A major paradigm shift: The Paris System of Reporting

Urinary Cytology – The Atypical Categories

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The American Cancer Society predicts that approximately 74,000 new cases of bladder cancer will be diagnosed in the year 2015 in the United States and approximately 16,000 people will die of the disease. Of these new cases only about 50% are detected by routine cytologic examination. The majority of bladder cancers (75%) are superficial in nature at presentation. Approximately 50% - 70% of these superficial tumors recur and 10% - 20% progress to be invasive at least into muscularis propria. This natural history of bladder cancer results in a very high overall disease prevalence.

The main purpose of urine cytology is to detect lesions that can be difficult to detect cystoscopically and to detect high grade urothelial lesions that are at a risk of developing into invasive carcinoma. Papillary low grade urothelial neoplasms are easily seen cystoscopically and therefore unlikely to be missed by the urologist, except those that occur in the upper urinary tract. Therefore, for practical purposes, high grade urothelial carcinoma is diagnosed on cytology, and unless a true papillary fragment with a discernible true fibrovascular core lined by atypical urothelial cells is seen on a cytology sample, a diagnosis of low grade urothelial carcinoma should not be rendered.

Until recently there has been a lack of a standardized/comprehensive reporting system for urinary cytology that is based on the current understanding of the pathogenesis of urothelial urinary cytology that is based on the current understanding of the pathogenesis of urothelial carcinoma (UC) and the clinical significance. Although
over ten years ago there was an attempt to create such reporting guidelines\textsuperscript{ii}, it lacked wide input of the cytopathology community, which most likely explains why it has never been fully implemented in practice. In recognition of this need, an international panel of cytopathologists with interest in urinary tract cytology and a urologist convened in Paris in May of 2013 at the 18\textsuperscript{th} International Congress of Cytology to discuss ways to improve the reporting and performance of urinary cytology, and to assess the value of ancillary tests in the screening and diagnosis of urinary neoplasms. With the mantra “the aim of urinary tract cytology is to detect the potentially life threatening high grade urothelial carcinoma” the group designed the \textit{Paris System of Reporting Urinary Tract Cytology}. In practice, this is very much like the Bethesda system for reporting cervical cytopathology \textsuperscript{iii} or the Bethesda system for reporting thyroid cytopathology.\textsuperscript{iv}

The \textit{Paris System of Reporting Urinary Tract Cytology}

1. Unsatisfactory/ Nondiagnostic
2. Negative for HGUC
3. Atypical urothelial cells
4. Suspicious for high grade urothelial carcinoma
5. High grade Urothelial carcinoma
6. Low grade Urothelial Neoplasm
7. Other malignancies, Primary and Secondary
1. **Unsatisfactory / Nondiagnostic**: This category is reserved for specimens that are virtually acellular, or when urothelial cells are obscured by red blood cells, neutrophils, or lubricant-type material. For detail please see handout on adequacy.

2. **Negative for High grade Urothelial Carcinoma**: meaning the sample is composed of benign urothelial cells and that cells that could remotely raise the suspicion of high grade urothelial carcinoma are conspicuously absent. As seen in the discussion under low grade urothelial neoplasm this category (NHGUC) does not and cannot exclude this possibility definitively as the cytomorphology of low grade urothelial neoplasms are remarkably similar to that of normal urothelial cells. The clinical approach for this diagnosis should be to proceed with the next regularly scheduled follow up.

3. **Atypical urothelial cells** - this is the category that causes the most controversy among pathologists and clinicians. There are several reasons for this; first of all urothelial atypia is not as well defined in the literature and thus it is in the eye of the beholder. Renshaw attempted to categorize atypical urine specimens based on cytomorphologic features and the risk associated with the different groups, however this is still a very difficult category to define, and one that is associated with considerable difference of opinion. Therefore there is a wide range of the percentage of atypia ranging between 2% to 30%. The criteria for AUC are defined as:
   - Non-superficial and non-degenerated urothelial cells with an increased nuclear cytoplasmic (N/C) ratio (N/C ratio > 0.5) (Required diagnostic criteria)
In addition, one of the following features is required to be present:

- Hyperchromasia
- Irregular coarse, clumped chromatin
- Irregular nuclear membranes (contours)

If the N/C ratio is > 0.7 and two other features defined above are present then the diagnosis should be “suspicious for high grade urothelial carcinoma” rather than “atypical urothelial cells present”.

Although there is not a universally defined benchmark for the atypia rate, it is prudent to keep the atypia rate considerably low, to keep it more meaningful. This important category should be used by the pathologist to convey concern and recognize the difficulty in interpretation of specimens that may require close clinical follow-up.

In addition, a subset of patients with a history of high grade urothelial carcinoma and a negative follow-up could have lesion in the upper tract that was not biopsied. As predicted, in these patients with a previous diagnosis of urothelial carcinoma there is a higher likelihood of a subsequent malignant diagnosis after an atypical specimen.\textsuperscript{vi}

Currently, the overall yield for a diagnosis of atypia is so low that most urologists pay little attention to it and most of the time they follow the patient up as if it were a “negative” diagnosis. However in cases where the patient has had a previously documented urothelial carcinoma, there is increased clinical suspicion for malignancy the patient should be followed up closely, and the specimen should be triaged using ancillary tests such fluorescence in situ hybridization, microsatellite analysis, or other markers for the detection of urothelial carcinoma.
4. **Suspicious for High grade Urothelial Carcinoma**, meaning the pathologist sees very rare cells with features that are compatible with urothelial carcinoma, or there are only some features of malignancy however either the paucity of these cells or insufficiently fulfilled malignancy criteria preclude a definitive diagnosis of malignancy.

A diagnosis of ‘suspicious for HGUC’ is defined as non-superficial and non-degenerated urothelial cells showing:

- Increased nuclear to cytoplasmic (N/C) ratio>0.7. ‘Required diagnostic criterion’.
- Hyperchromasia ‘Required diagnostic criterion’.

In addition, at least one of the two following features needs to be present

- Irregular clumpy chromatin.
- Irregular nuclear membranes.

In general, if this diagnosis is rendered the patients should be followed up closely with cystoscopy/ureteroscopy and surgical biopsies.

5. **High grade Urothelial Carcinoma** meaning there is an undeniable presence of tumor cells fitting the criteria for high grade urothelial carcinoma as outlined below.

At this point a surgical biopsy is warranted to determine the presence/depth of invasion, hence the stage of the neoplasm.

Cytologic features of high grade urothelial carcinoma are: Increased cellularity, presence of loose clusters and single cells, moderate to marked pleomorphism, high
N/C ratio, hyperchromasia, coarse chromatin, irregular nuclear membrane, and eccentrically located, enlarged, pleomorphic nuclei. Prominent nucleoli as well as squamous or glandular differentiation could also been seen. For detailed discussion on HGUC please refer to the HGUC handout.

6. Low grade Urothelial Neoplasm The cytologic atypia present in individual cells of low grade urothelial neoplasms is subtle and not well recognized by cytomorphology. The only time we can definitely make the diagnosis of low grade papillary urothelial carcinoma in instrumented urine is when well-defined fibrovascular cores with capillaries are present. This finding, however, is exceedingly rare. Occasionally the specimen may be very cellular and composed of very uniform, mostly single cells. In these cases umbrella cells are usually lacking or they are very rare. Individual cells have minimal cytologic atypia. In these cases one may suspect the presence of low grade papillary urothelial carcinoma and there are usually large tumors easily visualized on the cystoscopy. In general, it is recommended to compare results of urine cytology with results of cystoscopy and bladder biopsies, especially when considering the diagnosis “low grade urothelial neoplasm”. However if our diagnosis is based on those findings, it has to be clearly stated in the report. For detailed discussion on LGUN please refer to the LGUN handout.

7. Other malignancies, Primary and Secondary:
Primary malignancies: include squamous cell carcinoma, adenocarcinoma, small cell carcinoma

Secondary Malignancies in the bladder: Less than 10% of bladder tumors represent secondary neoplasms, most of which are direct invasion from prostate, cervix, uterus, or GI tract. The most common distant metastases are malignant melanoma, carcinomas of stomach, breast, kidney and lung.

For detailed discussion on other malignancies please refer to the specific handout.

Table summarizes the categories in the Paris System, the risk of malignancy and the management.

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk of Malignancy</th>
<th>Management</th>
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<tbody>
<tr>
<td>Unsatisfactory/Nondiagnostic</td>
<td>? (&lt;5%)</td>
<td>Repeat cytology, cystoscopy in 3 months if increased clinical suspicion</td>
</tr>
<tr>
<td>Negative for Malignancy</td>
<td>0-10%</td>
<td>Clinical follow up as needed</td>
</tr>
<tr>
<td>Atypical Urothelial Cells</td>
<td>8-35%</td>
<td>Clinical follow up as needed. Use of ancillary testing.</td>
</tr>
<tr>
<td>Suspicious for High Grade</td>
<td>50-90%</td>
<td>More aggressive follow up, cystoscopy, biopsy</td>
</tr>
<tr>
<td>Urothelial Carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Grade Urothelial Neoplasm</td>
<td>~10%</td>
<td>Need biopsy to further evaluate grade and stage</td>
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<td>-----------------------------------------------</td>
</tr>
<tr>
<td>High Grade Urothelial Carcinoma</td>
<td>&gt;90%</td>
<td>More aggressive follow up, cystoscopy, biopsy, staging</td>
</tr>
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<td>Other malignancy</td>
<td>&gt;90%</td>
<td>More aggressive follow up, cystoscopy, biopsy, staging</td>
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References:

i American Cancer Society, Cancer Facts and Figures 2015


