Prostate-Specific Antigen, High-Molecular-Weight Cytokeratin (Clone 34βE12), and/or p63

An Optimal Immunohistochemical Panel to Distinguish Poorly Differentiated Prostate Adenocarcinoma From Urothelial Carcinoma

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Abstract

An optimal immunohistochemical panel to distinguish poorly differentiated prostate (PCa) from urothelial (UCa) carcinoma was selected from a panel consisting of prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP), high-molecular-weight cytokeratin (HMWCK) (clone 34βE12), cytokeratin (CK) 7, CK20, p63, and α-methylacyl-coenzyme A racemase. The pilot group was composed of poorly differentiated UCa (n = 36) and PCa (n = 42). PSA and PAP stained 95% of PCa vs 0% and 11% of UCa cases, respectively. HMWCK and p63 stained 97% and 92% of UCa vs 2% and 0% of PCa cases respectively. CK7/CK20 coexpression was noted in 50% of UCa cases, whereas 86% of PCa cases were negative with both. A panel of PSA, HMWCK, and p63 was optimal for separating 95% PCa (PSA+/HMWCK and/or p63–) vs 97% UCa (PSA–/HMWCK and/or p63+). This panel was used on 26 diagnostically challenging cases and resolved 81% of cases as UCa vs PCa. The majority of PCa cases retain PSA. Negative PSA with positive HMWCK and/or p63 establishes a diagnosis of UCa.

Poorly differentiated prostate adenocarcinoma (PCa) and urothelial carcinoma (UCa) often share overlapping morphologic and clinical features. Although the diagnosis of well-differentiated forms of PCa and UCa is relatively easy, morphologic features alone frequently are insufficient to differentiate the poorly differentiated variants of these tumors. However, this distinction is critical because it has staging, therapeutic, and prognostic implications. In diagnostically difficult situations, confirmatory immunohistochemical stains usually are necessary to establish the origin of the tumor.

Although several markers have been analyzed to determine the prostatic or urothelial origin of poorly differentiated tumors, no marker to date has been sufficiently sensitive and/or specific. Prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) traditionally have been used to confirm a prostatic tumor origin; however, they are not expressed uniformly in poorly differentiated PCa and might be negative in up to 27% and 19% of cases, respectively.[1,2] Two markers have been proved useful in the diagnosis of PCa: α-methyl-acyl-coenzyme A racemase (AMACR), a positive diagnostic tissue biomarker of prostate cancer,[3,4] and p63, a basal cell marker for which usefulness in the diagnosis of PCa is supported by its lack of staining in atypical glands.[5,6] However, some studies have shown AMACR to be highly expressed in liver, kidney, and some UCas, in addition to prostate cancer.[7-9] Studies also have highlighted the usefulness of p63 as a positive biomarker in squamous carcinomas and UCa.[10,11]

Cytokeratin (CK)7, CK20, and high-molecular-weight cytokeratin (HMWCK) (clone 34βE12) have been studied as potential urothelial markers.[12-14] Although they are useful in certain situations, they are not entirely specific for UCa.

Recently, uroplakin, a membranous glycoprotein, has emerged as a highly specific marker of UCa. However it is only moderately sensitive and is expressed only in 50% to 60% of UCas, typically in well-differentiated tumors.[15-17] Therefore, its usefulness in resolving diagnostically challenging cases in day-to-day practice seems limited.

The aim of the present study was to select and evaluate an optimal immunohistochemical panel from an extended panel consisting of traditional (PSA, PAP, HMWCK [34βE12 clone], CK7, and CK20) and novel (p63 and AMACR) immunohistochemical markers to distinguish documented cases of poorly differentiated PCa from high-grade UCa. To our knowledge, no study to date has evaluated the usefulness of AMACR and p63 in differentiating poorly differentiated PCa from high-grade UCa. Also, no study to date has systematically evaluated the potential usefulness of an optimal panel of immunohistochemical markers in the workup of diagnostically difficult poorly differentiated tumors. Therefore, the second objective of this study was to assess and validate the practical diagnostic usefulness of this optimal panel in resolving a subset of diagnostically challenging cases of poorly differentiated tumors with the morphologic differential diagnosis of PCa and UCa.

Materials and Methods

Selection of Cases

For the initial pilot group for the study, we selected 42 cases of documented poorly differentiated PCa from radical prostatectomy (19) and autopsy (23) cases and 36 cases of documented high-grade UCa from radical cystectomy specimens from the archives of the Department of Pathology, University of Michigan, Ann Arbor. All 23 autopsy specimens represented hormone-refractory metastatic PCa.

In addition, 26 diagnostically challenging transurethral resection specimens with poorly differentiated carcinomas in which the origin of the carcinoma could not be distinguished by morphologic features alone also were evaluated.

Immunohistochemical Analysis

H&E-stained slides were reviewed in all cases to verify the histologic findings. Representative formalin-fixed, paraffin-embedded tissue blocks were selected for immunohistochemical staining, which was performed using an avidin-biotin-peroxidase complex technique. **Table 1** lists the antigen retrieval methods, dilutions, and manufacturer information for all the antibodies. HMWCK (clone 34βE12), p63, CK7, and CK20 were monoclonal antibodies, and AMACR, PSA, and PAP were rabbit polyclonal antibodies. Staining for HMWCK, p63, and AMACR was performed on an autostainer (DAKO, Carpinteria, CA). A Ventana Basic DAB Detection Kit was used according to the manufacturer's specifications for CK7, CK20, PSA, and PAP; staining was performed on the Ventana ES autostainer (Ventana Medical Systems, Tucson, AZ). To evaluate the specificity of the antibodies, positive control samples of benign prostate tissue for PSA, PAP, HMWCK (clone 34βE12), and p63, PCa for AMACR, colonic adenocarcinoma for CK20, and ovarian serous carcinoma for CK7 were used. In the negative control samples, the primary antibody was replaced by buffer.

Three of us (L.P.K., M.S., and R.B.S.) evaluated the immunohistochemically stained slides, which were interpreted as positive when more than 5% of tumor cells demonstrated strong reactivity with the antibody. Staining was considered diffuse when more than 50% of the tumor cells demonstrated reactivity and focal when 5% to 50% of the cells showed reactivity.

Differential Expression at the Transcript Level

Oncomine (http://www.oncomine.org), a bioinformatics platform and a cancer microarray meta-analysis database developed by our group,[18] was used to interrogate expression of the markers of interest. An oligonucleotide microarray platform–based study that identifies gene subsets with expression that typifies different carcinoma classes was used to study differential expression of PSA, p63, PAP, CK7, CK20, and AMACR in PCa and UCa.[19] HMWCK was not included because this study did not characterize any gene targeted by the clone 34βE12.

Table 1
Immunohistochemical Antibodies Used

Antibody	Antigen Retrieval	Dilution	Manufacturer
PSA	None	1:1,000	DAKO, Carpinteria, CA
PAP	None	1:1,000	DAKO
34βE12	Microwave heating, citrate buffer	1:100	DAKO
4A4 p63	Microwave heating, citrate buffer	1:200	Labvision, Fremont, CA
CK20	Protease 1	1:50	DAKO
CK7	Protease 2	1:50	DAKO
AMACR	Microwave heating, citrate buffer	1:5,000	Denatured recombinant antigen to AMACR

AMACR, α-methylacyl-coenzyme A racemase; CK, cytokeratin; PAP, prostatic acid phosphatase; PSA, prostate-specific antigen.

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Results

Pilot Group of Documented Poorly Differentiated PCa and High-Grade UCa

The immunophenotype of 42 documented poorly differentiated PCa and 36 documented high-grade UCa cases using an extended panel of antibodies is summarized in **Table 2**. PSA and PAP were diffusely positive in 36 (86%) of 42 PCa cases, focally positive in 4 (10%) of 42 cases, and negative in 2 (5%) of 42 cases. Both PCa cases that were negative with PSA and PAP were negative with all antibodies.

All 36 cases of high-grade UCa were negative with PSA, whereas a small subset of UCas (4/36 [11%]) showed focal expression of PAP (<20% of tumor cells).

All 42 PCa cases were negative with p63, whereas 1 (2%) case showed focal staining with HMWCK (clone 34βE12). In contrast, HMWCK and/or p63 were moderate to diffusely positive in 35 (97%) of 36 UCa cases. Only 1 case (3%) of high-grade UCa was negative with both HMWCK and p63.

Coexpression of CK7 and CK20 was noted in 18 (50%) of 36 UCa cases, whereas 36 (86%) of 42 PCa cases were negative with both. CK7 expression was noted in 34 (94%) of UCa cases vs 4 (10%) of 42 PCa cases, whereas CK20 expression was present in 19 (53%) of 36 UCa cases vs 2 (5%) of 42 PCa cases **Figure 1** (Table 2). One case (3%) of UCa was negative with both CK7 and CK20. AMACR was positive in 37 (88%) of 42 PCa cases vs 13 (36%) of 36 UCa cases (Table 2).

PSA and/or PAP positivity with HMWCK, p63, CK7, and CK20 negativity was consistent with the immunohistochemical profile of PCa, whereas HMWCK, p63, CK7, and/or CK20 positivity with PSA and PAP negativity seemed to be the immunohistochemical profile of UCa. AMACR was not useful in separating PCa from UCa (88% vs 36%).

A panel of PSA, HMWCK, and/or p63 was determined to be the most optimal for separating PCa from UCa in the majority of cases, with 95% of PCa cases (40/42) being PSA+/HMWCK and/or p63– vs 97% of UCa cases (35/36), which were PSA–/HMWCK and/or p63+ **Figure 2**. In cases in which PSA, HMWCK, and p63 were all negative, PAP, CK7, and CK20 were useful.

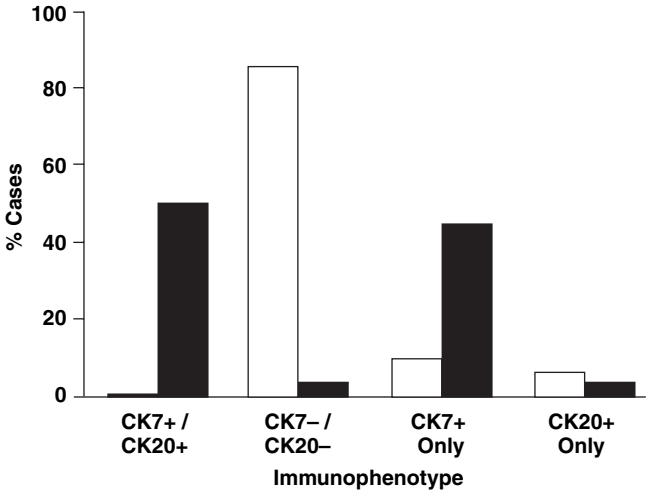

Figure 1 Protein expression of cytokeratin (CK)7 and CK20 in a pilot group of documented poorly differentiated prostate (white bar) and urothelial (black bar) carcinomas.

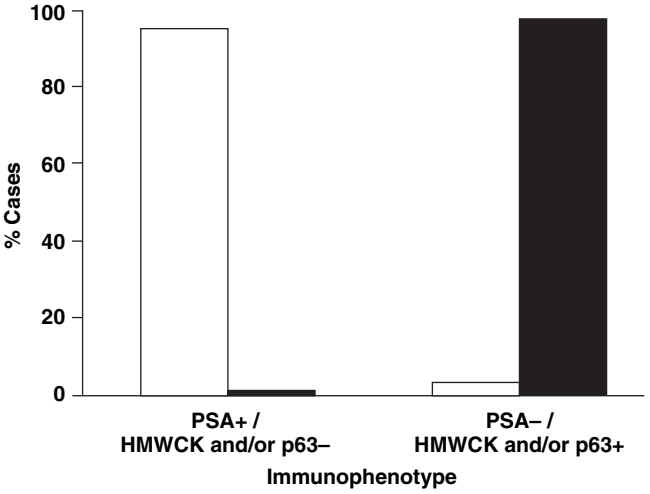

Figure 2 Protein expression of prostate-specific antigen (PSA), high-molecular-weight cytokeratin (HMWCK) (34βE12), and/or p63 in a pilot group of documented poorly differentiated prostate (white bar) and urothelial (black bar) carcinomas.

Table 2
Immunophenotype of Pilot Group of Documented Poorly Differentiated Prostatic Carcinomas and High-Grade Urothelial Carcinomas Using an Extended Immunohistochemical Panel*

Type of Carcinoma	CK7	CK20	34βE12	PSA	PAP	p63	AMACR
Prostate (n = 42)	4 (10)	2 (5)	1 (2)	40 (95)	40 (95)	0 (0)	37 (88)
Urothelial (n = 36)	34 (94)	19 (53)	35 (97)	0 (0)	4 (11)	33 (92)	13 (36)

AMACR, α-methylacyl-coenzyme A racemase; CK, cytokeratin; PAP, prostatic acid phosphatase; PSA, prostate-specific antigen.
* Data are given as number (percentage).

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Differential Expression of PSA, p63, PAP, CK7, CK20, and AMACR at the Transcript Level

We also studied the differential gene expression of these markers using Oncomine, a novel informatics tool. In a multicancer data set, PSA, PAP, and AMACR messenger RNA levels were overexpressed in PCa as compared with UCa; and CK7, CK20, p63 were overexpressed in UCa as compared with PCa **Figure 3**.

Diagnostically Challenging Cases

Of 26 diagnostically challenging cases, 21 (81%) could be resolved as PCa or UCa by using a panel of PSA, HMWCK, and p63 **Table 3** and **Image 1**. Eleven cases were resolved as PCa (PSA+/HMWCK and/or p63–; Image 1A-1D), and 10 cases were resolved as UCa (PSA–/HMWCK and/or p63+; Image 1E-1H).

Five cases were negative with all 3 markers and could not be resolved definitively with this panel alone. These cases were stained with CK7, CK20, and PAP. Of the 5 cases, 2 were positive with PAP and negative with CK7 and CK20, supporting the prostatic tumor origin, and 3 cases were negative for PAP with variable expression of both CK7 and CK20, supporting a urothelial tumor origin.

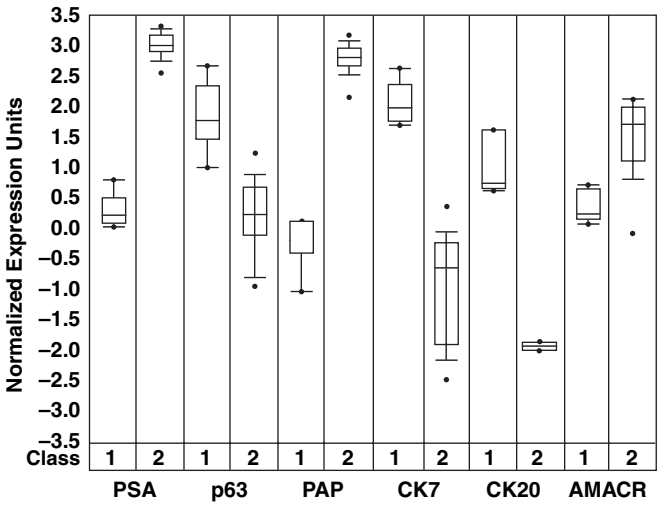

Figure 3 Differential expression of prostate-specific antigen (PSA), p63, prostatic acid phosphatase (PAP), cytokeratin (CK)7, CK20, and α-methylacyl-coenzyme A racemase (AMACR) transcripts in urothelial carcinoma (class 1) and prostate carcinoma (class 2), studied using Oncomine (http://www.oncomine.org), a Web-based informatics platform. Dots indicate the range of values; boxes, the interquartile range (25th-75th percentile); and whiskers, the 10th-90th percentile.

Table 3
Resolution of 26 Diagnostically Challenging Cases With a Preliminary Panel of PSA, HMWCK, and p63

	Final Diagnosis		
Immunohistochemical Panel	Prostate Carcinoma	Urothelial Carcinoma	Unresolved
PSA+/HMWCK, p63–	11		
PSA–/HMWCK, p63+		10	
PSA–/HMWCK, p63–			5

HMWCK, high-molecular-weight cytokeratin; PSA, prostate-specific antigen.

Discussion

Distinguishing poorly differentiated PCa arising in the urinary bladder neck from high-grade UCa with prostatic extension frequently can be a challenging task for surgical pathologists owing to overlapping morphologic characteristics and similar clinical manifestations in the two entities. This distinction has significant therapeutic and staging implications. Hence, an accurate diagnosis is essential for optimal patient care. By using an extended panel of traditional and novel immunohistochemical markers in a pilot group composed of documented poorly differentiated PCa cases and high-grade UCa cases, we selected and evaluated an optimal panel of antibodies composed of PSA, HMWCK, and/or p63 that can reliably and accurately distinguish poorly differentiated PCa from UCa in the vast majority of cases. In our series, 95% of documented PCas and 97% of documented UCas expressed a diagnostic immunohistochemical profile (PCa, PSA+/HMWCK and/or p63– vs UCa, PSA–/HMWCK and/or p63+; Figure 2).

Our study validates the results of other studies showing PSA to be a reliable marker of PCa,[12,13,16,20,21] with 95% of documented PCa cases in our series expressing this marker. Despite the fact that a small subset of poorly differentiated PCas might not express PSA, it seems to be a highly specific marker to confirm the prostatic origin of a poorly differentiated tumor. PSA expression frequently is heterogeneous; therefore, immunostains may need to be performed on multiple blocks containing tumor when dealing with challenging cases.[22]

However, in contrast with the findings of previous studies,[13,16,23] we found PAP to be slightly less specific for prostatic origin because a minority of documented UCa (11%) cases in our series expressed PAP focally. This discrepancy might be explained by the variability that results from the use of different antigen retrieval methods, type of antibody (monoclonal PAP vs polyclonal PAP), and/or different detection systems.[2] In our study, we used polyclonal PAP, in contrast with Genega et al[13] and Mhawech et al,[16] who used monoclonal PAP. This difference might account for the focal PAP expression in a small subset of documented UCa cases in our series.

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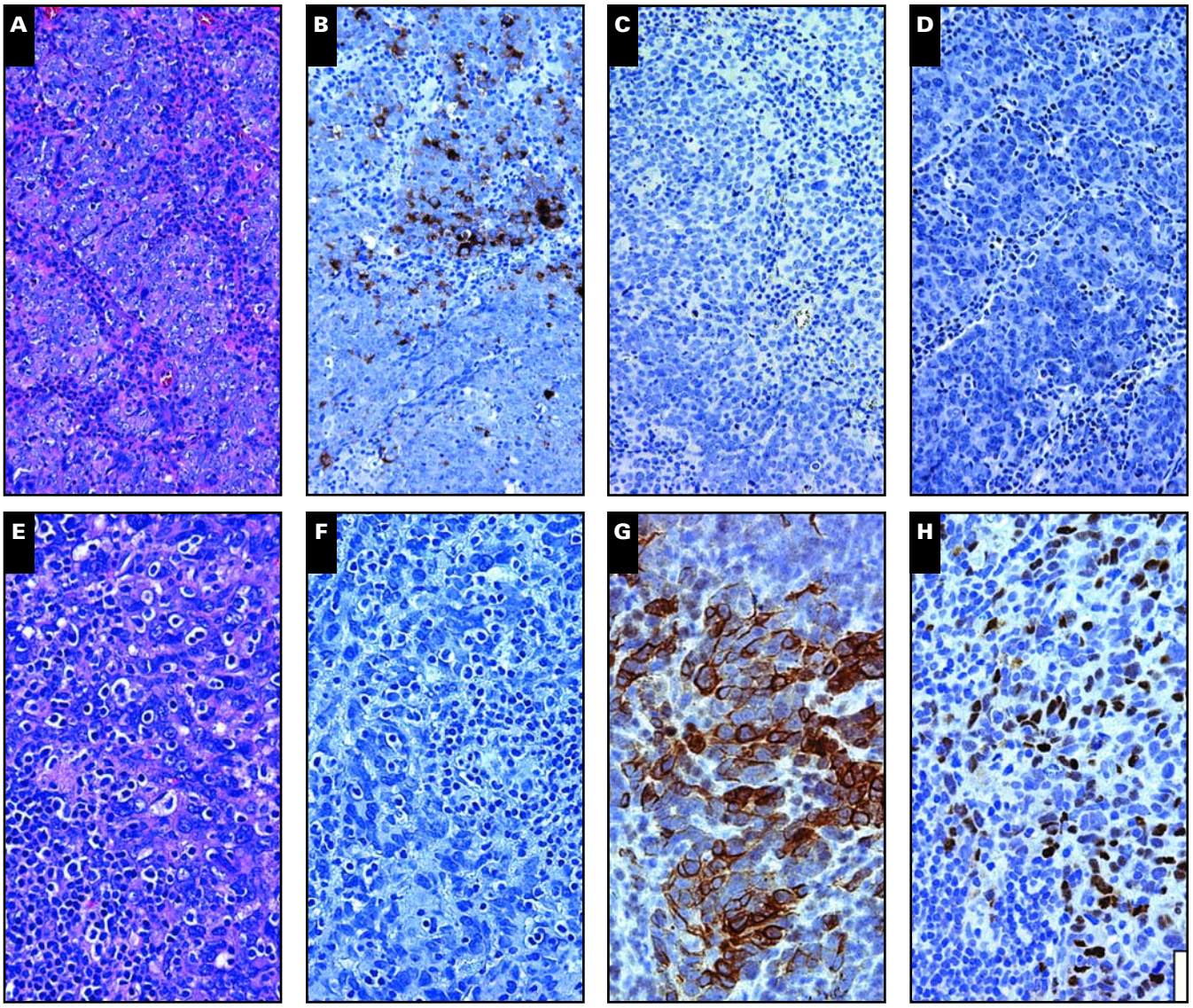

Image 1 **A**-**D**, Poorly differentiated carcinoma with differential diagnosis of urothelial vs prostate carcinoma (**A**, H&E, ×200), resolved as prostate adenocarcinoma, Gleason score 5 + 5 = 10. Tumor is focally positive for PSA (**B**, ×200) and negative for high-molecular-weight cytokeratin clone 34βE12 (**C**, ×200) and p63 (**D**, ×200). **E**-**H**, Poorly differentiated carcinoma with similar differential diagnosis (**E**, H&E, ×200), resolved as poorly differentiated high-grade urothelial carcinoma. Tumor is negative for PSA (**F**, ×200) and positive for high-molecular-weight cytokeratin clone 34βE12 (**G**, ×200) and p63 (**H**, ×200). PSA, prostate-specific antigen.

We found p63 to be a fairly sensitive and highly specific marker of UCa in this range of differential diagnosis with consistent diffuse nuclear positivity seen in 92% of all documented UCas. Unlike HMWCK (clone 34βE12), which might show focal positivity in PCa (2% in our study), a finding that has been documented by other studies as well,[14,24,25] p63 seemed to be specific for UCa in this diagnostic setting. We have, however, still included HMWCK (clone 34βE12) in our preliminary panel because it is a widely used antibody in diagnostic immunohistochemical analysis and the focal positivity seen in rare PCa cases is easily distinguishable from the strong diffuse cytoplasmic reactivity in UCa cases.

Like previous studies,[7-9] we found AMACR to be expressed in 36% of UCas. Thus, AMACR is not a useful marker to distinguish PCa from UCa because it is not a specific marker for the former.

Numerous studies have evaluated the usefulness of CK7 and CK20 expression for distinguishing between PCa and UCa.[12,13,16,23,26] Our study found high CK7 and/or CK20 expression in UCa. We found CK7 expression in 94% of cases of UCa and CK20 expression in 53% of UCa cases compared with literature reports of CK7 expression in UCa ranging from 80% to 88% and CK20 expression from 29% to 64%.[12,16,23,26,27] We found CK7 and CK20 in 10% and 5% of

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PCa cases, respectively, which is comparable to the 0% to 20% CK7 and 0% to 10% CK20 expression ranges reported in the majority of previous studies.[12,16,23,27] In contrast with the findings of our study, Genega et al[13] reported CK20 expression in a minority of UCa cases (22%), and Genega et al[13] and Wang et al[26] reported CK20 expression in a higher percentage of PCa cases (24% and 23%, respectively) compared with our findings (5%) while using a cutoff similar to ours (>1% positive cells in their studies vs >5% in our series). When coexpression of CK7 and CK20 were examined, the results of our study were comparable to those of other studies, with 50% of our UCa cases expressing both CK7 and CK20 (25%-89% in the literature) and 86% of our PCa cases negative for both markers (Figure 1; 62%-100% in the literature).[12,16,23,26,27] CK7 and CK20, when used alone, may be insufficient to distinguish the 2 entities owing to overlapping results. However, the coordinate expression patterns of CK7 and CK20 in conjunction with PAP may be very helpful in differentiating PCa (PAP+/CK7–/CK20–) from UCa (PAP–/CK7+/CK20+ or PAP–/CK7+/CK20–), especially when the results of the preliminary panel of PSA, HMWCK, and p63 are all negative. It is interesting that the protein expression profile of these markers in PCa and UCa is mirrored at the complementary DNA expression level, as demonstrated by Su et al.[19]

The greatest value of a panel of immunohistochemical stains would be its ability to resolve diagnostically challenging cases. Based on our results, we used a panel of PSA, HMWCK, and p63 to categorize 26 diagnostically difficult poorly differentiated carcinomas as PCa or UCa. To our knowledge, no study so far has analyzed the usefulness of these markers in clinically difficult cases. We were able to categorize 81% of these diagnostically challenging cases (21/26) as PCa or UCa by using our preliminary panel of PSA, HMWCK, and p63 (Table 3 and Image 1). We were unable to resolve 5 cases (19%) because all of these cases were negative with all 3 antibodies (PSA–/HMWCK–/p63–). In such situations, we recommend using an extended panel including PAP, CK7, and CK20. All of the remaining cases could be resolved by using the extended panel: 2 cases as PCa (PAP+/CK7–/CK20–) and 3 as UCa (PAP–/CK+/CK20+).

A confident diagnosis can be established in the majority of cases of poorly differentiated carcinoma with a differential diagnosis of PCa vs UCa by using an immunohistochemical panel of PSA, HMWCK, and/or p63. The majority of poorly differentiated PCa cases retain PSA expression in which diffuse or focal PSA expression establishes the diagnosis of PCa. Negative PSA with moderate to diffuse HMWCK and/or p63 expression is diagnostic of UCa. Rarely, poorly differentiated PCa might focally express HMWCK. In situations in which the panel of PSA, HMWCK, and p63 is negative, an extended panel including PAP, CK7, and CK20 might be helpful in resolving the diagnosis. The majority of PCa cases express PAP diffusely in contrast with a small subset of UCa cases, which might express PAP focally. Although coordinate expression of CK7 and CK20 usually is helpful (CK7+/CK20+ or CK7+/CK20– supports a urothelial origin, whereas CK7–/CK20– supports a prostatic origin), results frequently might overlap. AMACR is not useful for distinguishing UCa from PCa.

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