Diagnostic Pathology

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Revisiting the use of CK7 and CK20 immunohistochemical stains in pathological diagnoses

Bangchen Wang[1], Diana M. Cardona[2] and Jiaoti Huang[2*]

Abstract

Background Cytokeratin-7 (keratin-7; CK7) and cytokeratin-20 (keratin-20; CK20) have been among the most widely used markers in pathology for prediction of tumor site of origin or classification. However, with the increased availability of newer and more specific biomarkers and molecular techniques, it is timely to revisit the utility of CK7 and CK20 stains under different clinical settings.

Methods In the current study, we retrospectively reviewed 612 surgical pathology cases at our institution where CK7 and/or CK20 stains were performed and determined to what degree they contributed to the final diagnosis.

Results In CK7-and-CK20 cases, the stains had a major contribution in 5% of the cases. In CK7-only or CK20-only cases, the percentages of major contribution were 34% and 69% respectively. However, when only cases where CK7/CK20 stains were used to determine tumor site of origin, the contributions become more comparable across all three case types, where CK7/CK20 stains had major contribution in < 10% of cases. Notably, 11% of CK7-and-CK20 cases had no specific or suggestive diagnosis, and 40% of CK7-and-CK20 cases had staining patterns inconsistent with the final diagnosis. Detailed analysis demonstrates that CK7 and CK20 stains, used singly, are most useful in the diagnosis of a limited number of pathologic entities with distinct CK7 or CK20 expression patterns.

Conclusions Our results suggest that the coordinate expression of CK7 and CK20 is generally not helpful in arriving at the final diagnosis. Reducing unnecessary immunohistochemical stains will help mitigate the rising healthcare cost and preserve tissue for molecular testing.

Keywords Surgical pathology, Immunohistochemistry, Tumor origin, CK7, CK20, Healthcare cost

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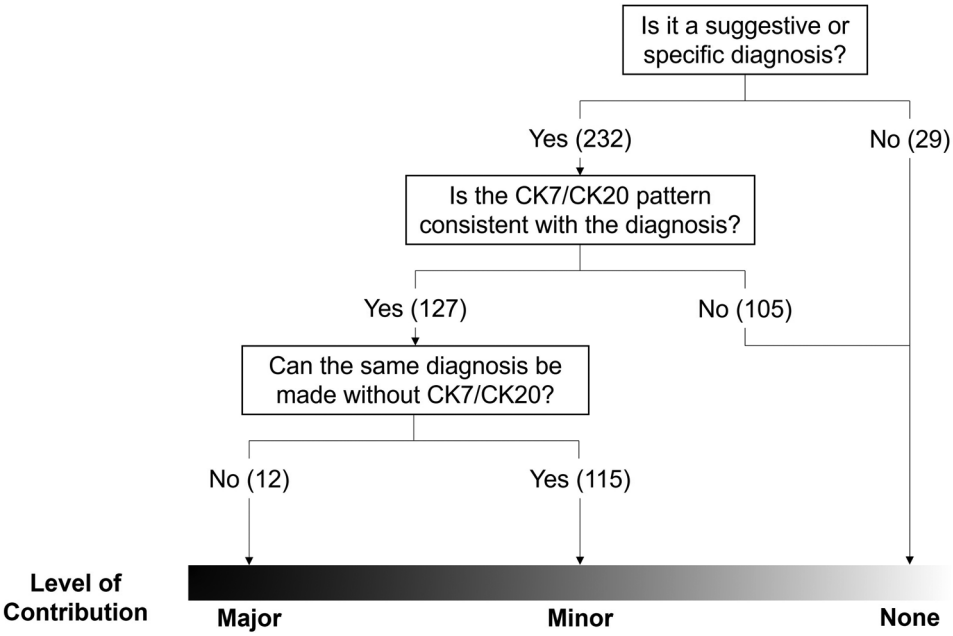

Fig. 1 The algorithm used to score the level of contribution of CK7 and/or CK20 stains. The numbers shown in parentheses are from the cases where both CK7 and CK20 stains were performed

Background

Since Dr. Allen Gown first described the diagnostic utility of the differential expression of cytokeratin-7 (keratin-7; CK7) and cytokeratin-20 (keratin-20; CK20) in 1995 [1], CK7 and CK20 have been among the most widely used markers in pathology for prediction of tumor site of origin or tumor classification. Many algorithmic approaches using immunohistochemical (IHC) profile have been proposed for carcinomas of unknown primary, and they almost always include the coordinate expressions of CK7 and CK20 [2–10]. However, with the increased availability of newer and more specific biomarkers and molecular techniques, it is timely to revisit the utility of CK7 and CK20 stains under different clinical settings. In the current study, we retrospectively reviewed over 600 surgical pathology cases at our institution where CK7 and/or CK20 stains were performed and determined to what degree they contributed to the final diagnosis.

Methods

From years 2016 to 2020, IHC stains for CK7 and/or CK20 were performed on 4421 surgical pathology cases at our institution (including biopsies and resections while excluding cytology cases). We randomly selected 612 cases (261 CK7-and-CK20 cases, 197 CK7-only cases, and 154 CK20-only cases) and retrospectively reviewed the CK7 and CK20 stains along with all other IHC stains performed at the time of the initial diagnostic evaluation. For each case, the level of contribution of the CK7 and/or CK20 stains to the final diagnosis was scored as one of the three categories: "none", "minor" or "major". The algorithm used for scoring is shown in Fig. 1. In summary, the CK7/CK20 staining was considered to have no contribution ("none") when their staining pattern was not consistent with the final diagnosis as referenced to Table 1 (adapted from previous studies [7, 9]) while the final diagnosis was made from the results of other, more specific markers. The CK7/CK20 staining was considered to have minor contribution ("minor") when their staining pattern was consistent with the final diagnosis, but the same diagnosis could be made without it. The CK7/CK20 staining was considered to have major contribution ("major") if the CK7/CK20 staining results were required for reaching the final diagnosis. This assessment was made by a pathologist trainee (BW) and senior pathologist (JH) to ensure accuracy.

To investigate the trend of CK7 and CK20 orders in carcinomas of unknown primary, we could not directly

Table 1 Differential expression of CK7/CK20 to determine tumor site of origin[7,9]

Site or Tumor Type	CK7	CK20
Urothelial, pancreatobiliary, ovarian (mucinous), upper GI	+	+
Lung, breast, endometrial, endocervical, ovarian (serous), mesothelioma, thyroid, salivary gland, RCC (papillary), pancreatobiliary, upper GI, urothelial	+	-
Colorectal, Merkel cell carcinoma, upper GI	-	+
Adrenocortical, HCC, RCC (clear cell), prostate, germ cell tumors, SqCC, NEC, NET	-	-

Abbreviations: GI, gastrointestinal; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; SqCC, squamous cell carcinoma; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor

compare the number of cases because the number of specimens significantly varied year-by-year. Instead, we calculated the percentage of CK7-and-CK20 cases out of all cases where CK7 and/or CK20 stains were ordered for each year from 2002 to 2020. The idea is that the majority of CK7-and-CK20 cases are carcinomas of unknown primary, and a higher percentage of CK7-and-CK20 cases correlates with more frequent use of CK7 and CK20 in such cases.

Statistical analyses were performed to compare cases with and without major contributions from CK7/CK20 stains using Fisher's exact test with $p < 0.05$ considered to be significant.

Results

A distribution of specimen sources is included in Fig. 2. Pulmonary and renal specimens account for the majority of the CK7-only cases (35% and 19% respectively). Urothelial and skin specimens account for the majority of the CK20-only cases (53% and 16% respectively). Pulmonary and gastrointestinal specimens are the most common among the CK7-and-CK20 cases (24% and 15% respectively). The 612 cases analyzed share a similar distribution of specimen sources as the 4421 total cases, supporting that they are a representative sample. As shown in Fig. 3A, in CK7-and-CK20 cases, the staining results had a major contribution in 5% of the cases. In CK7-only or CK20-only cases, the percentage of major contribution was increased to 34% and 69% respectively. However, when we only include cases where CK7/CK20 stains were used to determine tumor site of origin or tumor classification, the contributions become more comparable across all three case types (Fig. 3B), where CK7/CK20 stains had major contribution in only a small proportion of cases. Furthermore, the same findings are observed in both small biopsy specimens and larger resection specimens (Fig. 3C-D). A breakdown of cases where CK7/CK20 had no contribution was listed in Table 2. Notably, in the majority of the cases, CK7/CK20 results had no contribution because the staining pattern was inconsistent with the final diagnosis. Representative

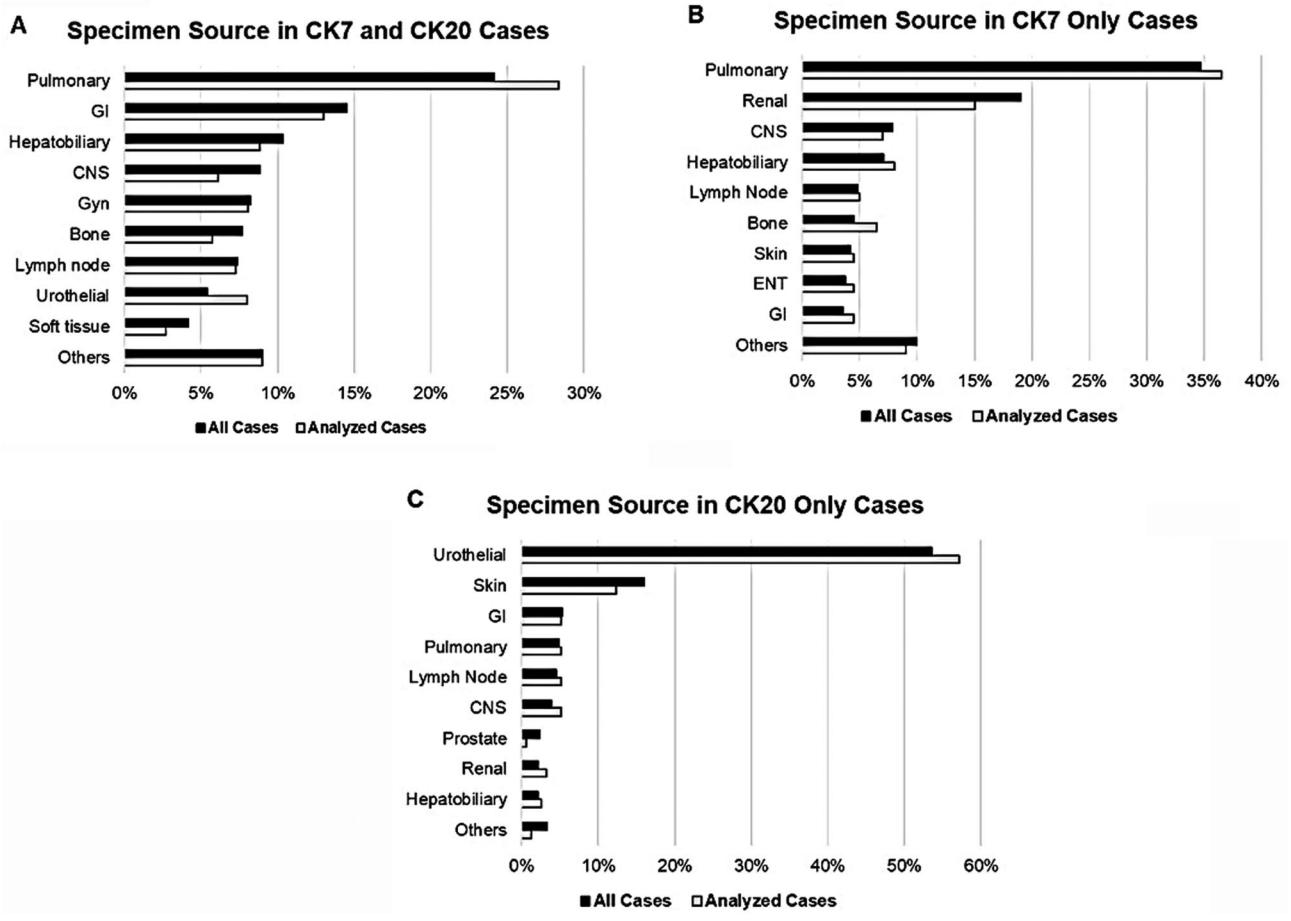

Fig. 2 The specimen sources of the three groups of cases in all cases and the analyzed cases. CK7, cases where only CK7 stain was performed; CK20, cases where only CK20 stain was performed; CK7 & CK20, cases where both CK7 and CK20 stains were performed. CNS, central nervous system; GI, gastrointestinal; Gyn, gynecological; ENT, head and neck

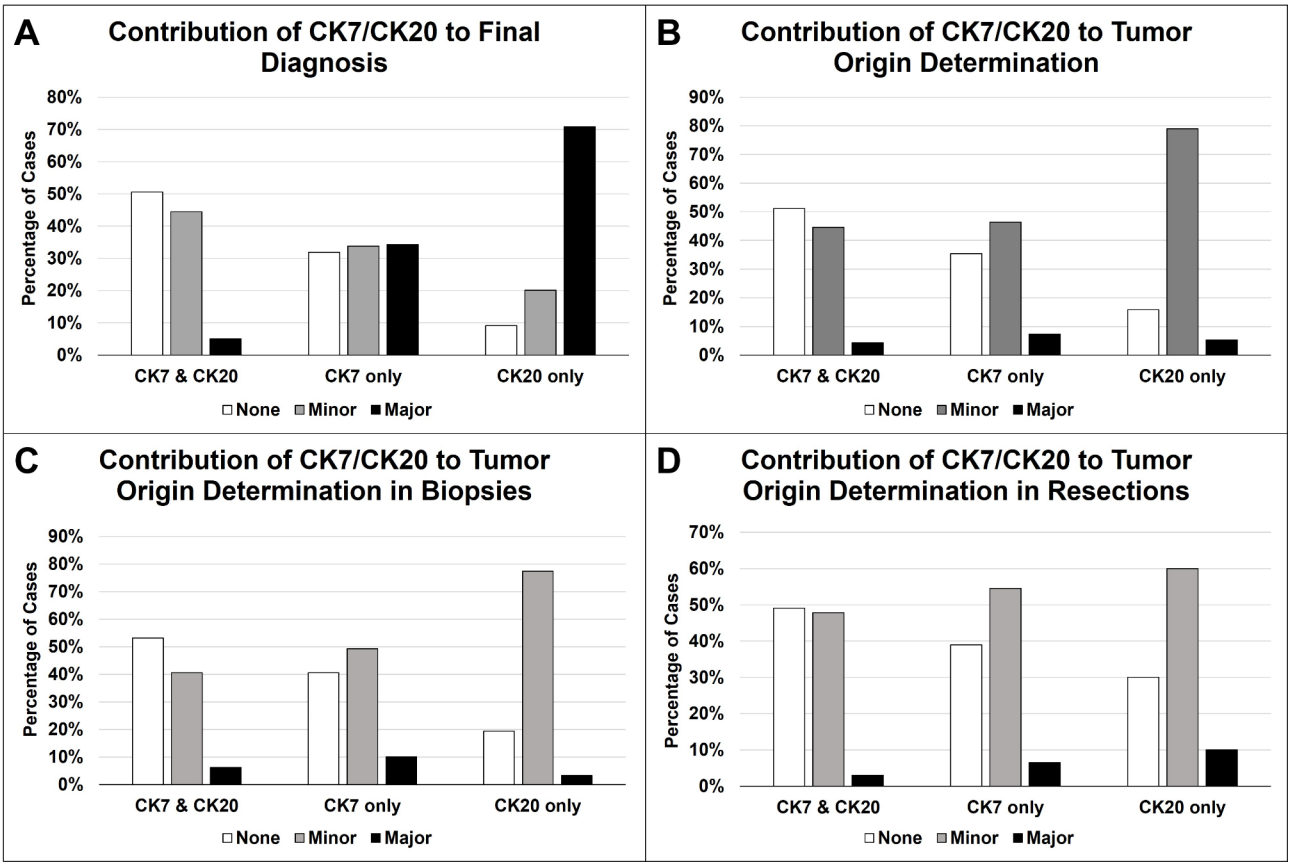

Fig. 3 Contribution of CK7 and CK20 stains to the diagnoses. **A**. Percentage of cases where CK7 and/or CK20 had major, minor, or no contribution to the final diagnosis among the three groups. $p < 0.00001$ by Fisher's exact test comparing the proportions of non-major contribution and major contribution among three groups. **B**. Percentage of cases where CK7 and/or CK20 had major, minor, or no contribution to the determination of tumor origin among the three groups. $p = 0.223$ by Fisher's exact test comparing the proportions of non-major contribution and major contribution among three groups. **C**. Percentage of cases where CK7 and/or CK20 had major, minor, or no contribution to the determination of tumor origin among the three groups in biopsy specimens. $p = 0.413$ by Fisher's exact test comparing the proportions of non-major contribution and major contribution among three groups. **D**. Percentage of cases where CK7 and/or CK20 had major, minor, or no contribution to the determination of tumor origin in among the three groups resection specimens. $p = 0.327$ by Fisher's exact test comparing the proportions of non-major contribution and major contribution among three groups

Table 2 Breakdown of cases where CK7/CK20 stains had no contribution

	CK7&20	CK7 only	CK20 only
Non-specific or suggestive diagnosis	29/261 (11%)	15/200 (8%)	4/154 (3%)
Inconsistent expression pattern	105/261 (40%)	49/200 (25%)	6/154 (4%)

microscopic images of cases from each category of CK7/CK20 contribution are shown in Fig. 4.

A breakdown of CK7/CK20 contribution score by individual organ systems is shown in Supplementary Fig. 1. After carefully examining the cases in each category including the case diagnosis, specimen source, and all IHC stains performed, we found that CK7 and CK20 stains, used singly, are most useful in the diagnosis of a limited number of pathologic entities with distinct CK7 or CK20 expression patterns, such as Paget's diseases, kidney tumors, flat urothelial lesions, Merkel cell carcinoma, etc. (Table 3). On the other hand, many tumor origins or tumor types show inconsistent or variable CK7/CK20 expression patterns; the most common entities are listed in Table 4.

As demonstrated in Fig. 5, across the nineteen-year period from 2002 to 2020, there was a significant decrease in percentage of CK7-and-CK20 cases, but it seemed to have reached a plateau at around 50% in the most recent years.

Discussion

Coordinate expression of CK7 and CK20 in determination of tumor site of origin

In the work up of carcinomas of unknown primary, CK7 and CK20 stains are often included in the first round of IHC orders. Various versions of Table 1 that show the expression patterns of CK7 and CK20 can be found in numerous publications and textbooks [3, 7, 9, 11–13] and are often posted on the walls of pathology sign-out

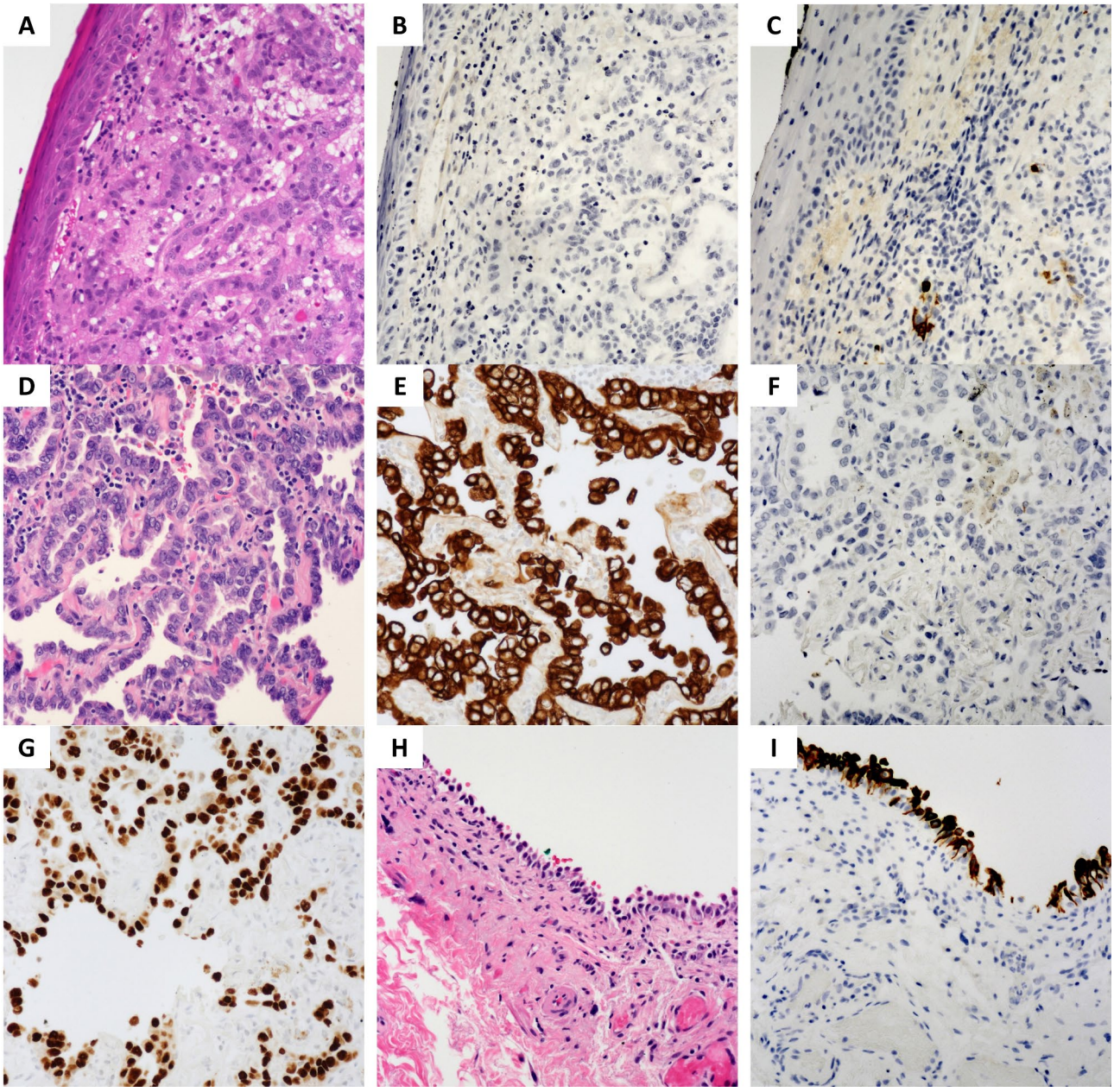

Fig. 4 Representative images demonstrating the contribution of CK7/CK20 combination in different settings. **A-C**: Adenocarcinoma of the esophagus for which CK7/CK20 made no contribution to the diagnosis. This particular case was negative for both but other patterns would also be unhelpful in determining the origin of the tumor because of the variable CK7/CK20 staining patterns in esophageal adenocarcinoma (**A**: H&E; **B**: CK7; **C**: CK20). **D-G**: Lung adenocarcinoma where a pattern of CK7+/CK20- made a minor contribution to the diagnosis as this pattern is consistent with adenocarcinoma of the lung. However, there are more specific markers such as TTF1 (**D**: H&E; **E**: CK7; **F**:CK20; **G**: TTF1). **H-I**: Urothelial carcinoma in-situ for which CK20 staining made a major contribution to the diagnosis. This bladder biopsy shows a very thin urothelial layer where the cells show darkly stained nuclei, high N: C ratio and loss of polarity. The differential diagnoses include reactive changes, residual basal layer after sloughing of surface urothelial cells and urothelial carcinoma in-situ (clinging type). Strong and diffuse staining for CK20 supports the diagnosis of urothelial carcinoma in-situ (**H**: H&E; **I**: CK20)

rooms and resident rooms [9]. However, as demonstrated by our study, there is limited use of performing CK7/CK20 IHC and corresponding reference tables. Firstly, these tables often have some discrepancies among different authors. One reason is that some tables are incomplete, only listing one common cancer type within an organ. For example, in the ovaries, serous carcinomas are usually CK7 positive CK20 negative; while mucinous adenocarcinomas are usually CK7/CK20 double positive [14, 15]. In the kidneys, clear cell renal cell carcinomas (RCCs) and MiTF/TFE family translocation-associated carcinomas are usually CK7/CK20 double negative [16,

Table 3 List of case types where CK7/CK20 stains had major contributions to the final diagnoses

CK7	CK20
Paget disease of the nipple	Merkel cell carcinoma
Extramammary Paget disease	Flat urothelial dysplasia
Renal cell carcinoma subtyping	
Highlighting background ducts in liver and salivary glands	

Table 4 List of common tumor origins with inconsistent CK7/CK20 expression patterns

Tumor Origin	Inconsistent patterns
Upper GI	Various expression patterns
Lung adenocarcinoma (non-enteric differentiation)	Can have patchy/focal CK20 expression
Large cell/small cell NEC	Can have CK7 and/or CK20 expression
Poorly-differentiated adenocarcinoma of various origins	Various expression patterns; diagnosis based on other markers and/or clinical/radiological findings

NEC, neuroendocrine carcinoma

17], but papillary, chromophobe, and mucinous tubular spindle cell RCCs are usually CK7 positive [16]. Another reason may be due to the difference in how pathologists interpret IHC. It is difficult to have a table with binary results when there is a whole spectrum of staining intensity and proportion of stained cells. Furthermore, the same tumor types can have different expression patterns. In the study published by Dr. Allen Gown[1] as well as many other studies [2, 4, 18, 19], the percentages of CK7/CK20 expression patterns were listed for specific tumor types, and some of them showed a variety of expression patterns. In one study for example [2], out of 39 gastric adenocarcinomas, 33% were CK7+/CK20+, 24% were CK7+/CK20-, 33% were CK7-/CK20+, and 10% were CK7-/CK20-. Although 89% of pancreatic adenocarcinomas were CK7+, 48% were CK7+/CK20+, and 41% were CK7+/CK20-.

The most striking finding in our study is probably the high proportion of cases where CK7/CK20 stains had no contribution at all to the final diagnosis. During the work up of carcinomas of unknown primary, pathologists often order CK7 and CK20 as a first step hoping to get a general sense of direction and narrow their differential diagnoses [7]. Interestingly, according to our study, in 41% of the cases where both CK7 and CK20 were ordered, the staining patterns were inconsistent with the final diagnosis (Table 2). This argues against using CK7 and CK20 as the initial step to narrow the differential diagnoses

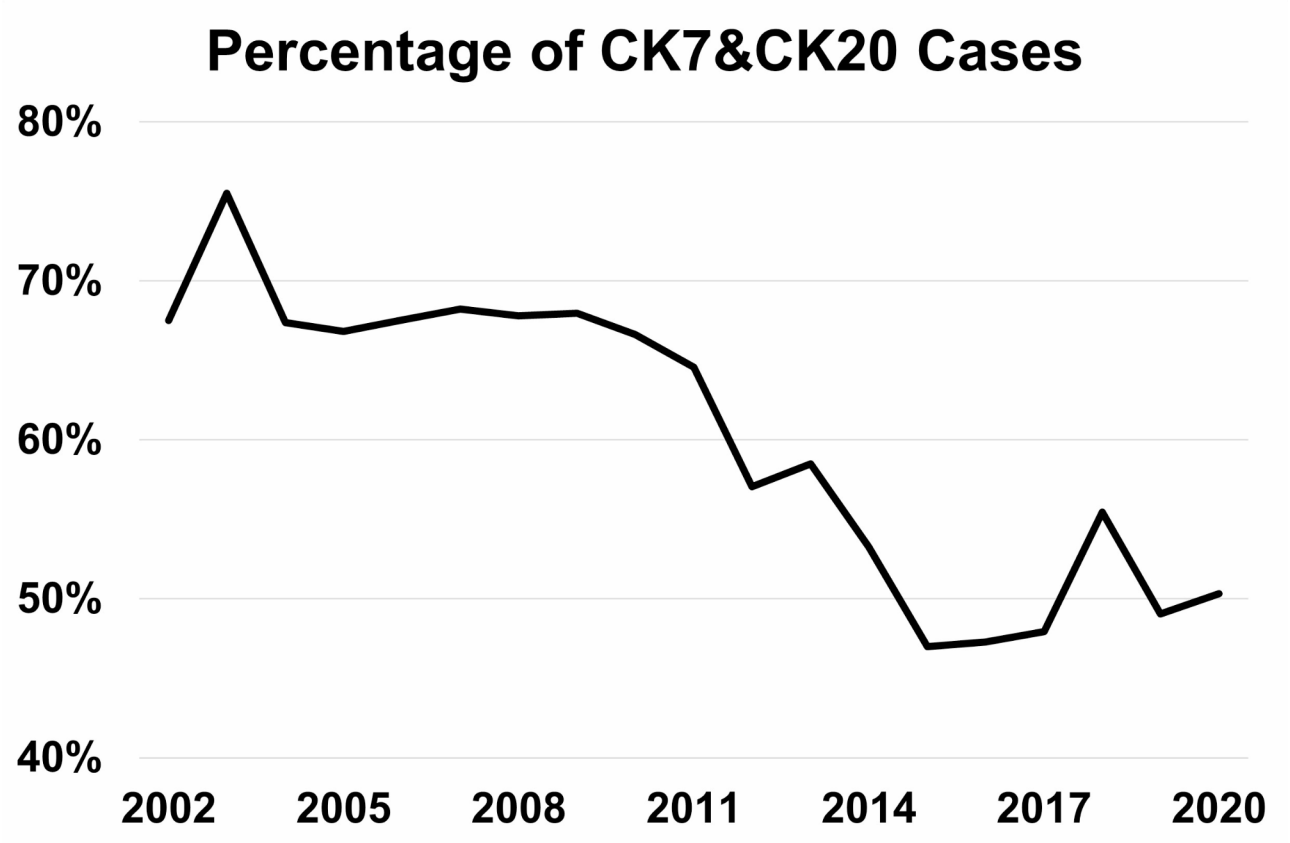

Fig. 5 The nineteen-year ordering trend of CK7 and CK20 stains. The percentage is calculated by dividing the number of cases where both CK7 and CK20 stains were performed by the number of cases where CK7 and/or CK20 stains were performed

because the staining results can be misleading 41% of the time.

In certain clinical-pathologic scenarios, using CK7 or CK20 stains individually can be quite valuable for diagnosing specific pathologic conditions, as shown in Table 3. However, most of these cases are not related to cancers of unknown primary origin but instead involve a particular differential diagnosis. When we focus solely on cases with unknown primary cancers, there are very few instances where CK7 or CK20 showed major contributions to the final diagnosis (Fig. 3).

During the retrospective review of cases, we noted that aside from histomorphology and IHC profile, correlation with clinical/radiological findings and morphologic comparison to prior specimens were of the most importance, especially in patients with a cancer history. In fact, in eight of the reviewed cases, none of the ordered IHC stains proved helpful; however, the pathologists were still able to reach specific diagnoses based on clinical correlations and morphologic comparisons with the patient's prior specimens.

Use of CK7 and CK20 in cases other than carcinomas of unknown primary

Contrary to the lack of usefulness in many cases of unknown primary, our study demonstrated that CK7 and CK20 are most useful when distinguishing between a limited number of differential diagnoses with distinct CK7 or CK20 expressions, as listed in Table 3. CK7 is often the single most important stain used in mammary and extramammary Paget disease [20, 21]. Almost all RCCs are negative for CK20, but CK7 is often key in distinguishing between oncocytoma (CK7-) and chromophobe RCC (CK7+) [22, 23] as well as distinguishing between clear cell carcinoma (CK7-) vs. chromophobe RCC or papillary RCC (CK7+) [24, 25]. Aside from staining lesional tissue, CK7 is also helpful in highlighting the background benign glands such as salivary glands and bile ducts. CK20, on the other hand, is well known for its characteristic perinuclear dot-like staining in Merkel cell carcinoma [26, 27]. Additionally, CK20 is one of the key markers for evaluation of flat urothelial lesions, particularly in distinguishing urothelial carcinoma in-situ from reactive atypia [28, 29].

Need for tissue preservation

Molecular testing has become increasingly available and is crucial for clinical decision making. Therapeutic interventions such as checkpoint inhibitors, EGFR inhibitors, and NTRK inhibitors may be initiated before a definitive histologic diagnosis is established [11]. For this reason, IHC should be performed judiciously in small biopsies to save as much tissue as possible for molecular testing. This is also expressively recommended in the 2021 WHO update of lung tumors [30]. However, in our study, 36% of CK7-only cases and 47% of CK7-and-CK20 cases were lung biopsies, and the CK7/CK20 stains made major contributions in only 7% and 4% of the time, respectively.

After extensive IHC work up, there were still a significant portion of cases left without a definitive diagnosis. This is especially prominent in cases where both CK7 and CK20 were ordered, where 11% of the cases do not have a specific or suggestive tumor site of origin. In these cases, molecular testing may be crucial in shaping the therapeutic strategy.

Cost for unnecessary IHC

Each additional IHC incurs additional health care cost that impacts patients, payors and laboratories, including equipment, materials, and the time spent by technologists and pathologists. As specified in the Centers for Medicare and Medicare's Physician Fee Schedule [31], the approximate global reimbursement for each additional IHC is $89.63 in 2022 (CPT code 88341). According to our study, CK7 and/or CK20 IHC may have been unnecessary in up to 95% of cases in which both tests were performed, 66% of CK7-only cases, and 31% of CK20-only cases. This equates to approximately $491,629 of avoidable costs in the five-year period. Furthermore, this does not take into account the cost of any subsequent testing performed unnecessary based on the CK7/CK20 results. Interestingly, Fig. 5 showed a decreasing trend in the percentage of CK7-and-CK20 cases, most pronounced around 2011–2014, possibly due to the availability of newer biomarkers; however, the observed decrease seemed to have reached a plateau in the most recent years.

Limitations and conclusions of current study

There are a few limitations of our current study. Firstly, only surgical pathology cases but not cytology cases were included in this study. The rationale was to exclude cases with limited samples that would make the interpretation of IHC difficult. However, this may also lead to sampling bias because it inevitably excluded all the fine needle aspirations, which are often performed in tumors of unknown primary. Another limitation of our current study is that retrospective review and scoring of cases may be subjective because it does not put us in the same circumstances at the time of the initial diagnosis. Despite these limitations, we believe that surgical pathology cases including biopsies and resections are the most relevant materials for such study and retrospective review provides a good landscape of over-utilization of certain IHC tests. By following the algorithm described in Fig. 1, we believe that we held a relatively objective view, especially in the cases where CK7/CK20 stains had no contribution.

Our study demonstrates that CK7/CK20 combination, which was once highly useful in certain differential diagnosis, continues to be frequently ordered despite the availability of more specific markers. Additionally, this combination has also been used frequently in tumors that do not display a single prevalent CK7/CK20 staining pattern, such as those of the stomach, pancreas and ovary. Over-utilization of C7/CK20 staining without good justification can generate results that may be confusing or misleading and can lead to wasting of precious biopsy tissue and potentially compromising the opportunity of definitive diagnosis. Finally, there is significant healthcare cost associated with unnecessary IHC testing. According to our estimate, if CK7 and CK20 stains had been ordered more judiciously in surgical pathology cases, we could have saved at least $100,000 per year at our institution alone. With the ever-rising healthcare costs, challenges with staffing shortages and the increasing need for molecular testing, our study provides strong evidence that pathologists should carefully consider their differential diagnoses and the impact on clinical management before ordering IHC panels.

Abbreviations

CK7	keratin-7
CK20	keratin-20
IHC	Immunohistochemistry
RCC	Renal cell carcinoma
GI	Gastrointestinal
HCC	Hepatocellular carcinoma
SqCC	Squamous cell carcinoma
NEC	Neuroendocrine carcinoma
NET	Neuroendocrine tumor

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13000-025-01638-x.

Supplementary Material 1

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Not applicable.

Author contributions
B.W. performed the acquisition, analysis and interpretation of data, statistical analysis, and wrote the manuscript text and prepared the figures and tables. J.H. performed study concept and design, the analysis and interpretation of data, and participated in the review and revision of the paper; D.C. provided technical and material support and participated in the review and revision of the paper. All authors read and approved the final paper.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Duke University Institutional Review Board (exempt review) and was performed in accordance with the Helsinki declaration.

Consent for publication
Not applicable.

Competing interests
Jiaoti Huang, MD PhD, is a consultant for or owns shares in the following companies: Amgen, Artera, Kingmed Diagnostics, Teddy Clinical Research Laboratories, MoreHealth, OptraScan, Genetron, York Biotechnology, Genecode, VIVA Biotech, Seagen Inc. and Sisu Pharma, and received grants from Zenith Epigenetics, BioXcel Therapeutics, Inc., Dracen Pharmaceuticals and Fortis Therapeutics.

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