Cytopathology in Focus: Paris System for urinary cytology: why and where now

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May 2017—It is well known that examination of urine dates back to antiquity, but it wasn't until the 19th century that cancer cells were microscopically documented in urine, by Hermann Lebert in 1845 and Vilem D. Lambl in 1856.[1,2] Over many decades, countless talented and noteworthy authors have contributed valuable observations and conceptual mechanisms to the study of urinary cytology, but a systematic, universally accepted, internationally recognized system with clear goals was missing. The Paris System for Reporting Urinary Cytology was created in response to perceived problems with diagnostic reproducibility and clinical utility in urinary cytopathology.[3]

The Bethesda System for Reporting Cervical Cytology and the Bethesda System for Reporting Thyroid Cytopathology,[4,5] which are predecessors to the Paris System, have shown the value of international bodies of experienced pathologists and clinicians coming together to agree on morphologic criteria, risk assessment, and reasonable clinical objectives. These systems have been maintained and updated through professional societies. The problem of older cytologic systems is that they tended to be individual efforts that existed in static forms within textbooks. As new information became known and new opinions were formed, practitioners tended to add their own interpretations to the information in the texts, and divergence in criteria would occur. This would result in decreased reproducibility among laboratories and individual cytopathologists. The Paris System was created to provide a way to increase the reproducibility by offering clear guidance with morphological criteria in addition to providing a pathophysiologic base around which to add new developments in the cytology of the urinary tract.[6] Multiple iterations of the Paris System are foreseen as adaptation to future information.

The reputation of urinary cytology has been stigmatized by reports of low sensitivity and specificity, which may be corrected by refocusing its aim. A central tenet of the Paris System is that urinary cytology has been burdened with an unreasonable goal, that of the diagnosis of "low-grade urothelial carcinoma."[7] Urinary cytology performs poorly at diagnosing low-grade urothelial carcinoma because the lesional cells that make up entities that are histologically diagnosed as low-grade urothelial neoplasms (urothelial papilloma, papillary urothelial neoplasm of low malignant potential, low-grade papillary urothelial carcinoma) are typically bland and resemble their non-neoplastic counterparts. For this reason, in the Paris System all low-grade urothelial neoplasms (papilloma, PUNLMP, LGUC, for example) are reported under the title low-grade urothelial neoplasm (LGUN). In the Paris System this diagnostic category has very restrictive criteria in which bland (non-high grade) urothelial cells are seen surrounding a fibrovascular core.

In fact, the concept of "low-grade urothelial carcinoma" is flawed on several levels. Since it was invented, the term malignancy refers to a neoplasm that has the life-threatening propensities of local invasion and distant spread. What has been termed "low-grade urothelial carcinoma" does neither of these. It tends to form exophytic papillary groups that stay in the epithelium. Further, the low-grade urothelial "carcinomas" have different genetic mechanisms (fibroblast growth factor receptor 3 protein, or FGFR3) than the more dangerous, invasive high-grade lesions that show p53 mutations.

The Paris System aids the urologist in important ways. Urologists can find the low-grade papillary urothelial lesions on cystoscopic examination but do not tend to be able to visualize the flat high-grade lesions that can invade. Alternatively, cytology is excellent at identifying high-grade urothelial carcinoma. Therefore, if the Paris System is used, urologists will no longer be frustrated with urinary cytology. They find the exophytic lesions and understand

that cytology will support them by detecting the high-grade carcinomas.

The Paris System has established as its central object for urine cytology the ability to detect high-grade urothelial carcinoma. Therefore, if properly used (abiding by the morphological criteria and reporting categories), the Paris System will not only increase the specificity and sensitivity of the test but also reduce the number of "atypical" diagnoses, which produce unnecessary anxiety in patients and cause skepticism and trust issues among urologists. This skepticism becomes significantly visible especially when the equivocal (including atypical and suspicious) diagnosis rate is very high, such as reported by Gopalakrishna, et al., where more than 50 percent of samples in a series were reported as equivocal.[8]

Overuse of atypia in cytologic reporting systems has forced change in our practice patterns. Human papillomavirus testing has become the standard of practice in response to an interpretation of atypical squamous cells of uncertain significance (ASC-US) in gynecologic cytology. Other ancillary methods including liquid-based preparations and computer-assisted screening evolved in the sometimes vain hope of lowering the atypia rate. In thyroid cytology, molecular testing is becoming increasingly common after a diagnosis of atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS). As more equivocal (i.e. atypical) diagnoses are rendered in any diagnostic system, there will be a response to try to resolve the uncertainty. Thus, more expensive, ancillary methods are employed and become the norm, increasing health care expenses often without significant overall benefits. Or clinicians may turn away entirely from cytology, reducing volumes of well-studied, well-understood, cheap, and reliable tests.[9]

The Paris System, like the Bethesda Systems, is showing wide acceptance. Numerous national and international presentations and workshops have been given and many more are planned. The text and atlas were translated recently into Japanese, and other developments are forthcoming. The publisher's website shows more than 7,900 downloads for chapters and whole versions of the atlas. The book is electronically available via Amazon Kindle, Apple iTunes, and Google Play.

The Paris System is open-ended and will be improved over time; users are encouraged to share suggestions. The last chapter of the text poses many questions and helps direct research

efforts that will lead to refinements. The purpose of these questions is to stimulate relevant research to be able to produce new, improved versions of the Paris System. Examples of "research wish-list" challenges posted in the last chapter are as follows: 1) to determine the reporting rates of all categories after proper usage of the criteria, 2) to perform outcome and interobserver reproducibility studies with the updated criteria, 3) to establish clear-cut management guidelines based on outcomes and with input from urologic surgeons and acceptance of patients, and 4) to develop quality control metrics in monitoring the usage of diagnostic categories in the Paris System.
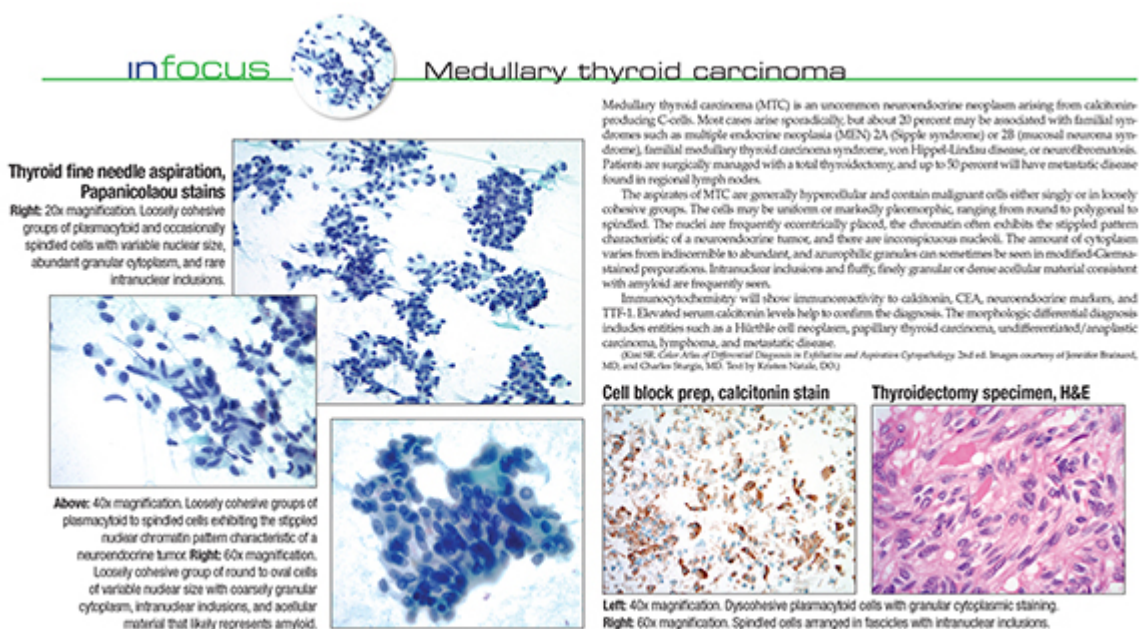
The first Paris Interobserver Reproducibility Study (PIRST) has been completed. It was modeled after the two interobserver reproducibility studies performed for the Bethesda System for Reporting Cervical Cytology.[10,11] The American Society of Cytopathology, International Academy of Cytology, and Papanicolaou Society helped support recruitment of more than 1,300 respondents to take a Web-based image survey of 85 images from the Paris System Image Atlas set. This survey was performed before the atlas was published when the concepts and criteria for the Paris System were new. Participants were drawn from across the world and the majority were board-certified cytopathologists, but cytotechnologists, cytopathology fellows, and residents also participated. As expected, the best agreement was found in images with expert interpretations of negative for high-grade urothelial carcinoma (NHGUC) (71 percent), the highly restricted low-grade urothelial neoplasm (LGUN) (62 percent), and high-grade urothelial carcinoma (HGUC) (57 percent). Indeterminate categories showed lower concordance. The PIRST will form a basis for future interobserver studies, and as familiarity with the Paris System grows, better correlations are expected between the diagnoses rendered by an expert panel and survey participants. The results were first presented in an abstract and in a workshop at the May 2016 International Congress of Cytology in Yokohama, Japan, and the final manuscript is in preparation. As familiarity with the Paris System grows, the test characteristics of urinary cytology are likely to improve, leading to greater acceptance and trust among urologists.

The official Paris System website is at http://Paris.soc.wisc.edu. It contains an outline of the tenets of the Paris System, diagnostic images, a self test, and a means to donate images to the Paris System.

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