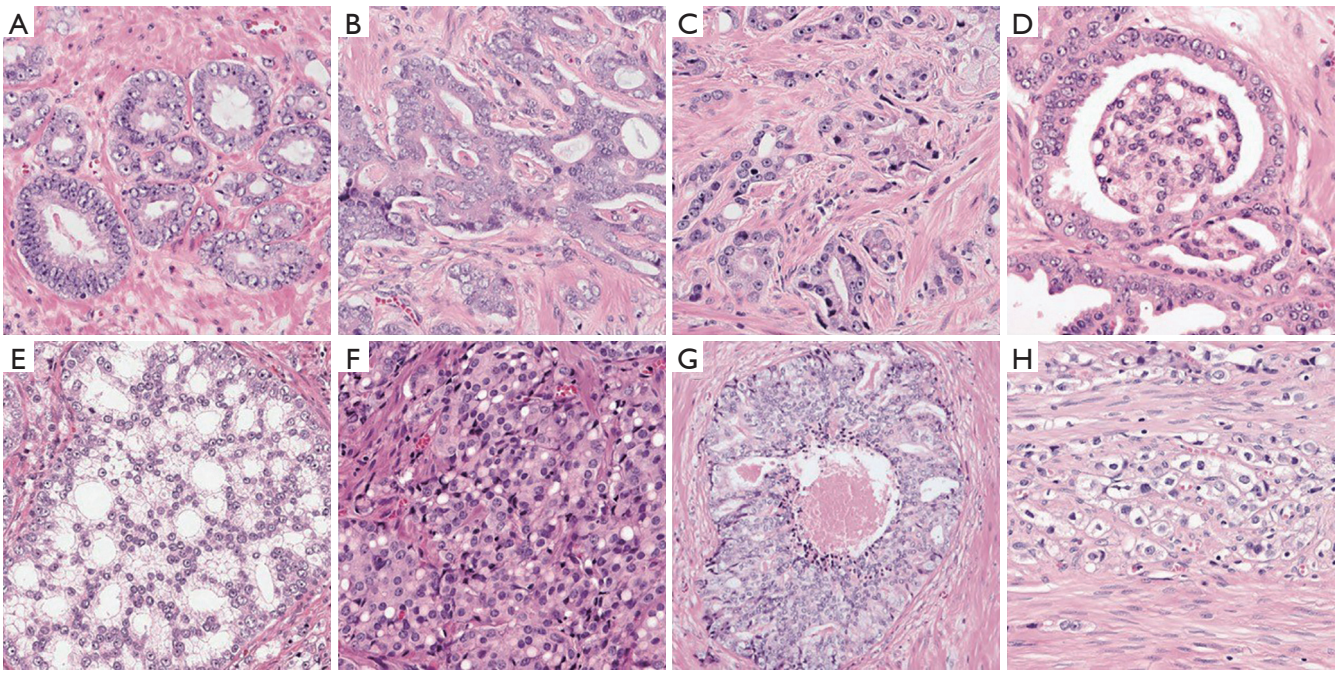

Figure 1 Contemporary Gleason grading patterns, hematoxylin and eosin stain, 200× magnification. (A) Well-delineated glands (Gleason grade 3); (B) fused pattern (Gleason grade 4); (C) ill-formed pattern (Gleason grade 4); (D) glomeruloid pattern (Gleason grade 4); (E) cribriform pattern (Gleason grade 4); (F) solid pattern (Gleason grade 5); (G) comedonecrosis (Gleason grade 5); (H) single cells (Gleason grade 5).

of the definitions, has since then received a worldwide acceptance (3). The Gleason score equals the sum of the two most common Gleason grades in radical prostatectomy, and, since 2005, the sum of the most common and highest Gleason grades in needle-biopsies (4). To date, the Gleason grading system is one of the most powerful predictors of outcome in prostate cancer. The Gleason grading system has undergone a major modification in 2005 and an additional minor one in 2014 during International Society of Urological Pathologists (ISUP) consensus conferences (1,4). Gleason patterns 1 and 2 are for instance no longer in use in biopsies and the current Gleason score 6 (3+3) of 10 is the lowest possible score. According to the ISUP 2014 consensus conference, Gleason grade 3 only comprises well-delineated malignant glands. At least four different growth patterns are recognized as Gleason grade 4: fused, ill-formed, glomeruloid and cribriform; while Gleason grade 5 includes solid sheets, comedonecrosis, single tumor cells and cords of tumor cells (*Figure 1*). Recently, the 5-tier prognostic grade grouping was introduced by the ISUP and recommended by the World Health Organization (WHO) (5). The grading system includes five distinct Grade Groups based on the modified Gleason score groups. Grade Group 1 = Gleason score ≤6, Grade Group 2 = Gleason score 3+4=7, Grade Group 3 = Gleason score 4+3=7, Grade Group 4 = Gleason score 8, Grade Group 5 = Gleason scores 9 and 10. Grade Grouping is not a novel grading system *per se*, but comprehensively distinguishes clinically significant patient cohorts.

The modifications of the Gleason grade have led to significant grade inflation (6,7). One group, for instance, reported a significant decrease in Gleason score 6 (3+3) tumors from 48% to 22% of cases, while score 7 (3+4 and 4+3) tumors increased from 26% to 68% (8). We believe that this relative increase is strongly associated with the inclusion of ill-formed glands as a Gleason grade 4 pattern since 2005. This pattern is, however, poorly reproducible among pathologists (9-14). Reproducibility in recognizing Gleason pattern 4 prostate cancer on needle biopsy is most critical for clinical decision-making. In general, patients with Gleason score 6 on needle biopsy do not need immediate treatment and are often candidates for active surveillance. While patients with modified Gleason score 6 on radical prostatectomy represent a group with excellent outcome, patients with Gleason score 7 demonstrate a wide range in clinical outcome. A significant proportion

of Gleason score 7 men may also be candidates for active surveillance. Risk stratification within the Gleason score 7 patient population remains, however, a challenge, and additional prognostic factors are urgently needed. This review specifically focuses on a specific histologic growth pattern prostate cancer, namely cribriform (*Figure 1E*).

Cribriform prostate cancer

Our group has previously found that presence of cribriform growth in radical prostatectomy specimens is a major predictive factor for distant metastasis and disease-specific death of prostate cancer in Gleason score 7 patients (15). In fact, cribriform growth was the strongest predictor of both adverse clinical events after surgical treatment in multivariable analysis, adjusted for other relevant clinicopathologic variables, such as age, PSA, Gleason score and pT stage (15). In the past years several other groups using different patient cohorts and various clinical endpoints additionally validated the association of cribriform growth with adverse outcome (16-22). We subsequently validated the independent prognostic value of cribriform growth in diagnostic needle biopsies using strong clinical endpoints. Importantly, we found that patients with Gleason score 3+4=7 without cribriform growth on diagnostic biopsy have similar patient outcomes as those with Gleason score 3+3=6, implying these patients may be potential candidates for active surveillance as well (23,24).

The cribriform pattern shows good interobserver reproducibility among pathologists, while patterns such as fused and ill-formed Gleason grade 4 are poorly reproducible (14). Another study showed that the percentage of fused and ill-formed glands was inversely correlated with agreement among pathologists, whereas the cribriform pattern had no significant correlation with interobserver variability (25). This supports the hypothesis that cribriform growth might be a valuable additional parameter in selecting patients for active surveillance.

Molecular pathology of cribriform prostate cancer

We subsequently demonstrated that cribriform prostate cancer is associated with increased genomic instability showing chromosomal deletions of 3p13, 6q15, 8p21-23, 10q23, 13q14, 16q21-24, 18q21-23, and amplification of 8q24 (*unpublished data*). The genetic losses and amplifications included several genes related to aggressive prostate cancer such as loss of *PTEN*, *RB1*, *TP53* and amplification of *MYC*. Our findings are in line with previous studies on genetic abnormalities related to cribriform and/or intraductal carcinoma using comparative genomic hybridization. Two studies observed more frequently loss of heterozygosity (LOH) in IDC than in the invasive prostate cancer component (26,27). Qian *et al.* showed gain of chromosomes 7, 12, and Y, loss of chromosome 8, and amplification of *c-MYC* in cribriform cancer compared to other Gleason grade 3 and 4 patterns (28). The latter three studies, however, contained small sample sizes, while our current study included a large number of patients. (*unpublished data*) In a meta-analysis on recurrent CNAs, Williams *et al.* compared 568 primary prostate cancer tumour samples from eight previous studies with 115 metastatic prostate cancer samples from five studies (29).

Remarkably, the prevalence of recurrent CNAs in metastatic prostate cancers corresponded with the CNAs found enriched in cribriform prostate cancer, such as *PTEN* and *NKX3-1*. More recently, using break-points regions to infer phylogenetic relationships, Lindberg *et al.* showed that the clone closely related to the distant metastasis was found in intraductal carcinoma that had cribriform architecture (30). Altogether, these findings further support a strong association of cribriform growth with molecular tumor progression. Vice versa, we did not find a statistically significant difference in genetic abnormalities between Gleason score 3+4=7 without cribriform growth and Gleason score 6 cases, supporting the notion that it is clinically relevant to distinguish cribriform-negative Gleason score 3+4=7 from Gleason score 3+3=6.

What about the other grade 4 patterns?

After the ISUP consensus conference in 2005, ill-formed (or poorly formed) glands were considered a Gleason grade 4 pattern (4). The authors additionally recommended that high-grade tumor of any quantity on needle biopsy should be included within the Gleason score. Thus, a needle biopsy that is involved by cancer with 98% Gleason pattern 3 and 2% Gleason pattern 4 would be diagnosed as Gleason score 3+4=7. The Gleason score system modification in 2005 led to a significant grade inflation, i.e., a decline in reported incidence of Gleason score 6 tumors and relative increase of Gleason score 7 tumors. The modification resulted in better clinical outcomes in both patient populations, a statistical artifact also known as the Will-Rogers phenomenon (6,31). Patients with Gleason score 6 prostate cancer are

considered candidates for active surveillance, whereas patients with Gleason score 7 generally undergo therapeutic intervention (32). Others and we have shown that the ill-formed pattern has a considerable intra- and interobserver variability among pathologists (9-14,33). This poorly reproducible pathologic variable is nonetheless an important clinical decision point for many patients. As a matter of fact, no studies to date have specifically validated the adverse prognostic value of the ill-formed pattern and its role in active surveillance enrolment of patients with prostate cancer. Zhou *et al.* recently suggested that adjacent tumour glands play an important role in decision-making in cases showing ambiguous ill-formed patterns (13). The authors recommend that >10 poorly formed glands not immediately adjacent to other well-formed glands should be considered to represent ill-formed Gleason pattern 4. In contrast, poorly formed glands that are intermixed with well-formed glands, or ≤5 poorly formed glands, regardless of their location, should be diagnostic features arguing against Gleason pattern 4. Although such criteria seem reasonable, they are—like many previous studies on the distinction of well-formed pattern 3 glands versus ill-formed pattern 4 glands—not based on clinical outcome data. Secondly, and perhaps more importantly, as demonstrated by Labov's linguistic work, endeavors to set a classification threshold for categories along a continuum leads to significant problems with category reproducibility (34). The ill-formed pattern is poorly reproducible and we agree with McKenney *et al.* that the specific histologic assessment of "ill-formed glands" will never reach a high level of diagnostic reproducibility for any group of pathologists, regardless of more specific criteria or increased education (21). We therefore believe that the ill-formed pattern itself should not be a criterion to exclude a patient from active surveillance, as the higher Gleason score most likely reflects a change in grading practice rather than tumor biology.

In 2009, Lotan *et al.* were the first to our knowledge to publish a paper on grading prostate cancer with glomeruloid features (35). In this study the authors claimed that the glomeruloid pattern is strongly associated with high-grade prostate cancer on the same biopsy core (36/45, 80%). Based on the observation that in several cases a transition could be seen among small glomerulations, large glomeruloid structures, and cribriform pattern 4 cancer, the authors additionally suggest that glomerulations represent an early stage of invasive cribriform cancer and are best graded as Gleason pattern 4. These observations lay the foundation for the current ISUP recommendations, which recommend that glomeruloid glands should be assigned a Gleason pattern 4, regardless of morphology (1,35). No clinical outcome data was, however, available from the study by Lotan *et al.* (35). Although their suggestion regarding grading seems both plausible and pragmatic, others and we could not find an association between glomeruloid and cribriform glands or high-grade cancer (15,22). Moreover, both our studies found that presence of glomeruloid glands is independently associated with a better outcome of Gleason score 7 prostate cancer in multivariable analyses, which contradicts the idea that glomeruloid glands represent a precursor lesion of an aggressive cancer type. McKenney *et al.* could also not find an association between glomeruloid glands and outcome (21). We believe that the smaller glomerulations surrounded by well-formed pattern 3 glands are more likely to show more indolent behavior than those transitioning to large glomerulations and/or cribriform glands. Interestingly, in our interobserver reproducibility study on Gleason grade 4 patterns we found that there is good interobserver reproducibility of small glomeruloid glands, but less in large glomeruloid glands as half of the observers considered these cribriform (14). Similar to the semantics in well-formed glands and ill-formed glands, there seems be a continuum in morphology of large glomeruloid and cribriform glands. The biology of glomeruloid glands, let alone their pathological meaning, remains unknown.

Intraductal carcinoma of the prostate

In recent years the clinical significance of intraductal carcinoma of the prostate—a morphological mimicker of invasive cribriform carcinoma—has been acknowledged. The current concept is that it represents divergent differentiation of a common precursor that either spreads invasively or via pre-existing ducts (36). Although not included in the Gleason grading system, intraductal carcinoma has been associated with Gleason grade 4 and 5 patterns, advanced tumor stage, biochemical recurrence and distant metastasis (37-42). While invasive cribriform carcinoma and intraductal carcinoma are strictly speaking two different pathologic entities, they morphologically mimic each other closely and it is likely they relate and exist on a pathological and biological continuum (43,44). In our studies we noticed in the majority of cases that both entities co-exist in the same tumor, which is in line with the current concept on cribriform and intraductal carcinoma (15,23,36). Intraductal carcinoma may represent

spread of high-grade prostate cancer into pre-existing ducts using these natural passages as low-resistance highways of rapid growth (26,43,45). On the other hand, invasive cribriform glands could also represent invasion of intraductal carcinoma into surrounding tumor glands. It should be kept in mind that lack of basal cells is not pathognomonic of invasive cribriform cancer as basal cells can be scattered and not visible in a particular slide. To date, little is known about how, for instance, intraductal carcinoma transitions to invasive cribriform cancer on a molecular and three-dimensional level. Are gland size or specific stroma-epithelial interactions creating a complex anastomosing network of tumor glands? In fact, we do not know what drives the formation of cribriform tumor glands and what possible biological advantage this morphology offers to a tumor. Although we find several genetic abnormalities associated with cribriform growth in prostate cancer, it remains unclear how the phenotype and genotype interact.

Percentage Gleason grade 4

Recent literature has suggested that quantifying the percentage of Gleason grade 4 may be a more useful tool for risk prediction (46-48). Although most Gleason score 3+4=7 disease are recommended to undergo active treatment, selected low-volume Gleason score 3+4=7 patients could be considered for active surveillance. Recent guidelines recommend that patients with low-volume Gleason score 3+4=7 should only be considered for active surveillance if there is focal presence of Gleason grade 4, i.e. accounting for 10% of the total tumor volume (49). Based on our study, higher Gleason grade 4 percentages are often associated with presence of cribriform tumor glands (50). Since in our study percentage Gleason grade 4 was inferior to presence of cribriform growth with regard to predicting patient outcome in a multivariable model, the quantifying approach does, to our opinion, not really offer a solution. Determining the Gleason grade 4 percentage greatly depends on core length and interobserver variability of high-grade patterns that are poorly reproducible. Although quantification of Gleason grade 4 percentage seems an objective tool, it is more likely a semblance of precision. We therefore endorse a more practical approach by establishing the presence of cribriform tumor glands, which is a reproducible qualitative pathologic feature instead of inherently imprecise quantification of growth pattern.

Correlation with radiology

As multiparametric magnetic resonance imaging (mpMRI) of the prostate progresses, better correlation with histology could possibly lead to pre-biopsy identification of cribriform tumor glands and at the same time used as a triage test to avoid unnecessary biopsies. To date, only two recently published studies have looked into the histologic correlation between MRI findings and cribriform growth, but they show conflicting results (51,52). However, as more research groups are becoming aware of the potential clinical relevance of cribriform prostate cancer, we expect that future MRI-correlation studies will give a better view on the pathologic-radiologic correlation.

Risk prediction

Previous studies have shown that the risk calculator number 3 (RC3) of the European Randomized Study of Screening for Prostate Cancer (ERSPC; www.erspc.org) based on the Rotterdam cohort is an adequate risk-stratifying tool in men before prostate biopsy (53-55). The RC3 uses pre-biopsy information such as PSA, digital rectal examination outcome and prostate volume to predict the probability of a biopsy-detectable prostate cancer and/or presence of Gleason score 3+4=7 cancer or higher. The current definition of clinically significant prostate cancer is, however, largely based on the presence of any amount of grade 4. We therefore suggest to include cribriform growth in a risk calculator as the parameter for clinically significant Gleason score 3+4=6 prostate cancer. Presence of other grade 4 patterns would then be acceptable. In a recent study we aimed to improve the RC3 by inclusion of cribriform pattern in the definition of clinically significant prostate cancer. Using cribriform-specific information we found that 10% of the patients that were initially considered of having low-risk prostate cancer were upgraded to high-risk prostate cancer, and vice versa 33% were downgraded (56). Incorporating cribriform-specific information could aid in the decision whether or not to do an MRI or biopsy. To date, Gleason score 7 has been used as an important clinical endpoint in many studies, and sometimes even defined as "high-risk disease", while it appears to be a rather subjective variable with doubtful clinical relevance. We therefore recommend including presence of cribriform growth in studies using Gleason score 7 cancer as an outcome measure, since this variable seems more reproducible and clinically relevant.

Identifying therapeutic targets

As described previously, cribriform prostate cancer is associated with an adverse outcome. Prognostic value does, however, not equal predictive value. In fact, we know little about the role of cribriform growth as a predictive marker for response to androgen-deprivation therapy or chemotherapy. Also, little is known about how cribriform tumors respond to radiotherapy. Interestingly, one recent study using patient-derived xenografts of patients with advanced prostate cancer has demonstrated that intraductal carcinoma lesions are more likely to persist after androgen deprivation therapy (57). Further understanding of the biology of cribriform growth may translate into preclinical studies to find effective therapeutic drugs for recurrent or metastatic cribriform prostate cancer.

Comprehensive genomic analysis of cribriform prostate cancer

Our study on copy number variations and genomic instability in cribriform prostate cancer is just a mere start to what can be explored (*unpublished data*). Further and more comprehensive studies including, for instance, transcriptomic and epigenomic data are needed to acquire a better understanding of cribriform growth in prostate cancer. *In situ* hybridization experiments could further elucidate whether specific copy number variations or differentially expressed genes are limited to the cribriform tumor glands or also seen in the surrounding tumor glands. Molecular studies could also give more insight into the differences between invasive and intraductal cribriform prostate cancer.

Biology of cribriform morphology

Cribriform morphology is not only seen in prostate adenocarcinoma, but in many other adenocarcinomas of various organs. By studying adenocarcinomas with cribriform morphology from different organs, we might find a common genetic denominator. Cribriform adenocarcinomas of the lung, stomach and colon are also associated with an adverse outcome, while cribriform adenocarcinomas of the breast and thyroid have an excellent outcome (58-63). According to the molecular classification of breast cancer, invasive cribriform carcinoma is mainly of the luminal A-type, as estrogen and progesterone receptors are positively immunoexpressed, while negative for increased expression and/or amplification of Her2 receptor (59). In lung cancer, Mackinnon *et al.* was unable to find a specific molecular signature for cribriform predominant carcinomas, whereas Warth *et al.* showed high rates of KRAS mutations, but none in EGFR (61,64). In micro-satellite unstable colon cancers, Kim *et al.* found an association between adverse outcome and cribriform morphology (62). In thyroid cancer, both the prognosis as well as the molecular alterations (i.e., presence of RET/PTC translocation, and no BRAF mutations) are similar to those discovered in conventional papillary thyroid carcinoma (60). Based on these findings, none of these cribriform tumors share a common genetic denominator, but they show aberrations seen in other adenocarcinoma subtypes in the same organ. However, data containing comprehensive description of genomic, transcriptomic and epigenomic changes in numerous different tumor types and/or subtypes are now increasingly available online, some of which also containing digital histological slides. Similar to what we have done in our study, all adenocarcinomas with cribriform morphology could easily be scored by pathologists and compared to each other.

Urine-based molecular diagnostics

No matter how many prostate needle biopsies are taken, there is always a risk of sampling error. If we could identify specific genetics events for cribriform prostate cancer, we could intercept the biopsy sampling error by analyzing the patient's urine. The prostate glands drain in the urethra prostatica. We therefore hypothesize that genetic material from cribriform prostate cancer that has been spread in preexisting ducts (intraductal carcinoma) can be more easily detected in voided urine than the genetic material from invasive tumor glands. From the latter we do not know if and how they are connected to the urethra prostatica. Voided urine is increasingly being used urological cancer diagnostics by measuring cancer-associated proteins, RNA transcripts, and methylation (65). Sample collection of urine is non-invasive and patient friendly. Although using copy number variation analysis may be suboptimal due to contamination with normal diploid cells from the urothelium and benign prostate epithelium, further studies on transcriptomics and epigenomics might reveal interesting candidate genes that can be more easily detected in urine.

Three-dimensional imaging

Histology is two-dimensional, while tumors grow three-dimensionally. Histology cannot provide a clear understanding on how glands in adenocarcinomas connect to each other. A three-dimensional approach might thus be interesting. In one study we, for instance, found that ill-formed glands are actually thinner versions of well-delineated glands, forming a similar kind of anastomosing network (66). Fused glands are also rather similar to grade 3 glands, but contain more intertwining connections. Little is known about the three-dimensional relation between various types of prostate cancer growth patterns. Since the disease is so heterogeneous and complex to understand, this might be a worthwhile avenue to explore.

Final recommendations

- Ask your pathologist to specifically report the presence of cribriform growth in the pathology report.
- Consider using cribriform growth as an exclusion criterion for active surveillance in Gleason score 3+4=7 patients.

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Footnote

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