# Utility of NKX3.1 Immunostaining in the Detection of Metastatic Prostatic Carcinoma on Fine-Needle Aspiration Smears

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## ABSTRACT

***Objectives:*** *NK3 homeobox 1 (NKX3.1) has been increasingly used to diagnose metastatic prostatic carcinoma in histologic samples. However, its utility and reliability in cytologic direct smears have not been studied.*

***Methods:*** *A total of 59 fine-needle aspiration (FNA) cases with a definitive diagnosis of metastatic carcinoma from the prostate were included. The cases were grouped based on different Gleason score in their corresponding primary tumors and morphologic variants. For each case, tumor cells were immunostained with NKX3.1, prostate-specific antigen (PSA), and prostatic acid phosphatase (PAP) on cell-transferred smears.*

***Results:*** *NKX3.1 was strongly and diffusely positive in all 40 metastatic prostatic adenocarcinomas, including those with ductal features, but negative for the 19 small cell carcinoma (SmCC) cases. NKX3.1 had a better detection rate than PSA (13/50, 26%) and PAP (0/47, 0%).*

***Conclusions:*** *NKX3.1 immunostaining on FNA smears is highly reliable for detecting metastatic prostatic carcinomas of conventional and ductal types but not for SmCC.*

Prostatic cancer, the second most common cancer in men in the United States and worldwide, is diagnosed in one of seven men during their lifetime. The mortality of prostatic cancer was closely related to metastatic disease.[1,2] An accurate diagnosis of metastatic carcinoma from prostatic origin is essential for an appropriate therapy and prognostic prediction.

Most metastatic prostatic carcinomas metastasize to regional lymph nodes and bones. Some tumors with a high Gleason score (GS), with a ductal morphology, or with small cell features have a propensity to metastasize to visceral organs such as lung and liver.[3,4] Diagnosis of metastatic prostatic carcinoma can sometimes be challenging, not only because some high-grade tumors may cytologically resemble carcinoma of other primary origins but also because the lung and liver are the most common recipient organs for distant metastasis from various primary malignancies. For example, metastatic prostatic carcinoma with ductal features in lung and liver may cytologically resemble some primary carcinomas from these two organs (ie, primary lung adenocarcinoma and cholangiocarcinoma, respectively). Fine-needle aspiration (FNA) is often used for sampling metastatic tumors because this minimally invasive procedure allows acquisition of samples from virtually any anatomic site at low cost and with fewer complications. However, FNA samples have intrinsic limitations such as a small number of tumor cells and the lack of reliable histologic architecture of a tumor. Thus, an ancillary study is often required to confirm a diagnosis of metastatic prostatic carcinoma in cytology practice.

Traditionally used biomarkers to confirm a carcinoma of prostatic origin are prostate-specific antigen

(PSA) and prostatic acid phosphatase (PAP). However, these markers are suboptimal in that they are of a cytoplasmic staining pattern and are often only focally expressed in metastatic prostatic carcinoma with reported detection rates of about 80% for PSA and 60% for PAP.[5-7]

In daily practice, it is not uncommon that cell block tissue is not available and direct smear is the only sample type that can be considered for immunoperoxidase studies. In our experience,[8,9] a nuclear staining marker with a high detection rate would be superior to a cytoplasmic staining marker in such a scenario. NK3 homeobox 1 (NKX3.1) is a nuclear marker and has been increasingly used to help diagnose carcinoma of prostatic origin in histologic specimens with a reported sensitivity ranging from 90.9% to 100%.[5,10,11] Previous studies demonstrated that NKX3.1 is generally very specific with regard to prostatic origin, although it is reportedly expressed in a small subset of breast carcinomas.[12,13] The reliability of this nuclear marker in detecting metastatic prostatic carcinoma in cytologic samples, especially smears, has not been studied previously. To date, NKX3.1 expression in cytology samples has been reported in only one study by using cell block sections instead of smears, and the sensitivity was reported as 68%.[14] In this study, we used FNA direct smears of 59 cases to evaluate the utility of NKX3.1 immunostaining in the confirmation of metastatic prostatic carcinoma. For comparison, PSA and PAP staining was performed simultaneously.

## Materials and Methods

### Case Selection

This study was approved by the Institutional Review Board of at The University of Texas MD Anderson Cancer Center in Houston. We retrospectively searched our institution's cytopathology database for FNA cases that had a definitive cytologic diagnosis of metastatic prostatic carcinoma. The final definitive diagnoses were based on a multidisciplinary approach that included clinical history, radiologic findings, and concurrent or subsequent core needle biopsy findings. Archived FNA slides of each case were retrospectively reviewed; only the cases with at least one spare Papanicolaou-stained smear containing sufficient tumor cells were selected for this study. The Papanicolaou-stained direct smears were prepared during routine patient care after the smears had been fixed in modified Carnoy's fixative (a 6:1 ratio of 70% ethanol to glacial acetic acid).

A total of 59 FNA cases (from different patients) were included, and each case had one spared smear used in this study. Of these, 36 cases were metastatic prostatic carcinoma of conventional type, and their corresponding primary prostatic carcinomas showed conventional morphologic features with a GS of 7 in eight cases, GS of 8 in 12 cases, GS of 9 in 13 cases, and GS of 10 in three cases. Four cases of metastatic prostatic carcinoma showed ductal morphology; their primary counterparts were called prostatic ductal carcinoma in two cases and prostatic carcinoma with ductal features in one case. For the fourth case, there was no available information in our electronic system regarding GS or type of its primary counterpart. Nineteen metastatic carcinomas were diagnosed as metastatic small cell carcinoma (SmCC). Based on clinical and radiologic correlation, the 19 cases were considered from prostate since none of these patients had other malignancies, and 16 of 19 patients received castration therapy. The primary counterparts of the 19 cases were prostatic SmCC in one case and conventional prostatic carcinomas in 18 cases (ie, GS of 7 in three cases, GS of 8 in three cases, GS of 9 in 10 cases, and GS of 10 in two cases).

### Cell Transferring and Immunostaining

Cell transfer was performed to allow for three immunostains performed on the cellular material from a single smear of each case. The technique was previously described.[8,15] Briefly, the tissue from each smear was peeled, lifted, and then divided into three pieces. One piece from each case was transferred to a new slide. Each new slide was mounted with 10 to 12 pieces from different cases, moistened with wet gauze, and applied with pressure to ensure that the pieces firmly adhered to the new slides. The three sets of new slides were each immunostained with one of the three markers: NKX3.1, PSA, and PAP, respectively.

For NKX3.1 staining, antigen retrieval was conducted by steaming one set of the new slides for 10 minutes in 10 mmol/L citrate buffer (pH 6.0). The new slides then were incubated for 15 minutes at room temperature with a NKX3.1 antibody (EP356, dilution 1:100; Cell Marque). For PSA staining, no pretreatment was performed. Another set of new slides was incubated for 15 minutes at room temperature with a PSA antibody (A0562, dilution 1:8,000; Dako). For PAP staining, the third set of new slides without antigen retrieval was blocked with Novocastra Protein Block (Leica) for 15 minutes at room temperature and then incubated with a PAP antibody (PASE/4LJ, dilution 1:6,000; Dako). Positive and negative controls were included and evaluated. The immunostain was developed using 3,3′-diaminobenzidine tetrahydrochloride as the chromogen. The slides were


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counterstained with Mayer hematoxylin. The staining of the three markers was scored by two pathologists (Q.G. and Y.G.) with use of light microscopic examination. Positive NKX3.1 staining was defined as more than 10% tumor cells showing nuclear staining; positive PSA and PAP staining was defined as any tumor cells showing cytoplasmic staining.[10,16-18] The percentages of positive cells and staining intensity (weak, moderate, and strong) were recorded.

In some cases, for which these markers had been stained during the original diagnosis, the original staining results were reviewed together with results of the current study.

## Results

Of the 59 patients included in this study, the mean age at the time of sampling the metastatic prostatic carcinoma was 65.3 years (range, 52-85 years), and the mean interval between diagnosis of the primary prostatic carcinoma and sampling of the paired metastatic tumors was 37 months (range, 0-126 months; median, 25 months). The 59 cases of metastatic prostatic carcinoma were classified into six groups according to the GS of their primary carcinomas and morphologic variant of metastatic carcinomas. Groups 1, 2, 3, and 4 included a total of 36 metastatic carcinomas; their corresponding primary prostatic carcinomas showed conventional morphologic features and had a GS of 7, 8, 9, and 10, respectively. The metastatic prostatic carcinomas of these groups showed compatible cytologic features to their primary counterparts, and the case numbers in groups 1, 2, 3, and 4 were 8, 12, 13, and 3, respectively. Group 5 included four metastatic prostatic carcinomas with a ductal morphology, and group 6 included 19 metastatic SmCCs from prostatic origin **Table 1**.

Aspiration sites were lymph nodes (n = 30, 51%) (27 regional lymph nodes and three distant lymph nodes, including left axilla, subcarinal, and left supraclavicular lymph nodes), iliac bone (n = 1, 2%), pelvic soft tissue (n = 8, 14%), liver (n = 19, 32%), and pancreas (n = 1, 2%). Visceral organ involvement was more often found in groups 4 (33%), 5 (50%), and 6 (74%), whereas lymph node involvement was more frequently seen in groups 1 (88%), 2 (75%), and 3 (85%) (Table 1).

NKX3.1 nuclear staining was strongly and diffusely positive in all (100%) of the 36 metastatic prostatic carcinomas in groups 1 to 4 and in all (100%) of the four metastatic prostatic carcinomas with a ductal morphology in group 5 **Table 2** and **Image 1**. In these cases, positive staining was found diffusely in more than 50% of tumor cells with strong intensity. For the 19 metastatic SmCCs in group 6, however, none was positive for NKX3.1 staining (Table 2 and Image 1). Of note, 13 of the 36 metastatic carcinomas in groups 1 through 4 had been previously stained for NKX3.1 at the time of diagnostic workup using formalin-fixed, paraffin-embedded (FFPE) samples (ie, cell block sections in six tumors and concurrent or subsequent core needle biopsy samples in seven tumors), and all 13 cases were reported to be positive for NKX3.1. This marker had not been previously performed in any case in group 5 and group 6.

Of the 59 cases, 50 had available cell-transferred material for PSA immunostaining, and positive cytoplasmic staining was found in 13 (26%) cases with a cytoplasmic (mostly focal) staining pattern **Table 3**. Positive staining for PSA was found in group 1 (2/3, 67%), group 2 (5/11, 46%), and group 3 (6/13, 46%) but not in groups 4, 5, and 6. Of the 59 cases, 47 had available cell-transferred material for PAP immunostaining. However, no case demonstrated positive PAP cytoplasmic staining.

## Discussion

Accurately diagnosing metastatic prostatic carcinoma can be challenging in some circumstances but is

**Table 1**
**Organs Involved by Metastatic Prostatic Cancer in Different Study Groups**

| Group No. | Gleason Score/Morphology in Primary Tumor (No.) | Metastatic Sites, No. (%) | | | |
|---|---|---|---|---|---|
| | | Lymph Node | Visceral Organs | Bone | Pelvic Soft Tissue |
| 1 | GS7 (8) | 7 (88) | 0 (0) | 0 (0) | 1 (13) |
| 2 | GS8 (12) | 9 (75) | 2 (17) | 0 (0) | 1 (8) |
| 3 | GS9 (13) | 11 (85) | 1 (8) | 0 (0) | 1 (8) |
| 4 | GS10 (3) | 1 (33) | 1 (33) | 0 (0) | 1 (33) |
| 5 | Ductal features (4) | 0 (0) | 2 (50) | 1 (25) | 1 (25) |
| 6 | SmCC (19) | 2 (11) | 14 (74) | 0 (0) | 3 (16) |
| Total | 59 | 30 (51) | 20 (34) | 1 (<2) | 8 (14) |

GS, Gleason score; SmCC, small cell carcinoma.





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**Table 2**
**NKX3.1 Immunostaining on Cell-Transferred Smear Slides in Different Study Groups**

| Group No. | No. of Cases in Each Group for NKX3.1 Staining | No. (%) of Cases With Positive NKX3.1 Staining | % of Cells With Positive NKX3.1 Staining | Intensity of NKX3.1 Staining |
|---|---|---|---|---|
| 1 | 8 | 8 (100) | 80-99 | Strong |
| 2 | 12 | 12 (100) | 50-95 | Strong |
| 3 | 13 | 13 (100) | 55-95 | Strong |
| 4 | 3 | 3 (100) | 95 | Strong |
| 5 | 4 | 4 (100) | 80-90 | Strong |
| 6 | 19 | 0 (0) | NA | NA |

NA, not applicable; NKX3.1, NK3 homeobox 1.

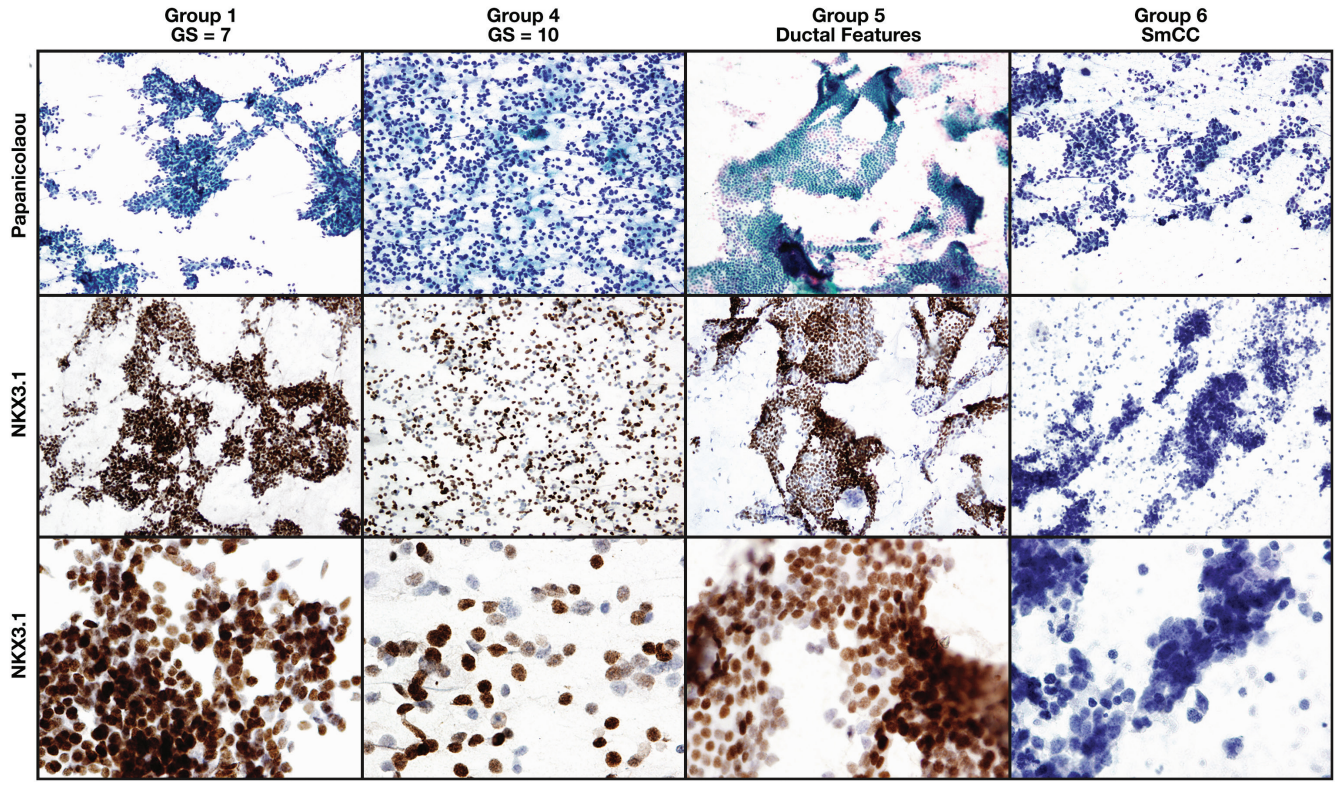


**Image 1** Representative pictures of Papanicolaou-stained smears and NK3 homeobox 1 (NKX3.1) immunostaining for study groups 1, 4, 5, and 6. Papanicolaou-stained smears, ×100; NKX3.1 immunoperoxidase stains, ×100; NKX3.1 immunoperoxidase stains, ×400. GS, Gleason score; SmCC, small cell carcinoma.

essential for an effective therapy. In the current study, using FNA direct smear of 59 cases, we evaluated the reliability of NKX3.1 staining in the detection of metastatic prostatic carcinomas. We found that NKX3.1 is a highly sensitive marker for confirming a metastatic carcinoma to be of prostatic origin except for SmCC of prostatic origin. All of the 36 metastatic prostatic carcinomas of conventional type (regardless of the GS of their primary counterparts) and the four metastatic prostatic carcinomas with a ductal morphology were positive for NKX3.1 with strong staining intensity and a diffuse pattern, indicating that NKX3.1 is a reliable marker to detect metastatic prostatic carcinoma on smears in the majority of occasions. This finding is similar to previously published studies in which NKX3.1 was stained in primary as well as metastatic prostatic carcinoma on histology sections, and the sensitivity was reported to be up to 100%.[5,10,11] However, the previous studies did not stratify cases based on tumor grade and did not have information about prostatic carcinoma with ductal morphology or prostatic SmCC. In a cytology study, Jia et al[14] reported sensitivity of 68% for NKX3.1 based on staining on cell block materials from metastatic prostatic carcinoma.


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**Table 3**
**PSA Immunostaining on Cell-Transferred Smear Slides in Different Study Groups**

| Group No. | No. of Cases in Each Group for PSA Staining | No. (%) of Cases With Positive PSA Staining | % of Cells With Positive PSA Staining | Intensity of PSA Staining |
|---|---|---|---|---|
| 1 | 3 | 2/3 (67) | 2-20 | Weak-strong |
| 2 | 11 | 5/11 (46) | 5-50 | Weak-strong |
| 3 | 13 | 6/13 (46) | 5-50 | Weak-strong |
| 4 | 1 | 0/1 (0) | NA | NA |
| 5 | 3 | 0/3 (0) | NA | NA |
| 6 | 19 | 0/19 (0) | NA | NA |

NA, not applicable; PSA, prostate-specific antigen.

In addition, our study showed a complete concordance of NKX3.1 staining results between smear slides used in this study and FFPE samples used in the original diagnostic workup in 13 metastatic prostatic carcinomas of conventional morphologic type. This finding indicates that direct FNA smear and FFPE section are equally reliable for NKX3.1 staining. The finding has practical value because, in daily cytology practice, aspirate smear may be the only sample type available for immunostaining since cell block or core needle biopsy specimen is often not available or contains insufficient tumor cells. The feasibility of NKX3.1 stain on smear tissue would avoid a repeat biopsy solely for immunostaining on FFPE samples. In an appropriate clinical setting, a single NKX3.1 staining could serve as a reliable adjunct and would be sufficient to confirm prostatic origin of a metastatic carcinoma if the stain is positive.

Previous studies indicated that NKX3.1 expression is highly restricted in prostate-originated cells. Gurel and colleagues[10] examined specificity of NKX3.1 in 349 nonprostatic tumors, including those from the urinary bladder, breast, colon, salivary gland, stomach, pancreas, thyroid, central nervous system, adrenal cortex, kidney, liver, lung, and testis. Using a criterion that any nuclear staining for NKX3.1 was considered positive, they found that only one case of invasive lobular carcinoma of the breast showed positive staining. Subsequently, Asch-Kendrick and coworkers[12] reported positive expression of NKX3.1 in two (2%) of 86 breast invasive ductal carcinomas and 10 (27%) of 37 invasive lobular carcinoma cases with a generally weak staining intensity. Of note, positive NKX3.1 staining appeared to be significantly associated with invasive lobular carcinoma of the breast and was seen only in estrogen receptor– and androgen receptor–positive carcinomas. In light of the rarity of male breast carcinoma and the fact that nearly all male breast carcinomas are ductal type,[19,20] a possibility of misdiagnosis caused by male breast carcinoma is essentially very low. Therefore, NKX3.1 is a reliable marker to confirm prostatic primary of metastatic tumors that are not SmCCs.

PSA and PAP immunomarkers are traditionally used to confirm that a carcinoma is of prostatic origin. In this study, we evaluated these two markers in parallel with NKX3.1 on cell-transferred smears to compare their performance and found that positive rates of PSA expression in groups 1 to 4, 5, and 6 were 46%, 0%, and 0%, respectively, which are much lower than the positive rates of NKX3.1 detection in these groups (Table 2). In addition, PSA expression seems more in low-grade tumors and tends to be negative in higher grade tumors (ie, groups 4-6). The latter observation is consistent with those in previous studies showing that PSA and PAP expression in tumor cells decreases with increasing Gleason grade.[6,7] PAP immunostaining was negative in all of the cases included in the current study. The superior performance of NKX3.1 staining over PSA or PAP staining in the detection of metastatic prostatic carcinoma has been previously reported in studies using FFPE tissue sections. Kristiansen et al[5] reported that the sensitivity was 100% for NKX3.1, 81% for PSA, and 66% for PAP by using 64 metastatic prostatic carcinomas (mostly in lymph nodes). The low positive rate of PSA and the lack of PAP detection in our study could be multifactorial. First, PSA and PAP expressions are of a cytoplasmic pattern, and thus interpretation of staining on cytologic smears can be challenging due to the cell distortion and disruption associated with the smearing procedure. Second, PSA and PAP stains are often focal and weak, even on FFPE sections.[18,21] The transfer technique, which divides one smear into multiple smaller pieces, each containing a small amount of tumor cells, is no doubt prone to false-negative staining results. Finally, the differences in fixation and processing between smear samples and FFPE sections may also be a contributory factor.

Prostatic carcinoma with a ductal morphology is a rare morphologic variant of prostatic carcinoma and accounts for less than 1% of primary prostatic carcinomas. It is characterized by columnar cells forming various histologic patterns (such as glandular, cribriform, or papillary), reminiscent of adenocarcinoma of other origins,[22] which is a potential diagnostic pitfall and causes diagnostic difficulty



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if an immunoperoxidase study is not performed. NKX3.1 expression in this morphologic variant has not been reported in the literature. Our study included four such cases and demonstrated that NKX3.1 staining performed on smear can reliably confirm prostatic origin of metastatic prostatic carcinoma with a ductal morphology.

Prostatic SmCC is very rare, found in only 0.5% to 2% of primary prostatic cancers. It may occur in men with conventional prostatic carcinoma after treatment with androgen deprivation therapy and has an aggressive clinical course with a high frequency of visceral metastases, including bone and brain.[23-25] In our study, 74% of the metastatic SmCC cases involved visceral organs (Table 1). The treatment for SmCC of prostatic origin is chemotherapy and/or radiotherapy for local palliation of symptoms, essentially similar to treatment for SmCC of other primary origins. However, if a prostatic origin of a SmCC can be defined based on a prostatic marker, clinical puzzling about its primary origin and possible imaging or laboratory workup can be minimized. Possible clinical puzzling stems from the fact that metastatic SmCC from prostatic origin not only cytologically resembles SmCC of other origins but also frequently involves visceral organs instead of locoregional lymph nodes. Furthermore, the corresponding primary prostatic carcinoma may not show a SmCC component. Of the 19 patients with metastatic SmCC in our study, 18 had a primary prostatic carcinoma showing conventional morphologic features, and only one had primary prostatic SmCC. Even in primary prostatic SmCC, a coexisting conventional acinar component in the same tumor is not uncommon, and needle biopsy tissue may sample only the non–small cell component of the tumor. Lotan et al[17] reported that 27% (6/22) of the primary prostatic SmCC cases contained a focal conventional morphologic component. Effort has been made in previous studies to detect prostatic origin by biomarkers. PSA and PAP were evaluated for this purpose; however, negative staining in SmCC of the prostate was reported in up to 80% of cases.[25,26] A similar detection rate was observed with NKX3.1 staining by Lotan and colleagues[17] by using FFPE sections in which positive NKX3.1 expression was found only in 18% (4/22) of primary prostatic SmCCs. Our study with direct smear tissues found that none of the 19 metastatic prostatic SmCCs demonstrated positive staining for NKX3.1, PSA, or PAP, indicating that diagnosing a SmCC from prostatic origin has to rely largely on the correlation of pathologic features with clinical and radiologic findings. The possible explanation for the presence of NKX3.1 expression in a subset of SmCCs in the literature but lack of NKX3.1 expression in all SmCC cases in our study could be due to differences in preanalytical factors such as sample fixation and processing.

In conclusion, in this cytology study using smear to evaluate NKX3.1, PSA, and PAP expressions in different grades and variants of metastatic prostatic carcinoma, we found that NKX3.1 staining in FNA smears is highly reliable for detecting metastatic prostatic carcinoma, including both conventional and ductal types, but not for SmCC. The detection rate and staining pattern of NKX3.1 are better than those of PSA or PAP. A Papanicolaou-stained smear is equally reliable to FFPE for NKX3.1 staining. Caution should be taken in metastatic malignancy showing features of SmCC because NKX3.1 immunostaining on smears in this type of tumor is essentially nonreactive. In such cases, correlation of cytologic features with clinical and radiologic findings is the key to reaching an accurate diagnosis.

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