Original Article

Diagnosis of dysplasia in upper gastro-intestinal tract biopsies through digital microscopy

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Abstract

**Background:** Whole slide digital imaging (WSDI) offers an alternative to glass slides for diagnostic interpretation. While prior work has concentrated on the use of whole slide digital imaging for routine diagnostic cases, this study focuses on diagnostic interpretation of digital images for a highly challenging area, upper gastro-intestinal (GI) dysplasia. The aim of this study is to study the accuracy and efficiency of WSDI in the diagnosis of upper GI tract dysplasia.

**Materials and Methods:** Forty-two hematoxylin and eosin (H and E)-stained slides representing negative, indefinite, low grade and high grade dysplasia were selected and scanned at 20x (Aperio XT). Four attending GI pathologists reviewed the WSDI, then glass slides, with at least 3–4 weeks between each media; glass slides were re-reviewed 16–18 months later.

**Results:** Intraobserver variability for three clinically relevant categories (negative, indefinite/low grade, high grade) was wider for WSDI to glass (kappa range 0.36–0.78) than glass to glass (kappa range 0.58–0.75). In comparison to glass slide review, WSDI review required more time and was associated with an unexpected trend toward downgrading dysplasia.

**Conclusions:** Our results suggest: (1) upper GI dysplasia can be diagnosed using WSDI with similar intraobserver reproducibility as for glass slides; however, this is not true for all pathologists; (2) pathologists may have a tendency to downgrade dysplasia in digital images; and (3) pathologists who use WSDI for interpretation of GI dysplasia cases may benefit from regular, on-going, re-review of paired digital and glass images to ensure the most accurate utilization of digital technology, at least in the early stages of implementation.

**Key words:** Digital microscopy, dysplasia, gastrointestinal biopsies

BACKGROUND

Whole slide digital imaging (WSDI) offers an alternative to glass slides for diagnostic interpretation. Prior work has mainly focused on WSDI for frozen section interpretation, with fewer studies on routine pathologic diagnosis and secondary consults.\cite{1-9} WSDI presents an attractive alternative to shipping glass slides for expert consultation in diagnostically challenging cases, eliminating turnaround time and potential damage or loss of diagnostically critical glass slides. Our institution has provided digital slide consultations for 2nd Affiliated...
Hospital, Zhejiang University, China, since 2010 and has utilized digital pathology embedded within the Department for research and tumor boards since 2008. Approximately 10,000 slides are scanned annually by our Department.

One high volume and diagnostically challenging area in pathology that could benefit from rapid expert consultation is the evaluation and grading of dysplasia in esophageal and gastric biopsies. We are unaware of prior studies addressing the use of WSDI for the evaluation of dysplasia in upper GI tract biopsies. Thus, we undertook the present study to examine the accuracy and efficiency of WSDI in diagnosing GI dysplasia. Both inter- and intraobserver variability in the glass slide diagnosis of esophageal dysplasia, even among expert pathologists, has been reported,[10-13] and our intention in this study was not to repeat these prior studies. Rather, given our prior experience with digital image diagnosis[10] and our expertise in gastrointestinal pathology, we sought to establish whether diagnostic variability between glass slides and WSDI was similar or different than those reported for glass slide to glass slide evaluation.

**MATERIALS AND METHODS**

One hundred of cases of upper GI biopsies with diagnosis of negative, indefinite, low grade or high grade dysplasia were identified from the UCLA Pathology database. Two of the authors (DG and SD) performed case selection and subsequent statistical analysis, but were not involved in interpreting digital images for this study. Forty-two cases (37 esophageal and 5 gastric) were selected for inclusion, as were a control set of 10 cases with classic diagnostic features (tubular adenoma - 3 cases, sessile serrated adenoma - 2 cases, hyperplastic polyp, rectal adenocarcinoma, Barrett’s esophagus without dysplasia, esophageal squamous mucosa with no dysplasia, and normal colonic mucosa). Criteria for inclusion included cases in which the two case screeners agreed on the diagnosis and slides that were free of artifacts (folded tissue, uneven sections, bubbles, thick sectioning, unusually dark or light H and E stains) that can result in poor quality digital images.[6,14] The final study set included 13 cases negative for dysplasia, 9 cases indefinite for dysplasia, 11 cases of low grade dysplasia, and 9 cases of high grade dysplasia [Figure 1].

Glass slides were anonymized to ensure pathologists were blinded to the diagnosis and scanned at 20x with an Aperio XT scanner (Aperio Technologies, Vista, CA) by Translational Pathology Core Laboratory (UCLA). The initial screeners (DG and SD) reviewed all digital images to ensure they were in focus and of high quality. Four specialty trained gastro-intestinal pathologists (BN, SH, DD, GC) with varying experience as an attending pathologist (6 months, 3 years, 9 years, and 13 years of experience) and computer skills reviewed the WSDI, then the glass slides after a minimum period of 3–4 weeks. Digital images were reviewed on standard Dell monitors with 1280 × 1024 pixel resolution and our computers were equipped with ATI Radeon HD2400XT video cards. Final diagnosis, time required, problems encountered and whether or not the pathologist felt the need for 40x magnification were recorded for all cases. The time required for the diagnosis was recorded by each pathologist from the time the digital slide opened in the Aperio viewer to diagnosis or from the time the slide was placed on the microscope stage to diagnosis.

Since the intention of this study was to examine variability in diagnosis between WSDI and glass slides, only intraobserver variability was calculated. Three different sets of intraobserver variability statistics were calculated for each pathologist: WSDI to glass diagnosis for the set of control slides, WSDI to glass diagnosis for dysplasia and glass to glass diagnosis for dysplasia. For dysplasia cases, intraobserver variability was calculated using two different criteria, as used by previous authors:[11] one approach used three clinically relevant categories (negative, indefinite/low grade, high grade) and the second approach used all four diagnostic categories (negative, indefinite, low grade, and high grade). Discrepancies in dysplasia diagnoses were recorded and defined as major or minor. A major diagnostic discrepancy was defined as a diagnosis of negative for dysplasia in one media versus a finding of any other diagnosis (indefinite, low grade, or high grade dysplasia) in the other. A minor discrepancy was defined as a difference in the grade of dysplasia assigned. For the

**Figure 1: Degrees of dysplasia: negative (a) indefinite (b) low grade (c) high grade (d) (hematoxylin-eosin stain, original magnification: x10)**
control slides, a minor diagnostic discrepancy was defined as a difference in dysplasia grade and a major diagnostic discrepancy was defined as any diagnosis other than that’s pathologist’s glass slide diagnosis or the diagnosis of the two authors who selected the cases. Kappa coefficient can be thought of as the chance-corrected proportional agreement, and possible values range from +1 (perfect agreement) to 0 (no agreement above that expected by chance) to –1 (complete disagreement).

**RESULTS**

All pathologists showed perfect correlation (1.0) between WSDI and glass diagnosis for the set of 10 control slides. All diagnoses also correlated perfectly with the diagnoses assigned by the two authors selecting the cases.

As expected, in the set of dysplasia slides, all pathologists had major and minor discrepant diagnoses on WSDI to glass slide review and for glass to glass slide review. Intraobserver kappa values for both WSDI to glass and glass to glass review were improved when calculated on the three clinically relevant categories [Table 1].

Overall, there was more variation in kappa values for WSDI to glass interpretation. Table 1 shows the kappa values for each pathologist as calculated by the three clinically relevant categories or by all four categories. For WSDI to glass review, the kappa statistics were 0.36 (fair), 0.42 (moderate), 0.71 (good), and 0.78 (good) for the three clinically relevant categories and 0.28 (fair), 0.37 (fair), 0.63 (good), and 0.75 (good) for all four categories. For glass to glass review, the kappa statistics were 0.58 (moderate), 0.70 (good), 0.70 (good), and 0.75 (good) for the three clinically relevant categories and 0.50 (moderate), 0.56 (moderate), 0.64 (good) and 0.68 (good) for all categories. Two pathologists had lower kappa values for WSDI in both sets of kappa calculations, while one pathologist had higher kappa value for WSDI [Table 1]. Table 2 shows the percentage of discrepant diagnoses by pathologist for both WSDI-glass and glass-glass review. With WSDI, total discrepant diagnoses (major plus minor) for each pathologist ranged from 21% to 36%; major discrepancies ranged from 7% to 14% and minor discrepancies from 12% to 24% [Table 2]. No correlation was noted between a pathologist’s experience and percentage of discrepant diagnoses on WSDI interpretation.

The specific diagnoses on glass and WSDI slides in the discrepant cases are listed in Table 3. Discrepant dysplasia diagnoses between WSDI and glass slides occurred in 57 of 168 (34%) total possible incidences (4 pathologists × 42 slides = 168 incidences). In 14 of these 57 discrepancies (25%), this involved only one pathologist with a discrepancy between their glass and WSDI diagnosis. In 16 of the 57 discrepancies (28%), two pathologists were discrepant between their glass and WSDI diagnosis, and in 27 of the 57 incidences (47%), three of four pathologists had discrepancies between their glass and WSDI diagnosis. Discrepant dysplasia diagnoses from glass to glass review occurred in 48 of 168 (29%) total possible incidences. In 14 of these 48 incidences (29%), this involved only one pathologist with a discrepancy between the two passes on glass slide. In 9 of the 48 incidents (19%), two pathologists were discrepant, in 4 of the 48 incidents (8%) three of four pathologists had discrepancies, and in 1 of the 47 incidents (2%) all four pathologists were discrepant between their first and second review of the glass slides.

Pathologists generally downgraded the degree of dysplasia on WSDI compared to the glass slides [Tables 4 and 5]. Dysplasia downgrading occurred in 53 of 60 WSDI cases (88%) and in 24 of 48 second review glass cases (50%). For WSDI, this included 26 of 29 cases (90%) with major discrepancies [Table 3]. Seven cases were “upgraded” on WSDI by three of the four pathologists; three cases indefinite on WSDI were called negative on glass, two cases low grade on WSDI were interpreted as low grade on glass; two cases high grade on WSDI were interpreted as low grade on glass. Scanning at 40× was requested in 10 cases; in 4 of these cases, the pathologist’s diagnosis was discrepant between WSDI and glass images.

WSDI review required more time than glass slide review (range 50% to 400% longer), depending on the case and the pathologist [Table 2]. The time required for glass slide review was similar for the first and second glass

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### Table 1: Intraobserver k values for three clinically relevant categories and for four categories

| Pathologist | 3 Categories: ND; IND/LGD; and HGD | 4 Categories: ND; IND; LGD; and HGD |
|-------------|-----------------------------------|-----------------------------------|
|            | WSDI - Glass | Glass #1 - Glass #2 | WSDI - Glass | Glass #1 - Glass #2 |
| #1         | 0.71         | 0.70                 | 0.63         | 0.56                 |
| #2         | 0.36         | 0.58                 | 0.29         | 0.50                 |
| #3         | 0.42         | 0.75                 | 0.37         | 0.64                 |
| #4         | 0.78         | 0.70                 | 0.75         | 0.68                 |

ND: No dysplasia, IND: Indefinite for dysplasia, LGD: Low-grade dysplasia, HGD: High-grade dysplasia, WSDI: Whole slide digital imaging
Table 2: Review time and discrepancies for each pathologist

| Pathologist | Review time | Discrepancies WSDI vs glass | Discrepancies glass pass #1 vs glass pass #2 | No of cases |
|-------------|-------------|----------------------------|---------------------------------------------|-------------|
|             | Glass (average) | WSDI (average) | Major discrepancies (%) | Minor discrepancies (%) | Observed agreements (%) | Major discrepancies (%) | Minor discrepancies (%) | Observed agreements (%) |
| #1          | 36.19s (15s-1 min) | 92.85s (1-4 min) | 4 (9.5) | 7 (14.3) | 31 (73.8) | 3 (7.1) | 10 (23.8) | 29 (69.1) | 42 |
| #2          | 70.98s (30s-2.5 min) | 88.57s (30s-4 min) | 9 (21.4) | 14 (33.3) | 19 (45.2) | 5 (11.9) | 10 (23.8) | 27 (64.3) | 42 |
| #3          | 66.26s (18s-1.55 min) | 126.23s (45s-3 min) | 13 (30.9) | 6 (14.3) | 23 (54.8) | 6 (14.3) | 5 (11.9) | 31 (73.8) | 42 |
| #4          | 55.23s (20s-1.5 min) | 60.11s (25s-2.5 min) | 3 (7.1) | 4 (9.5) | 35 (83.3) | 3 (7.1) | 6 (14.3) | 33 (78.6) | 42 |

Table 3: Specific diagnoses in the discrepant cases (WSDI vs glass)

| Pathologist | # Major discrepancies | Details | # Minor discrepancies | Details |
|-------------|-----------------------|---------|-----------------------|---------|
| #1          | 4                     | - 2 cases: indefinite on glass and negative on WSDI - 2 cases: low grade on glass and negative on WSDI | 7 | - 2 cases: low grade on glass and indefinite on WSDI |
| #2          | 9                     | - 5 cases: indefinite on glass and negative on WSDI - 2 cases: high grade on glass and negative on WSDI | 14 | - 1 case: indefinite on glass and low grade on WSDI - 3 cases: high grade on glass and low grade on WSDI - 1 case: low grade on glass and high grade on WSDI - 7 cases: high grade on glass and low grade on WSDI - 2 cases: high grade on glass and indefinite on WSDI - 5 cases: low grade on glass and indefinite on WSDI |
| #3          | 13                    | - 5 cases: indefinite on glass and negative on WSDI - 2 cases: high grade on glass and negative on WSDI - 3 cases: low grade on glass and negative on WSDI - 1 case: intramucosal carcinoma on glass and negative on WSDI - 2 cases: negative on glass and indefinite on WSDI | 6 | - 3 cases: low grade on glass and indefinite on WSDI - 3 cases: high grade on glass and low grade on WSDI - 3 cases: high grade on glass and low grade on WSDI |
| #4          | 3                     | - 2 cases: low on glass and negative on WSDI - 1 case: negative on glass and indefinite on WSDI | 4 | - 2 cases: high grade on glass and low grade on WSDI - 1 case: low grade on glass and high grade on WSDI - 1 case: indefinite on glass and low grade on WSDI |

WSDI: Whole slide digital imaging

Slide review. Other comments for WSDI interpretation included three cases for which the pathologist mentioned that the location of the biopsy would have helped and one case was “far too blue/dark to accurately evaluate nuclear atypia.”

DISCUSSION

Digital slide review offers potential advantages for pathologists, clinicians, and patients. Prior studies in frozen section correlation and second opinion diagnoses
Table 4: Dysplasia downgrading or “upgrading” (WSDI vs glass)

| Pathologist | Total discrepancies, no. (%) | Downgrading diagnosis on WSDI compared to glass slide, no. (%) | Upgrading diagnosis on WSDI compared to glass slide, no. (%) | No. of cases |
|-------------|------------------------------|--------------------------------------------------------------|-----------------------------------------------------------|--------------|
| #1          | 11 (26.2)                    | 9 (21.4)                                                     | 2 (4.8)                                                   | 42           |
| #2          | 23 (54.8)                    | 23 (54.8)                                                   | 0                                                         | 42           |
| #3          | 19 (45.2)                    | 17 (40.5)                                                   | 2 (4.8)                                                   | 42           |
| #4          | 7 (16.7)                     | 4 (9.5)                                                      | 3 (7.1)                                                   | 42           |

WSDI: Whole slide digital imaging

Table 5: Dysplasia downgrading or “upgrading” (glass pass#1 vs glass pass#2)

| Pathologist | Discrepancies no. (%) | Downgrading diagnosis no. (%) | Upgrading diagnosis no. (%) | Total cases |
|-------------|-----------------------|------------------------------|----------------------------|-------------|
| #1          | 13 (31.0)             | 5 (11.9)                     | 8 (19.0)                   | 42          |
| #2          | 15 (35.7)             | 11 (26.2)                    | 4 (9.5)                    | 42          |
| #3          | 11 (26.2)             | 7 (16.7)                     | 4 (9.5)                    | 42          |
| #4          | 9 (21.4)              | 1 (2.4)                      | 8 (19.0)                   | 42          |

have indicated that digital slide review can enhance efficient use of expert pathologists’ time, increase the experience of reviewers for frozen sections and result in more rapid second opinion diagnoses.\cite{1-4} The number of hospitals and reference labs with scanners continues to increase, and it is likely this will increasingly become part of routine pathology practice.

WSDI has been utilized by the UCLA Department of Pathology since 2008, including substantial experience with the use of WSDI for tumor boards and research studies. Since 2010, we have also used WSDI as part of our consultation practice. Prior internal studies involving digital interpretation of routine GI cases show our pathologists have perfect concordance (kappa 1.0) between WSDI and glass slides for routine cases such as gastric adenocarcinoma, Barrett’s esophagus without dysplasia, chronic gastritis with or without \textit{H. pylori} and \textit{Candida esophagitis}. However, we wished to further establish whether there might be difficulties in digital interpretation of more diagnostically challenging cases such as GI dysplasia, especially as questions related to GI dysplasia represent a large part of our current glass slide consultation practice. Indeed, for WSDI interpretation to become fully integrated into pathologists’ routine practice, WSDI interpretations need to be comparable to their glass slide interpretations for all cases, both routine and challenging.

Our results show a greater range of intraobserver variability for WSDI to glass versus glass to glass interpretation among a group of four specialty trained GI pathologists. As reported by others, our kappa values were higher when clinically relevant categories (negative, indefinite/low grade, high grade) were considered.\cite{11} Kappa values for three clinically relevant categories (negative, indefinite/low grade, high grade dysplasia) on WSDI were fair for one pathologist (0.36), moderate for one pathologist (0.42) and good for two pathologists (0.71 and 0.78); by contrast, for glass-to-glass kappa values were moderate for one pathologist (0.58) and good for three pathologists (0.70, 0.70, and 0.75). Our kappa values for intraobserver variation of dysplasia for glass-to-glass interpretation are similar to that previously reported by Montgomery and colleagues.\cite{11} In that study, kappa values ranged from 0.64 to 0.68 for the clinically relevant categories and 0.42–0.76 for the distinct histologic categories,\cite{11} compared to our values of 0.58–0.75 and 0.50–0.68, respectively. Most other studies spanning the full range of dysplasia diagnoses calculated interobserver variation only.\cite{12,13,15}

One pathologist in our group showed a large jump in kappa scores between media, from a fair score for WSDI-glass (0.42) to the highest kappa score (0.75 - good) for glass–glass review. Interestingly, this pathologist reported a lack of diagnostic confidence in several WSDI cases (10 of 42 total cases, or 24%), and indicated the need for glass slide review in these cases to render an accurate diagnosis. This suggests that pathologists will have different degrees of comfort in adapting this new technology to their practice, especially for more subtle and problematic diagnoses (like dysplasia grading) as compared to diagnosing cancer versus normal tissue. Another pathologist had the lowest kappa score on both WSDI and glass, which suggests that intrinsic factors that account for intraobserver variability may not be significantly influenced by the medium (digital versus glass) used for interpretation. These findings suggest that pathologists who decide to use WSDI for interpretation of GI dysplasia cases may benefit from regular, on-going, re-review of paired digital and glass images for continuing education, at least in the early stages of adoption. The most unexpected and significant result of our study is the finding that pathologists overwhelmingly downgraded dysplasia grade in WSDI versus glass slides. We did not expect this result at the
beginning of the study, and thus did not design our study to address this finding specifically. Why this occurred is not clear from our results and will require further research. Possible causes include scanning magnification, color balance/dynamic range of the WSDI relative to glass slides, quality/resolution of the viewing monitors, and pathologist experience with dysplasia diagnosis using digital microscopy. While the scanning magnification used in this study (20×) could play a role, pathologists only indicated the further need for 40× magnification in 10 out of a total of 168 cases. Moreover, only 4 discrepant diagnoses were found out of the 10 cases where 40× magnification was requested. Thus, while scanning magnification may have contributed to some discrepant diagnoses, it did not account for all discrepancies. In our study, pathologists used their standard computer monitor for imaging viewing. It is possible that interpretation using a high resolution monitor (such as BARCO Coronis Fusion wide-screen diagnostic color display system) or a larger monitor would have led to different results. One pathologist did mention that one WSDI was too blue and dark to interpret nuclear detail properly; it is possible that subtle variations in color balance or dynamic range in the digital images led to misinterpretation of nuclear features which are critical for the evaluation of dysplasia. Finally, it is possible that, with experience, there would be fewer cases of downgrading on digital images. Again, this unexpected finding requires further study.

On average, WSDI took two to four times longer than glass slide interpretation for all pathologists. With multiple slides and cases, this difference could be substantial for a practicing pathologist. Pathologists may become faster in WSDI interpretation with experience, and we plan additional studies to address this question. However, for the present, WSDI does present additional technical challenges relative to glass slides. These include the speed with which images can be loaded into the viewer and the quality of the display monitor. Furthermore, most digital slide viewers continue to rely on standard computer accessories (mouse and keyboard) that limit efficiency and ease of viewing. Differences in hardware (scanners) and software (viewers) may impact the pathologist’s interpretation of the image reviewed or their diagnostic confidence. Moreover, optimal scanning magnification needs to be considered. Scanning at 40× takes significantly longer than 20× scans, and varies depending on the size of tissue being scanned and the scanner itself. We find 40× scans require from 50% to 500% more scanning time in our laboratory and result in files several fold larger than those of 20× scans. In a routine high throughput clinical practice, these incremental differences could significantly impact scanning time and server storage space.

As a profession, our experience with WSDI for rendering clinical diagnoses is limited but growing rapidly. We believe several of the concerns raised by this study (time required, discrepancies, confidence in diagnosis) are related to our limited experience with digital dysplasia diagnosis and speculate these problems will dissipate with increased usage of the digital platform. Moreover, the rapid improvements witnessed in the hardware and software used for digital slide scanning and interpretation also would be expected to mitigate some of these concerns.

**CONCLUSION**

In conclusion, our results indicate that pathologists can interpret upper GI dysplasia similarly on WSDI and glass slides, and thus WSDI potentially can be used for clinical diagnosis. However, some pathologists may encounter more challenges than others in using WSDI for this purpose. Pathologists who adopt WSDI for the evaluation of GI dysplasia cases presumably should benefit from regular, on-going, re-review of paired digital and glass images for continuing education, at least in the early stages of adoption. Furthermore, until additional studies are available, we believe our data support a judicious approach to digital dysplasia interpretation and indicate that, in some cases, pathologists may prefer to review the glass slides in order to render a diagnosis with confidence.

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