Diagnostic Utility of Selective Upper Tract Urinary Cytology: A Systematic Review and Meta-analysis of the Literature

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The diagnosis of upper tract urothelial carcinoma (UTUC) can be a challenging diagnostic pursuit. To date, there is no large-scale study assessing the statistical utility (eg, sensitivity and specificity) of selective cytology. Herein, we systematically reviewed and meta-analyzed the published literature to evaluate the efficacy of selective cytology for the detection of UTUC in patients with a suspicious clinical profile Selective cytology confers a high specificity but marginal sensitivity for the detection of UTUC. The sensitivity is greater for high-grade UTUC lesions. The statistical assessment of its utility is limited by the heterogeneity and bias of previous studies. UROLOGY 96: 35–43, 2016. © 2016 Elsevier Inc.

Upper tract urothelial carcinoma (UTUC) represents 5% to 6% of all urothelial tumors, and patients have a 5-year disease-specific survival of 75%.[1] UTUC diagnosis is difficult and is usually triggered by at-risk patients presenting with nonspecific complaints, such as hematuria (75%), flank pain (30%), or urinary tract symptoms.[2] Currently, the "gold standard" for detecting UTUC is computed tomography (CT) urography, which has a sensitivity of 96% and a specificity of 99%.[3] CT urography is often supplemented with additional diagnostics, including cystoscopy, intravenous urography, ureteropyeloscopy, and urinary cytology (either voided or selective upper tract cytology). The false negative rate of voided cytology for the detection of UTUC ranges from 50%[4] to 89%.[5] The cytological accuracy may be increased by using specimens obtained by ureteral catheterization (eg, washing and brushing), and selective cytology sensitivity has been reported to be as high as 97%.[6] The European Association of Urology (EAU) recommends that patients with suspicious findings (eg, hematuria, upper tract filling defects) undergo selective cytology.[2] However, the diagnostic approach to a suspicious upper tract lesion remains variable. A more comprehensive analysis of upper tract cytology accuracy would improve the urologist's paradigm to the UTUC diagnostic workup. The current study was designed to systematically review and meta-analyze the published literature to evaluate selective upper urinary tract cytology for detecting UTUC in patients with a suspicious clinical picture.

MATERIALS AND METHODS

Meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[7]

Literature Search

The published and gray literature was searched using standardized bibliometric strategies for diagnosing UTUC predicated on the pathologic diagnosis based on nephroureterectomy, distal or segmental ureterectomy, biopsy, and cytology with pathologic confirmation. These strategies were established using a combination of standardized terms and key words, and were implemented in PubMed (1946-present), Embase (1947-present), the Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Review Effects, Cochrane Central Register of Controlled Trials, Proquest Dissertations and Theses, and FirstSearch Proceedings. Searches were limited to humans and to English-language citations using database-supplied filters. All searches were completed in March 2016. The search results were exported to EndNote, and 1526 duplicates were identified and removed, for a total of 2539 unique citations. Automated retrieval was complemented with a manual search of bibliographies and review articles (n = 5).

Study Selection

The titles and abstracts of 2544 studies were screened, and obviously irrelevant studies were excluded. The full text of the remaining 56 potential studies was then read independently, and studies meeting inclusion criteria were identified. Studies that reported diagnostic outcomes of selective cytology in patients with

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suspected UTUC were included. Diagnostic selective upper tract catheterization using either aspiration or lavage techniques was the primary preoperative urinary source for cytological analysis. In the original inclusion criteria, only studies that used extirpative tissue diagnosis (eg, nephroureterectomy, distal ureterectomy) as the "gold standard" for comparison with preoperative selective cytology were included. The results from these studies were used to calculate the sensitivity of preoperative upper tract cytology. However, determining specificity of cytology using extirpative pathology as the reference standard requires a benign surgical nephroureterectomy; there are few reports in the literature that present these data. Consequently, limiting the systematic review to only include studies with final surgical pathology as the reference standard did not yield sufficient studies to determine the specificity of cytology. Therefore, the inclusion criteria were expanded to include tissue biopsy as a reference standard for calculating specificity. Due to the variability of cytologic analysis and qualification over time, a modern cohort was selected to include publication in 2005 and after. These dates correspond to the most recent World Health Organization (WHO) classification of urothelial neoplasms,[8] the cytology recommendations from the 2004 Papanicolaou Society of Cytopathology Practice Guidelines Task Force,[9] and an era with increased utilization of ureteroscopy.

Studies investigating novel tumor markers (eg, nuclear matrix protein 22, telomerase activity, bladder tumor antigen, fluorescent immunohistochemistry (ImmunoCyt test [Scimedx]), and p53 quantification) were included if selective cytology data were given as a separate comparison arm (eg, fluorescence in situ hybridization vs selective cytology compared to final pathology; only data from the selective cytology arm were used in the present study). Voided or catheterized bladder cytology, as well as brush cytology, was excluded. No patient restrictions based on age, gender, race, comorbidities, healthcare setting, or concomitant bladder cancer were applied. Studies that specifically excluded patients with concurrent bladder cancer were noted and evaluated in a subanalysis that excluded patients with possible known lower tract malignancy, as there is a noted concern for contamination of even instrumented selective cytology in patients with a history of bladder cancer.[10] Studies with patients receiving neoadjuvant chemotherapy or having undergone prior cystectomy were excluded, unless the data from these excluded patients were easily separable from the rest of the study's cohort.

Data Extraction

Information extracted included: (1) characteristics of study participants (age, gender, presenting symptoms); (2) type of selective cytology (washing, aspiration); (3) definition of benign vs malignant vs atypical cytology; (4) method of final diagnosis (extirpative tissue, biopsy tissue); (5) cytology diagnostic accuracy numbers (true positives, false positives, true negatives, false negatives); and (6) correlation of cytology sensitivity to tumor grade. Three authors of reviewed manuscripts were contacted for further information. All responded, and one provided numerical data on 6 patients who had undergone brush biopsy rather than selective cytology; the data from these six patients were subsequently excluded from analysis.

Different pathologic grading categorizations were used throughout the literature; some studies graded tumors as either "high grade" or "low grade" (based on the 2004 WHO system), whereas other studies assigned a grade 1 through 4 (based on the 1973 WHO system). A recent comparison of the 1973 and 2004 WHO grading systems found a significant overlap in overall survival between grade 2 and grade 3 tumors.[11] Thus, for this meta-analysis, low-grade pathology was defined as "low grade" or "grade 1," whereas high grade was defined as "high grade" or "grades 2, 3, or 4."

Methodological Quality Assessment

Quality assessment of each study was performed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist.[12] Four domains were evaluated for risk of bias and applicability at study level: (1) patient selection; (2) index test; (3) reference standard; and (4) flow and timing. The quality assessment was performed by 2 independent reviewers, with disagreement resolved by discussion with the senior author.

Statistical Analysis

The extracted rates of false negatives and false positive cytology were used to calculate the sensitivity and specificity of selective cytology in the diagnosis of UTUC. Statistical analysis was performed using the metafor package from R version 3.2.0.[13] A random-effects model was chosen to estimate overall sensitivity and specificity. Sensitivity and specificity estimates and confidence intervals were based on log odds and were reconverted back to percentages. Heterogeneity was assessed with the I^2 statistic (scale 0% to 100%, where 0% indicates homogeneity and 100% indicates that all variance is due to study heterogeneity). Publication bias was assessed using the Egger bias test.[14]

RESULTS

Literature Search

Figure 1 shows the flow diagram of the studies. Following title and abstract screening for relevance, 2488 records were excluded. Detailed reading of the remaining articles excluded an additional 23 records. Complementary manual search yielded 5 additional studies for inclusion. Overall, 33 articles met inclusion criteria, with 21 comparing selective cytology to final pathology as the reference standard[4-6,15-32] and 12 comparing selective cytology to tissue biopsy.[10,33-43] Fifteen studies were published in the modern cohort (2005 to present).

Study Characteristics

Table S1 provides the details of each of the 33 studies. Notably, there was great heterogeneity in how each study distinguished cellular "atypia" from malignancy and benignity. Ten studies simply listed cytology as either "positive" or "negative" and did not distinguish atypical findings (although 4 of these did report a third category of "insufficient" cytology). The remaining studies made allowance for some pathologic uncertainty, including classifications such as "suspicious" or "atypical." However, there was further inconsistency among these series, as some studies considered "suspicious" cytology as "positive" whereas others considered it as "negative." For the purposes of the meta-analysis, "atypical" or "insufficient" cytology was considered negative for series that listed cytology in separate categories (eg, positive for malignancy, negative for malignancy, atypical, or insufficient). Conversely, cytology categorized as "suspicious" was combined with the malignant cytology category. A separate meta-analysis was

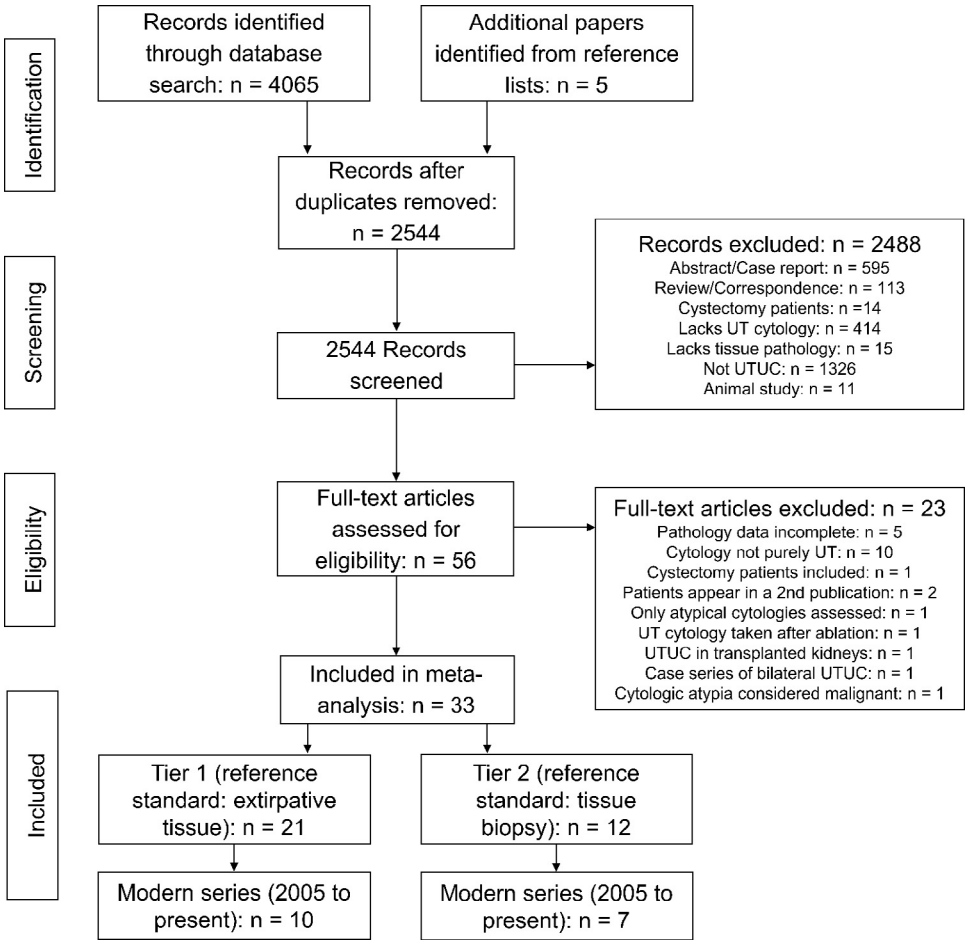

Figure 1. Flow of articles during systematic review. UT, upper tract; UTUC, upper tract urothelial carcinoma.

performed, which excluded any study that did not define atypia (Table S2).

Quality Assessment

Assessment of the quality of included studies using the QUADAS-2 model is depicted in Figure 2. Most of the studies had a high risk of patient selection bias (Fig. 2A), given that very few enrolled a consecutive or random sample of eligible patients with suspected disease. Risk of bias in the flow and timing in each study was also likely high, as the period of timing between cytology collection and final pathology determination was not specified, which may have lowered the sensitivity of cytology if cytology was not collected soon before pathology was determined. Risk of bias for the reference standard (either final extirpative pathology or tissue biopsy) was likely significant in all of the included studies. Namely, all studies using biopsy as the "gold standard" likely had a high risk of bias, as biopsy has been shown to have a relatively poor sensitivity for detecting UTUC.[44] Further, as most studies did not indicate whether tissue pathology results were interpreted without prior knowledge of cytology results, there is the theoretical consideration that this may also have introduced some degree of bias. Concern regarding the applicability of each study's use of selective cytology was determined to be high for all 33 series (Fig. 2B), as the interpretation of cytology results has yet to be standardized across institutions.

Sensitivity and Specificity Analyses

Pooled sensitivities and specificities from the modern cohort are shown in Figure 3A,B, respectively. Separate analyses were performed for those studies with a reference standard of final pathology and biopsy pathology. Within the modern cohort, the pooled sensitivity of selective cytology with respect to final pathology was 53.1% (95% confidence interval [CI] = 42.3-63.6; I^2 = 86.0%) (Fig. 3A). When excluding series that did not delineate cytology "atypia" and hence only reported cytology dichotomously as "positive" or "negative," sensitivity remained unchanged at 53.6% (95% CI = 37.9-68.7; I^2 = 90.5%). The pooled specificity for selective cytology based on biopsy pathology was 90.0% (95% CI = 85.4-93.2; I^2 = 0%) (Fig. 3B); no modern series reported specificity data based on final pathology. When including only series that explicitly excluded bladder cancer patients, sensitivity based on final pathology was 55.3% (95% CI = 31.4-77.0; I^2 = 94.5%), and specificity based on biopsy pathology was 90.7% (95% CI = 81.5-95.5; I^2 = 0.0%). When limiting the meta-analysis to only modern series that explicitly employed dedicated cytopathologists, 2 series remained that reported

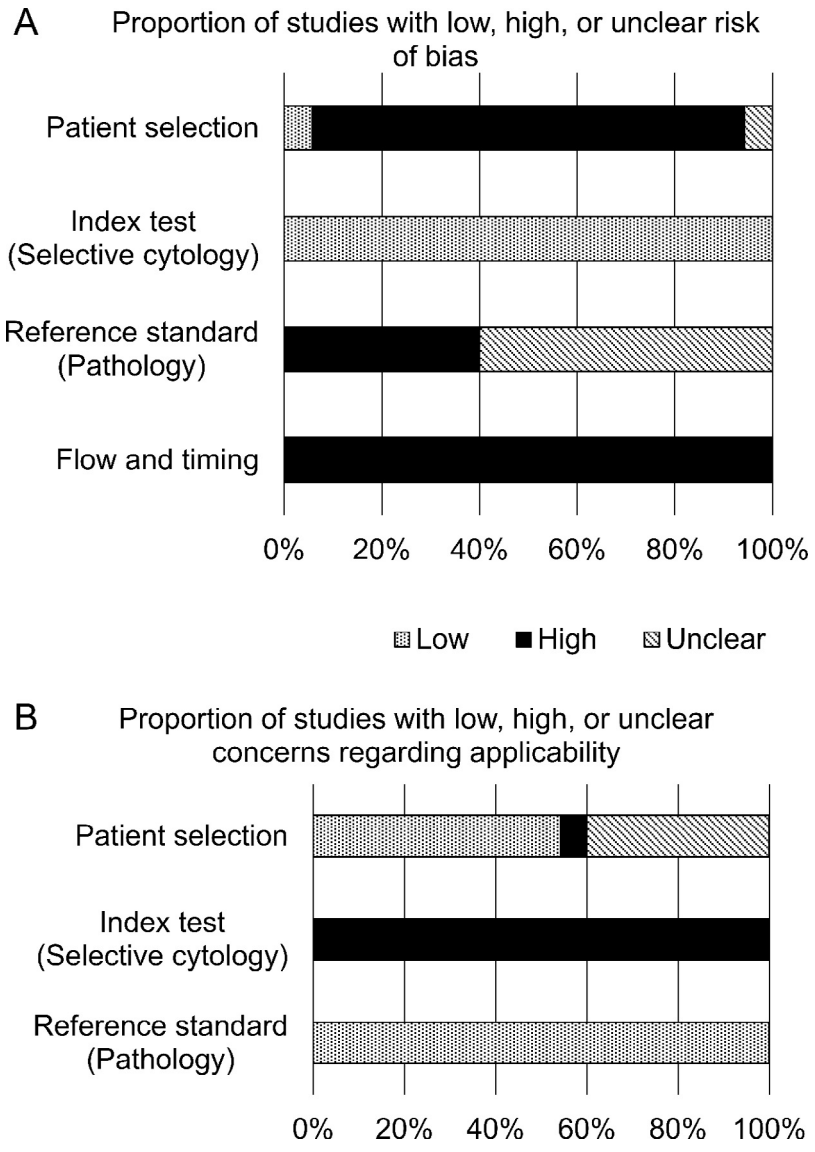

Figure 2. Assessment of quality using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) model. **(A)** Proportion of studies with low, high, or unclear risk of bias. **(B)** Proportion of studies with low, high, or unclear concerns regarding applicability.

sensitivity based on biopsy pathology,[10,42] and 3 series remained that reported specificity based on biopsy pathology[10,27,42]; the resulting pooled sensitivity and specificity were 34.3% (95% CI =21.0-50.5; I^2 = 0.0%) and 88.6% (95% CI 75.6-95.1; I^2 = 43.8%), respectively. Meta-analyses of sensitivity and specificity from data included in all publication dates (1946 - present) are given in Table S2.

The pooled sensitivity of selective cytology stratified by tumor grade in modern series is shown in Figure 3C. The resulting pooled sensitivities were 45.6% (95% CI = 31.8-60.1; I^2 = 33.1%) for low-grade tumors and 69.9% (95% CI = 56.2-80.8; I^2 = 68.6%) for high-grade tumors.

Publication Bias

For modern publications reporting sensitivity based on final pathology, the Egger's regression intercept was –0.71 (two-tailed *P* value = .737). For modern publications reporting specificity based on biopsy pathology, the Egger's regression intercept was 1.28 (two-tailed *P* value = .206). Funnel plots (Figure S1) did not reveal obvious evidence of asymmetry. These results indicate no evidence of publication bias among modern series.

DISCUSSION

The present study provides the first pooled analysis of the literature regarding the diagnostic capacity of selective cytology. Overall, sensitivity based on final pathology was 53.1% (95% CI = 42.3-63.6), and specificity based on biopsy was 90.0% (95% CI = 85.4-93.2). Notably, the sensitivity and specificity did not appreciably change when including only studies that explicitly excluded bladder cancer patients (55.3% and 90.7%, respectively). Although the

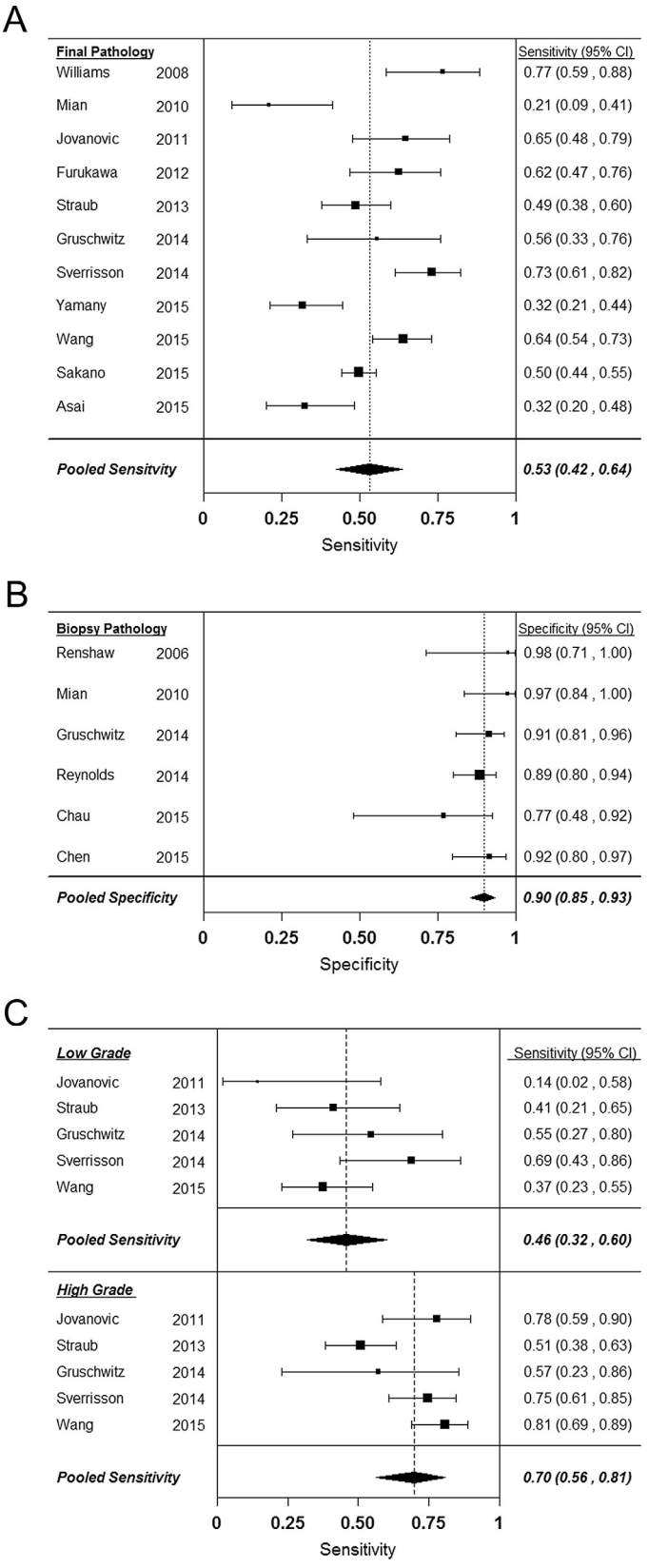

Figure 3. Forest plots from series published between 2005 to present of **(A)** pooled sensitivity estimates based on final pathology, **(B)** specificity estimates based on biopsy pathology, and **(C)** pooled sensitivity estimates based on final pathology grade (high grade = grades 2, 3, or 4 vs low grade = grade 1). CI, confidence interval.

exact likelihood of contamination of an upper tract sample by a bladder source is unknown, these results suggest that the diagnostic accuracy of selective cytology is not appreciably affected by concomitant bladder cancer. Interestingly, the findings from the present study are similar to those found in the meta-analysis of cytology for the detection of bladder cancer conducted by Glas et al. The authors found a sensitivity of 55% (95% CI = 48-62) and a specificity of 94% (95% CI = 90-96).[45] In their discussion, the authors describe similar challenges to a robust analysis, given the heterogeneity of the studies and the nonrandom and nonconsecutive cohorts included in the analysis.

The rarity of UTUC makes establishing strategies to direct diagnosis and management difficult. Despite the challenges, both the EAU and the National Comprehensive Cancer Network have put forth guidelines. The National Comprehensive Cancer Network recommends cytology in each patient undergoing a workup for an upper tract lesion.[7] Likewise, the EAU guidelines specifically mention the importance of a positive voided cytology in those patients without visible changes to the bladder urothelium, thereby providing a grade "A" recommendation for cytology.[2] Importantly, neither organization indicates whether the cytology should be done selectively. Future clarification of this, which may be made possible by the present analysis, may help the practicing urologist.

Despite the usefulness of selective cytology, false negatives occur (up to 60%[25]) and are especially prevalent for low-grade UTUC, precluding the use of selective cytology as a screening tool for UTUC. The most utilitarian examination in the diagnosis of UTUC is CT urography. Based on a meta-analysis including 5 studies, CT urography has a pooled sensitivity of 96% (95% CI = 88-100) and a specificity of 99% (95% CI = 98-100).[3] Appropriately, CT urography is the most commonly used tool when pursing a diagnosis of UTUC.[46] It is worthy of note, however, that although many small lesions (<0.5 cm) are detected by CT urography,[47] it is possible that very small lesions may result in false negatives. The series from which the CT urography meta-analysis is derived represent small numbers of patients with UTUC, making generalizations difficult. Furthermore, ~60% of new cases of UTUC present with invasive histology and therefore may be more likely to manifest less subtle radiographic findings.[48] In clinical scenarios in which a negative cytology conflicts with other suspicious findings, such as abnormal CT urography, adjunctive procedures should be employed (ie, ureteroscopy). Overall, selective cytology represents a useful tool in the urologist's armamentarium in the clinical evaluation of a suspicious upper tract lesion. However, as an independent test, selective cytology does not approach the efficacy of CT urography. Its use in conjunction with other tests represents the most practical clinical scenario.

The findings presented herein may assist the urologist in particular clinical circumstances. In those patients presenting with ambiguous findings on CT urography, a selective cytology at the time of a mandatory cystoscopy may aid in the confirmation of an UTUC. Selective cytology may also be used to prompt ureteroscopy and biopsy, and in this modern era (eg, after 2005), upper tract cytology is useful in conjunction with ureteroscopy for a worrisome upper tract lesion. Furthermore, a common situation encountered by urologists is one in which CT urography is unremarkable, but selective cytology is positive. Given the high specificity of selective cytology, ureteroscopic evaluation with potential biopsies is critical in such a scenario.

Ureteroscopy can provide invaluable information as part of the workup of an upper tract lesion in many cases. Ureteroscopic approaches provide for visualization of the lesion, detection of areas worrisome for carcinoma in situ, and the ability to perform a brush or ureteroscopic biopsy. Brush biopsy may be employed conveniently at time of ureteroscopy; although studies of its effectiveness are limited, its sensitivity is poor (34%), and the specificity is comparable to upper tract cytology.[33] Although ureteroscopy has many advantages, it is not a panacea. The pitfalls of diagnostic ureteroscopy and biopsy have been well described (eg, inability to obtain sufficient tissue, inconsistent ureteroscopic visualization of tumor, upgrading and upstaging at time of nephroureterectomy).[44] Therefore, there may be some situations in which cytology may provide useful information in a nonconfirmatory ureteroscopic biopsy. Perhaps most importantly, given the poor sensitivity for even high-grade disease, patients can be more accurately counseled about their risk of UTUC, and future management decisions (eg, necessity for repeat testing or observation) may be better informed.

Given the inadequate sensitivity of selective cytology and some of the difficulties in establishing reliable ureteroscopic biopsy information, the future study of complimentary tests may improve the ability to detect UTUC, derive prognostic information, and better counsel patients. Traditionally, the use of biomarkers has been focused on serum and urinary proteins, but none have been established for the detection of UTUC or bladder cancers. For example, preoperative serum C-reactive protein has been associated with advanced stage and recurrence-free survival in patients with UTUC, although it is not used for the detection of a new or recurrent UTUC.[49] Although serum and urine tests are more convenient, tissue-based biomarkers provide an in situ context relative to the location of the biomarker within a cell or the surrounding tissue field.[50] Gayed et al recently demonstrated the feasibility of obtaining genetic biomarker profiles from ureteroscopic biopsies. The authors performed immunohistochemical staining for p21, p27, p53, cyclin E, and Ki67.[51] They found Ki67 positivity most frequently in the malignant specimens (13/15, 87.7%). Ki67 has shown promise in its prognostic capacity; it predicts recurrence-free and cancer-specific survival.[52] Recently, Bagrodia et al evaluated 300 cancer genes in radical UTUC specimens.[53] The authors discovered that the *TP53/MDM2* and *FGFR3* genes were uniformly related to negative and positive clinicopathological results, respectively. Unfortunately, the aforementioned genetic biomarkers do require tissue and are not available for screening or initial diagnosis of UTUC.

Other contemporary techniques may provide for future research collaborations and the possibility of enhanced and accurate detection of UTUC. Caraway et al investigated the use of urinary cytology with techniques such as quantitative digital cytometry.[54] The authors found a relationship of these tests with urothelial cancer recurrence after cystectomy. With further study, this approach may provide an opportunity for assessment of a patient with a de novo finding such as hematuria or abnormal CT urography. Finally, advanced optical diagnostics provide an intriguing area of future research and development. Narrow band imaging and photodynamic diagnosis aim to improve visualization via enhanced contrast of tissues. Optical coherence tomography and confocal laser endomicroscopy were designed with the intent of conferring real-time histological evaluation. These techniques are in their infancy and require navigation of present technical and equipment obstacles before they will be available for routine use.[55]

Limitations of the present study are largely a product of the biases held by the studies analyzed. As a result of these biases and inconsistencies, the heterogeneity is high (I^2 =86.0% for selective cytology sensitivity). For example, some studies included patients with known UTUC. Studies enrolling participants with known disease and a control group without the condition may exaggerate diagnostic accuracy.[56] Thus, these studies may be biased toward finding a greater sensitivity as compared to studies that include patients with suspected disease but an unconfirmed diagnosis (ie, difficult to diagnose patients). Perhaps one of the most obvious inconsistencies that this review encountered was the lack of consensus regarding the criteria used for assigning and diagnosing urothelial malignancy and "atypia." Although this inconsistency may partly reflect the evolving nature of how pathologists have interpreted cytologic malignancy over the decades,[57] Table S1 illustrates the marked heterogeneity even among modern series in how malignant cytology is classified. Several series did not include the category of atypia (only listing "positive" or "negative"), whereas others added additional categories (eg, "suspicious" or "insufficient for diagnosis").

Cytology would ideally be interpreted by dedicated cytopathologists, which was documented in only 5 series.[10,27,34,38,42] Although the most recent guidelines from the WHO and the Papanicolaou Society of Cytopathology may help to eventually establish cytology standardizations, the statistical heterogeneity encountered when limiting our meta-analysis to modern series may, in large part, be due to continued inconsistency in cytology interpretation. In addition, poor inter- and intraobserver agreement regarding the grading of urothelial carcinoma from urine cytology has previously been documented.[58] Clearly, further work is needed to establish universal pathologic classifications to facilitate comparison among cytology outcomes. Alternatively, future work may be dedicated to advancing automated, computer-based image analysis of cytologic specimens.[59] Finally, the specificity calculation based on final pathological specimens was not feasible, given the paucity of literature within which a benign nephroureterectomy rate was reported. Although a recent study by Hong et al described the incidence of benign nephroureterectomy, selective cytology was rare in their series.[60]

CONCLUSION

The utilization of cytology is convenient for the urologist who intends to perform ureteroscopy or ureteral catheterization. The results of a selective cytology should be interpreted in the context of the results of this meta-analysis. Selective cytology should be used in conjunction with other diagnostic modalities (eg, ureteroscopy) to work up a suspicious upper tract lesion or clinical presentation. However, the heterogeneity and publication biases present in the available literature make it difficult to make robust statistical conclusions. Overall, selective cytology is a specific test and can be employed to help confirm a diagnosis of UTUC. Subanalysis demonstrated that sensitivity is greater in those patients with high-grade UTUC tumors. However, the overall marginal sensitivity it affords precludes its use as a screening test.

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APPENDIX

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.urology.2016.04.030.