Reporting Trends, Practices, and Resource Utilization in Neuroendocrine Tumors of the Prostate Gland: A Survey among Thirty-Nine Genitourinary Pathologists

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Abstract

Background: *Neuroendocrine differentiation in the prostate gland ranges from clinically insignificant neuroendocrine differentiation detected with markers in an otherwise conventional prostatic adenocarcinoma to a lethal high-grade small/large cell neuroendocrine carcinoma. The concept of neuroendocrine differentiation in prostatic adenocarcinoma has gained considerable importance due to its prognostic and therapeutic ramifications and pathologists play a pivotal role in its recognition. However, its awareness, reporting, and resource utilization practice patterns among pathologists are largely unknown.* ***Methods:*** *Representative examples of different spectrums of neuroendocrine differentiation along with a detailed questionnaire were shared among 39 urologic pathologists using the survey monkey software. Participants were specifically questioned about the use and awareness of the 2016 WHO classification of neuroendocrine tumors of the prostate, understanding of the clinical significance of each entity, and use of different immunohistochemical (IHC) markers. De-identified respondent data were analyzed.* ***Results:*** *A vast majority (90%) of the participants utilize IHC markers to confirm the diagnosis of small cell neuroendocrine carcinoma. A majority (87%) of the respondents were in agreement regarding the utilization of type of IHC markers for small cell neuroendocrine carcinoma for which 85% of the pathologists agreed that determination of the site of origin of a high-grade neuroendocrine carcinoma is not critical, as these are treated similarly. In the setting of mixed carcinomas, 62% of respondents indicated that they provide quantification and grading of the acinar component. There were varied responses*

regarding the prognostic implication of focal neuroendocrine cells in an otherwise conventional acinar adenocarcinoma and for Paneth cell-like differentiation. The classification of large cell neuroendocrine carcinoma was highly varied, with only 38% agreement in the illustrated case. Finally, despite the recommendation not to perform neuroendocrine markers in the absence of morphologic evidence of neuroendocrine differentiation, 62% would routinely utilize IHC in the work-up of a Gleason score 5 + 5 = 10 acinar adenocarcinoma and its differentiation from high-grade neuroendocrine carcinoma. ***Conclusion:*** *There is a disparity in the practice utilization patterns among the urologic pathologists with regard to diagnosing high-grade neuroendocrine carcinoma and in understanding the clinical significance of focal neuroendocrine cells in an otherwise conventional acinar adenocarcinoma and Paneth cell-like neuroendocrine differentiation. There seems to have a trend towards overutilization of IHC to determine neuroendocrine differentiation in the absence of neuroendocrine features on morphology. The survey results suggest a need for further refinement and development of standardized guidelines for the classification and reporting of neuroendocrine differentiation in the prostate gland.*

Keywords

neuroendocrine tumor, prostate gland, survey, small cell carcinoma, large cell carcinoma

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Introduction

Neuroendocrine differentiation in the prostate gland encompasses various entities, ranging from the presence of focal neuroendocrine cells in an otherwise conventional acinar adenocarcinoma to a small cell or large cell neuroendocrine carcinoma.[1–5] Neuroendocrine neoplasms of the prostate occur in two settings: de novo disease (in a treatment-naïve setting) or as a post-therapy transdifferentiated phenotype of a typical adenocarcinoma (Figure 1). Moreover, neuroendocrine neoplasm of the prostate gland represents a rare subtype of prostatic malignancies,[2–5] the most common by far being a small cell neuroendocrine carcinoma and mixed small cell and acinar adenocarcinoma.[3–5] It is estimated that up to 10% of PC patients with the androgen-resistant disease following long-term androgen deprivation therapy (ADT), develop high-grade neuroendocrine carcinoma, mostly associated with acinar adenocarcinoma.[2–5] With the continual clinical and molecular data emerging from the study of PC treated with contemporary ADT, there has been a steady attempt to refine the terminology for neuroendocrine lesions in the prostate gland.[2,5,6] The WHO Classification 2016 is an excellent framework, classifying these entities into five distinct subgroups: neuroendocrine cells in the usual prostate cancer; adenocarcinoma with Paneth cell-like differentiation; well-differentiated neuroendocrine tumor; small cell neuroendocrine carcinoma; large cell neuroendocrine carcinoma. This classification is based solely on histomorphology and immunohistochemical (IHC) studies.[7] Despite this classification, several issues still persist on a practical level with regard to certain entities like Paneth cell-like change, which could be a potential area of uncertainty and could be misinterpreted as a high-grade neuroendocrine carcinoma or pattern 5 adenocarcinoma.[7–10] Besides, there also exist a group of tumors, that do not clearly fit into the proposed WHO groups that show morphology neither classical for a high-grade acinar adenocarcinoma nor small cell neuroendocrine carcinoma /large cell neuroendocrine carcinoma; however, they express prostatic and neuroendocrine markers (often diffuse).[10] Pathologists play a crucial role in the process that leads to therapeutic decision-making and further prognostication of these patients. This is especially true when a diagnosis of neuroendocrine differentiation is made on needle core biopsies, as there is significant therapy-related difference when compared to the usual type of prostatic adenocarcinoma.[3] Additionally, there is inconsistency in identification and reporting, as well as non-uniformity in the utilization of the IHC.[5–7,10] This prompted us for a practice defining research with a multi-institutional survey across the globe to assess the reporting trends and practices among the genitourinary (GU) pathologists.

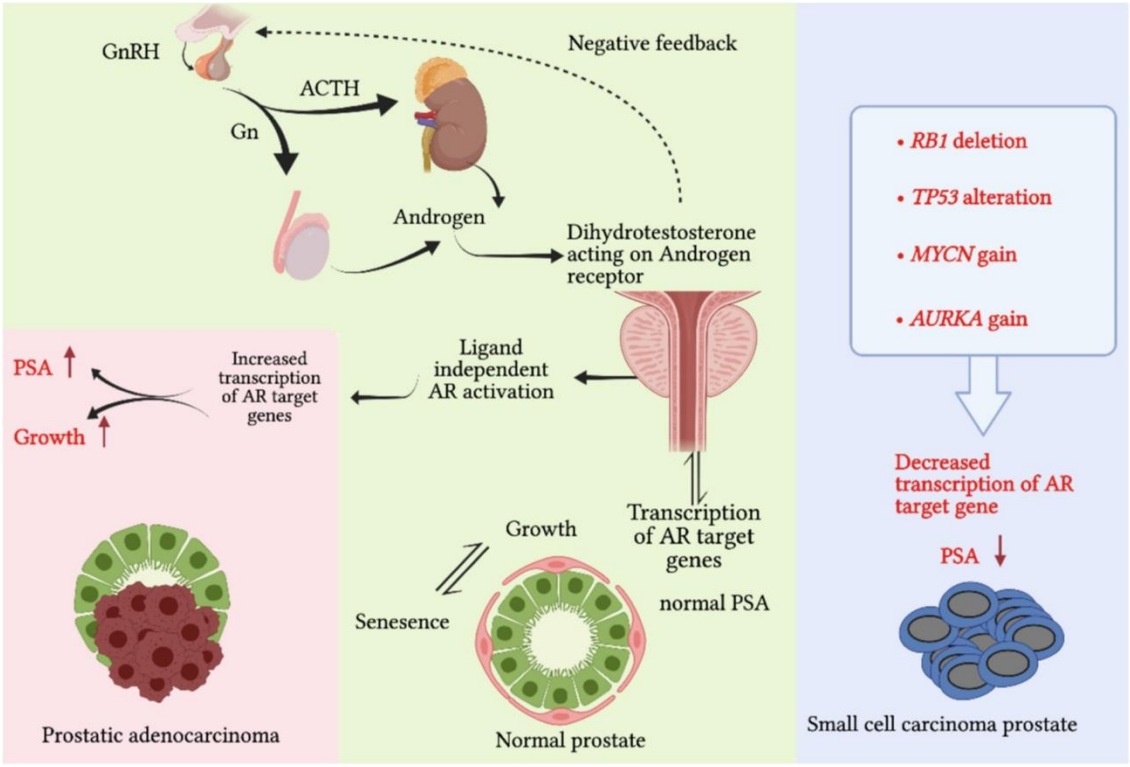

Figure 1. Possible pathogenic mechanism of the neuroendocrine differentiation and androgen-independence in prostate cancer by transdifferentiation. The proliferation of the prostatic acini is a strictly controlled mechanism with feedback inhibition from dihydrotestosterone modulating the release of gonadotropin releasing hormone (GnRH) from the hypothalamus and gonadotrpin (Gn). GnRH stimulates the release of luteinizing (LH, a Gn) and adrenocorticotropic hormones (ACTH) from the pituitary gland.[11] LH acts on the leydig cells of the testis to release testosterone, which acts on the androgen receptors to produce growth factors for prostate. ACTH acts on the zona reticularis of the adrenal glands and produces weak-acting androgens known as dehydroepiandrosterone and androstenedione. They bind to androgen receptors with weaker affinity but can also be converted to testosterone in the peripheral tissues if produced at high amounts.[12] Dysregulation of this mechanism in any form either gain of function of AR or other causes of increased transcription of growth factors leads to prostatic adenocarcinoma. On the other hand oncogenetic aberrancies such as *RB1* deletion, *TP53* alteration, or *MYCN* gain-of-function mutation/*AURKA* gain-of-function mutation leads to decreased transcription of AR target genes with the development of small cell carcinoma prostate.[13] Abbreviations: AR, Androgen Receptor; *RB1*, Retinoblastoma gene; *AURKA*, Aurora Kinase A.

Material and Methods

This study was conducted after approval from the institutional review board. A questionnaire and scenario-based survey was carried out among the GU pathologists on their reporting trends, practices, and appropriate resource utilization in reporting neuroendocrine tumors of the prostate gland. An online survey containing 25 questions including images related to the various entities described in WHO 2016 was prepared by two of the authors (SKM and JD) and circulated among 47 GU Pathologists across four continents (Supplement 1).The images provided in the survey were selected by the survey authors (SKM and JD) those that they felt would best describe the entity in the question. There were 15 questions related to WHO categories; 6 related to IHC; 1 question each related therapy and indication of biopsy in a

metastatic castrate-resistant cancer. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent was obtained from the pathologists through e-mails and the intended use of the data was explained. The pathologists were given the option of authorship at the onset of the survey and were given the option to withdraw participation at any time including at the completion of the survey or afterward. Each participant was grouped based on their practicing experiences in years as <10 years, >10 years and >20 years. Specific questions were included as to whether, when, and how the respondents would classify the image-based entity as follows: Paneth cell-like differentiation; neuroendocrine carcinoma (small and large cell); high-grade prostatic adenocarcinoma. The requirement, usage frequency, and indications of IHC (neuroendocrine, prostatic lineage-associated, and androgen receptor [AR]), therapy- and biomarker-related variables with respect to these entities were also included in the survey. Analyses of the survey responses were carried out using the SurveyMonkey software (www.surveymonkey.com; SurveyMonkey, Santa Clara, CA, USA). The software was used to enter the questions and multiple choices were provided for each question. Respondents were asked to choose the best possible answer based on their practice and recommended guidelines. De-identified and anonymized respondent data was tabulated and analysed by routine statistics. The responses were scored as a percentage for each question, tabulated, and accordingly assessed to record and evaluate the existing reporting practices.

Results

Thirty-nine (83%) participants completed the survey and 38 pathologists were included in the study including the two survey authors (SKM and JD). One participant completed the survey and provided manuscript feedback but asked to be excluded from authorship. Participants represented Asia (n = 22; 56%); North America (n = 15; 38%); Europe (n = 1; 3%); Australia (n = 1; 3%) (Question #2). Eight (21%) of the participants had <10 years experience; 11 (28%) participants had 10-20 years of practice experience and 20 (51%) had >20 years experience in reporting GU pathology cases (Question #1).

Normal Histologic Distribution of Neuroendocrine Cells in the Prostate Gland

Focal neuroendocrine cells are widely distributed within the epithelium of the prostate gland in all anatomic zones.[5–7] They are not readily recognizable on H&E-sections; however, they can be identified when they are present as round to cuboidal cells between the secretory and basal cells with granular eosinophilic cytoplasm. These cells typically do not extend to the lumen but often have narrow apical and lateral dendritic extensions. A subset of respondents (n = 15; 38%) agreed that neuroendocrine cells are readily recognizable between the basal cells and the secretory cells on H&E-stained sections and contain Paneth cell granules, while 11 (28%) pathologists indicated that neuroendocrine cells do not contain Paneth cell granules and therefore are not readily visible on H&E-stained sections. Seven (18%) participants indicated that neuroendocrine cells are neither visible on routine histology, nor do they contain Paneth cell granules or extend into the lumen. Four (10%) indicated that the prostate gland would contain the least number of neuroendocrine cells among the GU organs. Of note,

2 (6%) pathologists indicated that prostatic markers such as NKX3.1 and AR could be used to delineate the presence of neuroendocrine cells (Question #3).

Histopathologic Classification of Neuroendocrine Neoplasm

Neuroendocrine Cells in Usual Prostate Cancer

We asked the participants whether they would routinely perform IHC markers for neuroendocrine cells in all prostatic adenocarcinomas. Twenty-six (67%) agreed that they would do this, whereas 13 (33%) would not do it routinely (Question #4).

Adenocarcinoma with Paneth Cell-Like Neuroendocrine Differentiation

Most of the respondents (n = 33; 84%) recognized a provided example of adenocarcinoma with Paneth cell-like neuroendocrine differentiation, however there was no consensus among group regarding the Gleason score (GS) of the case included in the survey, with 20 (51%) pathologists scoring it as GS 4 + 3 = 7 (Grade Group 3) and 13 (33%) scoring it as a GS 3 + 4 = 7 (Grade Group 2) (Figure 2). Two (4%) pathologists identified this lesion as conventional prostatic adenocarcinoma and a single (3%) participant categorized the lesion as a pure neuroendocrine carcinoma. Twenty-two (56%) pathologists would have performed neuroendocrine markers in this case (Question #8,9). With regard to the prognostic implication of identifying Paneth cell-like neuroendocrine differentiation in prostatic adenocarcinoma, 13 (33%) pathologists considered this feature of no prognostic significance, and another 13 (33%) indicated that this morphologic feature would confer a worse prognosis. Eight (21%) suggested that this feature would have a better prognosis, whereas 5 (13%) were not familiar with the specific prognostic impact (Question #10). With respect to the clinical and pathologic features of this entity the responses were as follows. Twelve (32%) answered that the proliferation index of this entity was low, while 2 (5%) participants responded that this entity has a high proliferative index. Four (11%) had the opinion that conspicuous nucleoli and granular eosinophilic cytoplasm were the morphologic features of this lesion. Three (8%) pathologists believed that this entity should not be graded. Three (8%) respondents felt the requirement of IHC in the diagnosis of this lesion. The remaining 14 (36%) pathologists chose a combination of the above aspects to best describe this entity (Question #11).

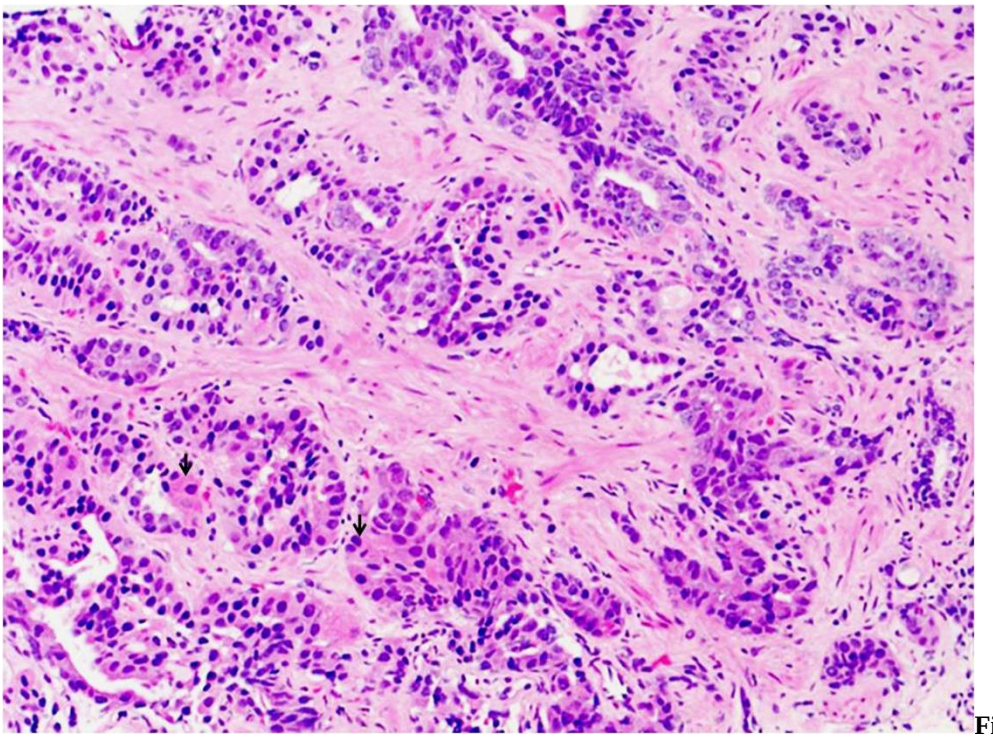

Figure 2. An example of prostatic adenocarcinoma with Paneth cell-like neuroendocrine differentiation (original magnification, ×200 hematoxylin and eosin).

Well Differentiated Neuroendocrine Tumor (Carcinoid Tumor)

Regarding the clinicopathologic features of this lesion, varied responses were obtained. While 16 (41%) pathologists responded that the serum prostate specific antigen (PSA) may be positive in a subset of cases, 13 (33%) had the opinion that this lesion should not be associated with concomitant acinar adenocarcinoma, 8 (21%) believed that this lesion arises from the prostatic parenchyma, and 2 (5%) indicated that Ki-67 proliferation index of this lesion would be low (Question #12).

High-Grade Neuroendocrine Carcinoma-Small Cell Carcinoma

Two-thirds of the participants (n = 25; 64%) interpreted a provided case as small cell neuroendocrine carcinoma, whereas 10 (26%) classified the tumor as a mixed neuroendocrine carcinoma-acinar adenocarcinoma (Figure 3) (Question #13). Only 4 of the 39 (10%) participants considered morphology alone to be sufficient to identify the lesion, while 35 (90%) participants would prefer using IHC. Combinations of markers preferred were as follows. Twenty-four (64%) pathologists would apply neuroendocrine markers, AR, thyroid transcription factor-1 (TTF1), and NKX3.1. Of the remaining, 4 (11%) uropathologists would use neuroendocrine markers alone, 3 (8%) would use neuroendocrine markers with TTF1, and another 3 (8%) would use neuroendocrine markers with AR (Question #14). Twenty-nine (74%) pathologists identified small cell neuroendocrine carcinoma by its histologic features and were of the consensus that open chromatin and prominent nucleoli would argue against the diagnosis of a small cell neuroendocrine carcinoma. Three (8%) participants believed the presence of small nucleoli would disregard the diagnosis of a small cell neuroendocrine carcinoma (Question #16). Regarding the setting of small cell neuroendocrine carcinoma, 28 (72%) participants indicated that it is usually seen following long-standing ADT, and 6 (15%)

suggested that this entity could also arise in a de novo treatment-naïve setting. Four (10%) pathologists concluded that this entity would be diagnosed at a metastatic location and 1 (3%) participant concluded that this morphology would be seen following ADT (Question #15). We included a question based on the clinicopathologic features of small cell neuroendocrine carcinoma and the responses were as follows: 2 (5%) indicated that de novo tumors are rare and should be treated aggressively; 2 (5%) indicated that serum PSA levels would be low and the tumor is associated with weak to absent ERG expression; 3 (8%) indicated that this tumor would be seen in the long standing ADT, metastatic, or castrate-resistant setting; 1 (3%) specified that DNA mismatch repair gene mutations and small cell histology are mutually exclusive of each other; 22 (56%) chose a combination of all the above statements to best describe this lesion; 9 (23%) selected from a combination of the remaining options consisting of it being essential to establish a prostatic or extraprostatic origin of the tumor, DNA repair mutations and small cell histology being mutually inclusive of each other, and serum PSA level being usually very high with higher expression of ERG and high level amplification for *TMPRSS2-ERG* fusion signals by FISH (Question #17).

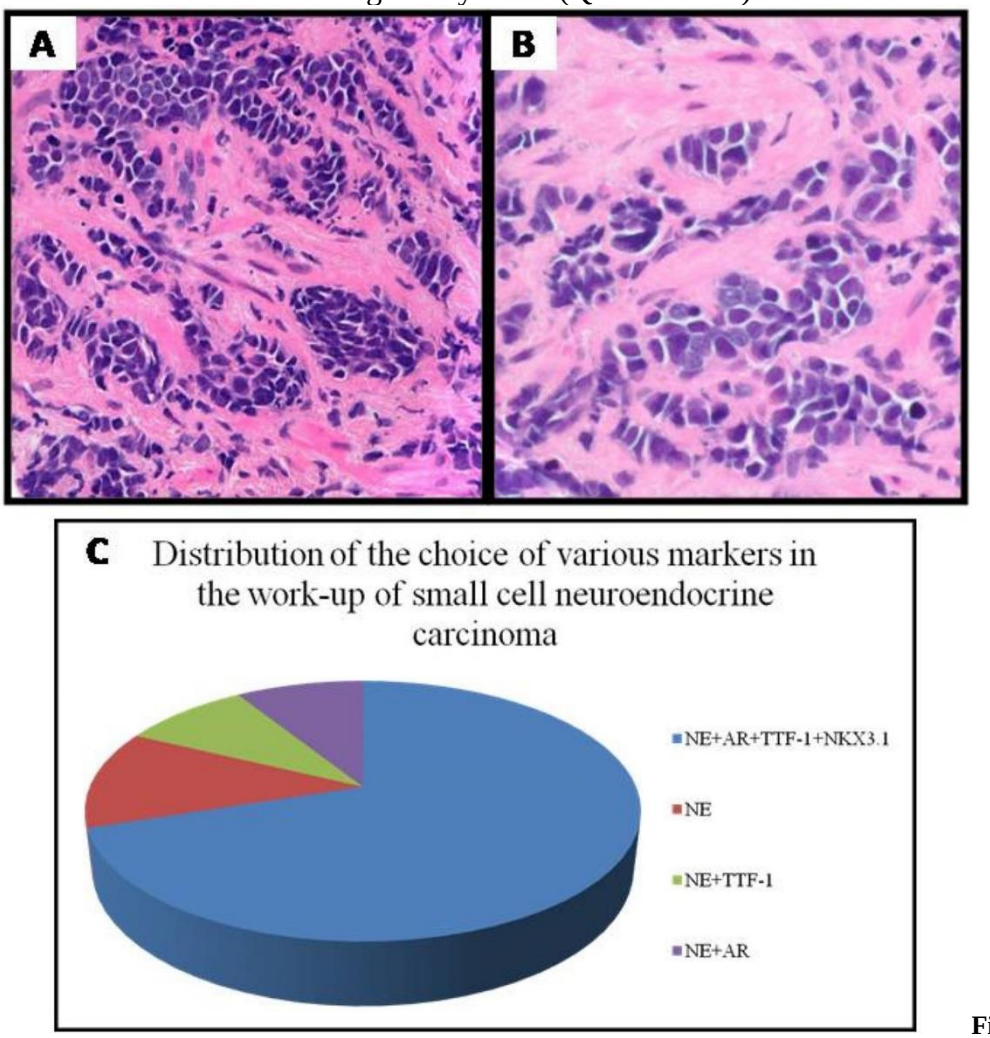

Figure 3. A and B: An example of prostatic small cell neuroendocrine carcinoma (A, original magnification, ×200 hematoxylin and eosin; B, original magnification, ×400 hematoxylin and eosin); C: A pie-chart showing the the distribution of choice immunostains in the work-up of small cell

neuroendocrine carcinoma by the pathologists. Abbreviations: NE, Neuroendocrine; AR, Androgen receptor; TTF1, Thyroid transcription factor.

High-Grade Neuroendocrine Carcinoma-Large Cell Carcinoma

For an example case intended to show large cell neuroendocrine carcinoma, responses were varied, including: large cell neuroendocrine carcinoma (n = 15; 38%); mixed neuroendocrine carcinoma -acinar adenocarcinoma (n = 11; 28%); high-grade Gleason score 10 acinar adenocarcinoma (n = 9; 24%); and small cell neuroendocrine carcinoma (n = 4;10%) (Figure 4) (Question #18). Twenty-seven respondents (69%) would utilize both prostatic and neuroendocrine markers (PSA, NKX3.1, AR, synaptophysin, chromogranin, and CD56) to confirm the diagnosis. Seven (18%) would opt for the same panel minus chromogranin, 3 (8%) would only use neuroendocrine markers, and the remaining 2 (5%) pathologists would not require IHC for the diagnosis (Question #19). Regarding the setting of large cell neuroendocrine carcinoma, 23 (62%) respondents concluded that it was usually seen following long-standing ADT, 11 (30%) suggested that this entity could also arise in a de novo treatment-naïve setting, and 3 (8%) concluded that this entity would be diagnosed at a metastatic location (Question #20). There was a question on exact quantification of the components and grading of the acinar component in mixed carcinoma cases and have been voted by 62% respondents (Question #21,22).

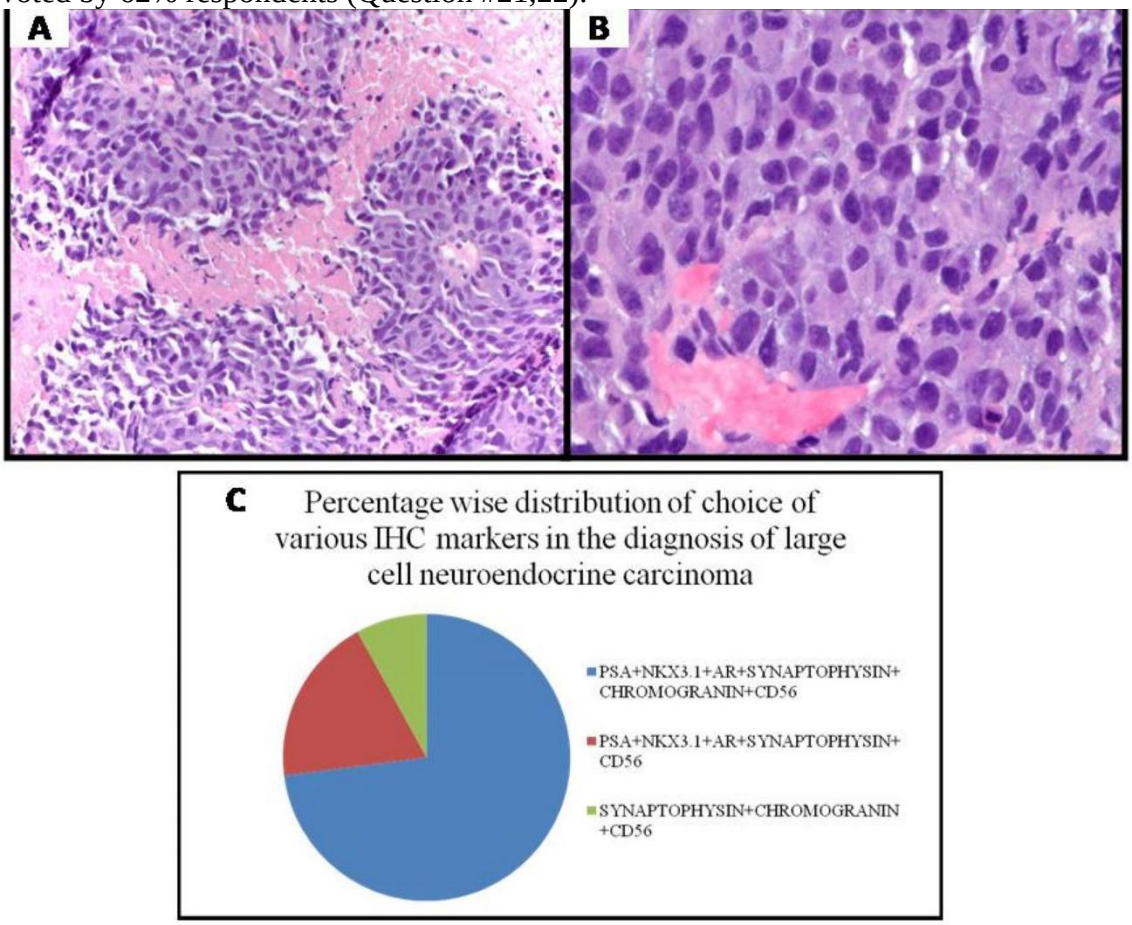

Figure 4. A and B: An example of prostatic large cell neuroendocrine carcinoma (A, original magnification, ×100 hematoxylin and eosin; B, original magnification, ×400 hematoxylin and eosin); C. a pie-chart showing the distribution of choice of immunostains in the work-up of

large cell neuroendocrine carcinoma by the pathologists. Abbreviations: PSA, Prostate specific antigen; AR, Androgen receptor.

Acinar Adenocarcinoma

For an illustrated case intended to show high-grade (Gleason score 10) acinar adenocarcinoma that consists of a solid growth pattern with prominent nucleoli, the interpretations were as follows: 24 (61%) Gleason score 5 + 5 = 10 acinar adenocarcinoma; 2 (5%) small cell neuroendocrine carcinoma; 1 (3%) mixed small cell neuroendocrine carcinoma-acinar adneocarcinoma; 1 (3%) should not be graded; 11 (28%) would require synaptophysin and chromogranin to exclude a small cell neuroendocrine carcinoma (Figure 5) (Question #5). Concerning work-up, 15 participants (38%) would use a wide panel of all markers, consisting of AR, PSA, NKX3.1, synaptophysin, chromogranin, and CD56, while 15 other pathologists (38%) would not use IHC. The remaining responses were divided in their choice for the IHC panel and consisted of 4 (10%) in favor of synaptophysin/chromogranin/CD56/Ki-67, 3 (8%) in favor of AR/P501S/PSA/NKX3.1, and 2 (5%) participants were in favor of AR/NKX3.1/AMACR (Question #6).

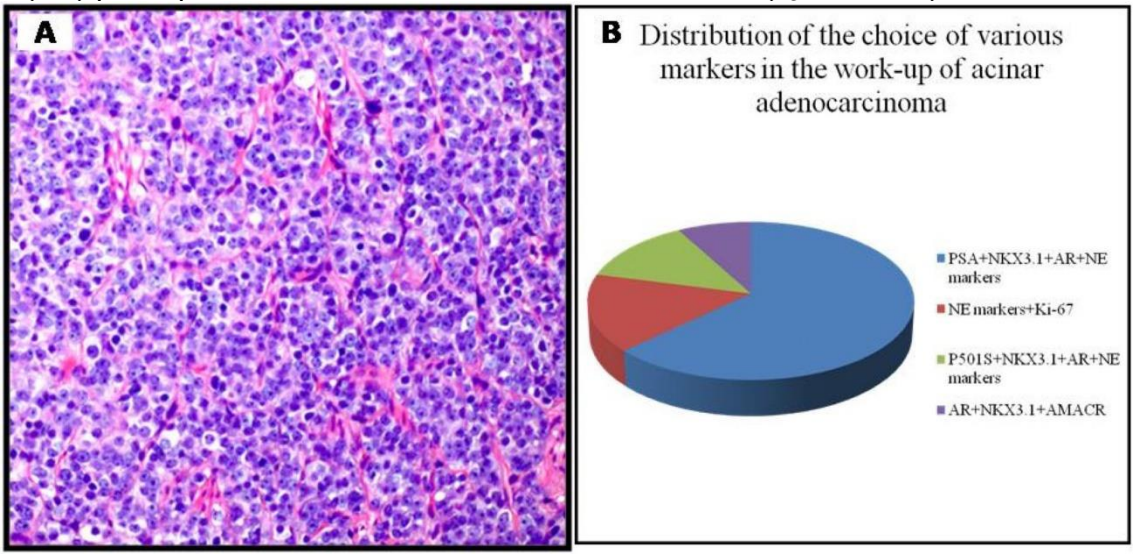

Figure 5. A: An example of acinar adenocarcinoma, Gleason score 10 (A, original magnification, ×200 hematoxylin and eosin); B: A pie-chart showing the distribution of choice of immunostains in the work-up of acinar adenocarcinoma by the pathologists. Abbreviations: PSA, Prostate specific antigen; AR, Androgen receptor; AMACR, Alpha methyacyl CoA racemase; NE, Neuroendocrine.

Imuunohistochemical Markers

A few questions were asked about IHC utilization only. When the respondents were questioned about a comparable Ki-67 proliferation index between Gleason score 10 acinar adenocarcinoma and small cell neuroendocrine carcinoma, 23 (59%) participants indicated this statement as false (a different proliferation index between the two entities) and 16 (41%) responded that both entities had an analogous Ki-67 proliferation index (Question #7). With regard to IHC stains, the participants would prefer not to use in the diagnosis of a small cell neuroendocrine carcinoma, the responses were as follows; INI1 (n = 17; 44%); TTF1 (n = 7; 18%); CD44 (n = 7;18%); STAT3/STAT5a (n = 4;10%); CyclinD1 (n = 2; 5%); AR (n = 2; 5%) (Question #24). When we asked in the survey, whether TTF1 immunoreactivity in small

cell neuroendocrine carcinoma would indicate a secondary involvement from a primary lesion in the lung, the majority of (33; 85%) participants disagreed, although 6 (15%) agreed (Question #25).

Discussion

The concept of neuroendocrine prostate cancer and neuroendocrine differentiation in the prostatic adenocarcinoma has recently attracted considerable attention as potentially significant entities with major prognostic and therapeutic ramifications.[1–5,7,9,10] Along with expertize in the diagnosis, grading, and staging, the pathologist plays a pivotal role in guiding subsequent tissue-based biomarker testing and their clinical utility.[5] Due to the highly aggressive nature of the neuroendocrine carcinoma, and its association with androgen resistance/independence and metastasis, rapid recognition of this entity is crucial. Neuroendocrine carcinomas are treated with platinum-based chemotherapy and do not respond to ADT alone.[2,5,6] Therefore urologists and uropathologists need to understand and be updated with the current terminologies.[5–7,10] Due to the discrepancies in reporting in the pathology community and non-uniformity in the utilization of resources, this multi-institutional survey was conducted to assess the reporting trends and practices in a geographically diverse population of GU pathologists.

WHO Subtypes

Although the WHO 2016 stratified prostatic neuroendocrine neoplasm into distinct subgroups, some issues related to the misinterpretation of Paneth cell-like change as a high-grade neuroendocrine carcinoma and the inappropriate usage of the term neuroendocrine differentiation in prostatic adenocarcinoma continue to persist.[6,7,10,14] We individually sought to clarify the terminology of each subgroup as well as elucidate the definition and utilization of appropriate resources towards each entity (Figure 6).

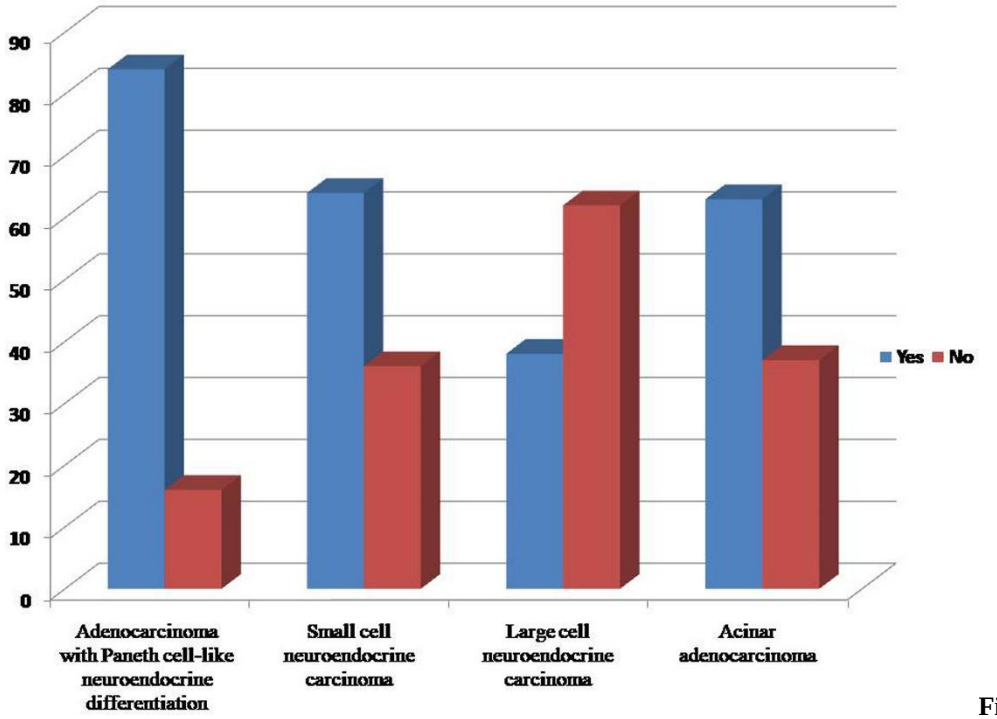

Figure 6.
Morphologic diagnosis of various image based entities by the survey participants.

Neuroendocrine Cells in Usual Prostate Cancer

These are usual acinar or ductal adenocarcinoma of the prostate gland with variable immunoreactivity for the neuroendocrine markers.[5,15] Interestingly, these neuroendocrine cells may also express PSA, indicating a dual biologic potential.[16] However, the prognostic significance of focal neuroendocrine cells in a usual prostatic adenocarcinoma is controversial and failed to show an independent effect on survival and prognosis.[8] Thus, it is not recommended to routinely use IHC for neuroendocrine markers in the absence of architectural and/or cytologic evidence suggestive of neuroendocrine differentation.[5–8,10] However, 67% of the survey participants would use neuroendocrine markers in the morphologic absence of neuroendocrine differentiation in a usual prostatic adenocarcinoma, and only a subset (33%) would not perform neuroendocrine marker IHC in the absence of neuroendocrine differentiation.

Adenocarcinoma with Paneth Cell-Like Neuroendocrine Differentiation

This phenomenon represents a typical prostatic adenocarcinoma containing a varying proportion of cells with prominent eosinophilic granules that expresses neuroendocrine markers and PSA.[5,7,8,10,14–16] Paneth cell-like change is technically a misnomer, as these cells are in fact more similar to gastrointestinal neuroendocrine cells with small eosinophilic granules (usually basally located) rather than true Paneth cells (usually apically located and larger granules). Nonetheless, this change may be seen across the spectrum of Gleason grades, regardless of treatment status.[5,7,8,10,14] From a prognostic standpoint, it appears that solid nests and single cells with this pattern are not as unfavorable as Gleason pattern 5. Therefore, current consensus is that solid nests of these eosinophilic cells should be excluded from grading, and grading should be based on any associated conventional carcinoma.[5,7,8,14] A comment may be provided on the favorable prognosis of this morphologic feature.[14] In a study of 80 cases of so-called Paneth cell-like differentiation in prostatic adenocarcinoma, it

has been shown that a minority of these tumors are associated with conventional higher grade adenocarcinoma and a minority have progressed following treatment.[14] Since the majority have favorable outcome, it is recommended that they be distinguished from Gleason score 10 adenocarcinoma, which rare tumors may closely mimic.[14] Also, in a recent study, these tumors were associated with amplification of the Aurora Kinase A (*AURKA*) gene (45% of the cohort).[17] Most pathologists recognized an image-based example of this phenomenon (84%) and were aware of the low Ki-67 proliferation index. However, there was variation in the Gleason grade for the provided image. There was some variation in interpretation of the prognostic impact by the respondents. Experts recommendation is that these tumors should not be graded because they have a more favorable prognosis than the one expected based on its Gleason score; however, there are rare occasions in which high grade tumors with extraprostatic extension and seminal vesicle invasion show areas of Paneth cell-like differentiation while other areas do not. If a given pathologist has had this experience, this could interfere in answering the question when it is related to one image only, especially in the case shown that demonstrates gland fusions and early cribriform glands.

Well-Differentiated Neuroendocrine Tumor (Carcinoid Tumor)

True well-differentiated neuroendocrine tumors of the prostate gland are extremely rare.[5,7,10,18–24] Traditionally, the criteria used for diagnosis are as follows: a. not closely associated with concomitant prostatic adenocarcinoma; b. neuroendocrine marker expression with negativity for PSA; c. a prostatic parenchymal origin.[7] The survey revealed varied responses on diagnostic criteria for this entity, perhaps reflecting its extreme rarity and controversial nature.

High-Grade Neuroendocrine Carcinoma- Small Cell Neuroendocrine Carcinoma

Small cell neuroendocrine carcinoma is an aggressive neuroendocrine prostate cancer that may occur either in its pure form or adjacent/admixed with the conventional prostatic adenocarcinoma, reflecting a transdifferentiation from a conventional prostatic adenocarcinoma.[5–7,9,10,25–34] Therapy-associated tumors are commoner than the de novo counterpart.[5–7,9,10,25–34] There may be subtle morphologic differences between a pulmonary and a prostatic small cell neuroendocrine carcinoma. Although a visible nucleolus argues against a pulmonary tumor, small nucleoli in a subset of tumor cells with an otherwise typical small cell neuroendocrine carcinoma morphology may be observed in prostatic small cell neuroendocrine carcinomas.[5,7,10] A morphologic evaluation for small cell neuroendocrine carcinoma should be considered in all patients with metastatic castrate-resistant prostatic adenocarcinoma. Despite a large metastatic burden and visceral disease, PSA levels may continue to remain low in small cell neuroendocrine carcinoma.[2,26,27] In general, small cell neuroendocrine carcinoma expresses neuroendocrine markers with a markedly high Ki-67 proliferation index, often exceeding 90%.[5,6,8,10,31,34] Prostatic markers and AR immunoreactivity are often decreased, positive in as little as 17% to 25% cases.[5–7,10,28–30] TTF1 IHC has limited utility in distinguishing a prostatic from a metastatic pulmonary small cell neuroendocrine carcinoma, as both may be positive.[5–7,10,35,36] However, this distinction has less clinical relevance as these tumors are usually treated similarly, both with platinum-based chemotherapy.[2,5,6,8,25] Moreover, some pathologists may use positive TTF1 labeling as

supportive of a diagnosis of small cell neuroendocrine carcinoma, since this is rarely positive in conventional adenocarcinomas. The importance of discriminating small cell neuroendocrine carcinoma from acinar adenocarcinoma lies in the fact that the former is managed with a combination of ADT and cisplatin-based therapies, followed by consolidative surgery or radiation therapy.[2,5,6,8,25,37] The participants of our survey readily recognized an example of small cell neuroendocrine carcinoma by morphology, and 64% respondents would chose a panel of prostatic and neuroendocrine markers along with AR to confirm the nature of these lesions, especially while making a diagnosis at a metastatic site and in a castrate-resistant setting. There was a low usage of TTF1, especially in a metastatic setting.

High-Grade Neuroendocrine Carcinoma - Large Cell Neuroendocrine Carcinoma

This entity represents an aggressive and high-grade tumor with an organoid, trabecular, or palisading architecture. The tumor cells contain abundant amphophillic cytoplasm, coarsely clumped chromatin, and macronucleoli; frequent geographic necrosis and brisk mitotic rate are present.[2,5,7,10,38] The neuroendocrine differentiation is supported by at least one neuroendocrine marker.[5,7,10] Large cell neuroendocrine carcinoma in its pure form is exceptionally rare and most cases represent a progression from prior prostatic adenocarcinoma following long standing hormonal therapy.[5,38] Evans et al reported the largest series of seven such cases, of which 6 patients had a prior history prostatic adenocarcinoma, status post hormonal therapy, and all these tumors exhibited hybrid morphology with features of both large cell neuroendocrine carcinoma and conventional prostatic adenocarcinoma.[38] As Gleason score 10 prostatic adenocarcinoma may occasionally express neuroendocrine markers, the consensus was that the definition of large cell neuroendocrine carcinoma should be more restrictive and there should be morphologic evidence of neuroendocrine differentiation rather than just based on IHC expression of neuroendocrine marker(s).[5,38] Our survey made it evident that recognition of large cell neuroendocrine carcinoma is not uniform among the GU pathologists as only 38% agreed on an example case that was illustrated, whereas others had a mixed opinion ranging from conventional Gleason score 10 tumor to mixed neuroendocrine carcinoma-acinar adenocarcinoma, and hence 69% pathologists would need IHC for categorization. However, on the basis of very limited data, more standardized criteria and definitions are needed to clearly delineate this entity.

Acinar Adenocarcinoma

Our purpose of including this category in the survey was to clearly delineate this entity in its pure form, especially in cases of Gleason score10 prostatic adenocarcinoma from a high-grade neuroendocrine carcinoma or a mixed carcinoma. Such high-grade tumors exhibit a solid sheet-like arrangement, and the individual cells have clear to finely granular cytoplasm and nucleomegaly with prominent nucleoli. A fraction (38%) of participants would report such cases without any IHC; however, 62% would utilize both prostatic and neuroendocrine markers for confirmation. This leads to overutilization of the resources and potential confusion in the patient management.

Utility of Immunohistochemical Markers

Neuroendocrine marker (synaptophysin, chromogranin, and CD56) expression in isolation does not confirm a diagnosis of small cell or large cell neuroendocrine carcinoma.[5–7,10] Current recommendations of the International Society of Urological Pathology molecular pathology working group state that for clinically localized prostatic adenocarcinoma, unless there are clear morphologic neuroendocrine features, IHC for neuroendocrine markers is not recommended.[6] Given its clinical implications, the term neuroendocrine differentation is best reserved for high-grade cancers and not the usual type prostatic adenocarcinoma or well-differentiated neuroendocrine tumors.[5–7,10] Ki-67 appears to have some role in neuroendocrine prostate cancer. Neuroendocrine carcinomas typically have much higher Ki-67 proliferative index (>50%) compared to conventional high-grade prostatic adenoacrcinoma.[5–7,10] Most of our respondents supported the association between neuroendocrine carcinoma and Ki-67 index.

We acknowledge the following limitations. This is just a survey and we attempted to choose images reflective of each diagnosis; however, there may be subjectivity on the interpretation, resource utilization, and reporting trend. This could have been accounted for some of the discrepancies. Also, the survey is based on the WHO classification of tumors from 2016 and now the new book is coming out in 2022 where there is modification to the classification of neuroendocrine neoplasms of the prostate. While neuroendocrine cells in usual prostate cancer and adenocarcinoma with Paneth cell-like neuroendocrine differentiation are eliminated, treatment-related neuroendocrine prostatic carcinoma is included as a new entity.[39] Another reason for the lack of uniformity of the responses could be the design of the questions. For example, the question regarding normal neuroendocrine cells in the prostate is interesting but is more academic than practical. Identification of normal neuroendocrine cells in the prostate is not part of everyday surgical pathology practice. Also, since the choices of markers were grouped together, some participants may have chosen a group of markers in which they do not necessarily use all (Question #6,14,19, and 24).

Our survey demonstrated that while a majority of the participating urologic pathologists were aware of neuroendocrine neoplasms of the prostate gland including their clinicopathologic settings, there is disparity in the practices regarding a diagnosis in high-grade carcinomas (acinar and neuroendocrine) and in the application of IHC markers. This often leads to overutilization of the resources and potential confusion in the patient management. Some debate still exists regarding the morphologic features of small cell neuroendocrine carcinoma with variable practice approaches and diagnostic and prognostic impact of Paneth cell-like change in prostatic adenocarcinoma. There continues to persist some ambiguity in the evaluation of a Gleason score 10 acinar adenocarcinoma and large cell neuroendocrine carcinoma. Also, recent literature raises the question of whether “carcinoid tumor” (well-differentiated neuroendocrine tumor) truly exists in the prostate gland. The most striking finding is the lack of uniformity in the answers, or the poor agreement among pathologists. This could be secondary to the broad selection of GU pathologists from different parts of the world, where formal training in urologic pathology is not available and the GU pathologists are self designated as such given the nature of their practice. This calls

for a formalized GU pathology training following residency across the globe. More caution needs to be exercised in reporting tumors with neuroendocrine differentation, with further refinement of the morphologic classification and more standardized guidelines to clearly define each entity.

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Author Contributions

Conception and Design: SKM, SRW, and JB. Development of Methodology: SKM, SRW, JB. Acquisition of Data: All the authors. Analysis of Data: SKM, SRW, JB, AL. Interpretation of Data: All the authors. Writing and review/revision of the manuscript: All the authors. Study Supervision: SKM, SRW, RBS, MV, CMG.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent was obtained from the pathologists through e-mails and the intended use of the data was explained. The pathologists were given the option of authorship at the onset of the survey and were given the option to withdraw participation at any time including at the completion of the survey or afterward.

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Notes

Trial Registration

This study does not include a clinical trail.

Supplemental Material

Supplemental material for this article is available online.

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