MULTIMODAL SPECTROSCOPY AS A TRIAGE TEST FOR WOMEN AT RISK FOR CERVICAL NEOPLASIA: HISTOPATHOLOGY REVIEW PROCEDURES AND RESULTS

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OBJECTIVE: Evaluation of new modalities for the detection of neoplasia requires confidence that the gold standard by which sensitivity and specificity of the new modality are calculated is reliable. For cervical neoplasia, this is especially challenging because the histopathological threshold between cases determined to be positive vs. negative for disease can be subtle, for example the difference between a Cervical Intraepithelial Neoplasia (CIN1) and CIN2 lesion. The objective of the current study was to develop and evaluate a reliable histopathology quality assurance procedure that would aid in the assessment of a new cervical cancer modality, *viz.*, multimodal hyperspectroscopy (MHS).

METHODS: In this seven-center pivotal study, 1,607 women at risk for cervical neoplasia were tested using MHS (LightTouch, Guided Therapeutics, Inc. Norcross, GA), including 1,456 with abnormal Papanicolaou (Pap) cytology, one with no Pap results and 150 with normal or benign cytology but were at risk for other reasons including positive Human Papilloma Virus (HPV) results, previous dysplasia and/or recurrent benign findings. Histopathologists at each participating center classified tissue samples as belonging to one of three categories: Normal (including metaplasia, inflammation, reparative changes and other benign conditions), CIN1 (including HPV changes and flat condylomas) and CIN2+ (CIN2, CIN3 or carcinoma). Representative slides for all 1,607 subjects were sent to Quality Assurance (QA) Histopathologist 1, Dr. Wilkinson (QA 1). If QA 1 agreed with the diagnosis of the participating site's histopathologist (Site), then for the purposes of the study, the diagnosis was final. If QA 1 disagreed with the diagnosis from the site, the slides were sent to QA Histopathologist 2, Dr. Raab (QA 2). In that case, for each individual tissue sample, agreement by two of the three pathologists was sufficient for final diagnosis. Three way disagreements were considered discordant and if the discordant biopsy had a CIN2+ diagnosis by any pathologist then that subject was considered non evaluable for the assessment of MHS. Each histopathologist was blinded to the diagnosis of the other histopathologists and no review meetings were held to resolve differences in diagnoses. This procedure was initially employed in a previous multicenter evaluation of MHS (DeSantis et al, J. Lower Gen. Tract, Vol 11, no. 1, 2007, 18 - 24).

RESULTS: For the 1,607 women in the MHS study, there were 3,302 histopathology samples including 1,885 from biopsies and 1,417 endocervical curettages. For these tissue samples, QA 1's diagnosis agreed with that of the Site 76% of the time (2,524/3,302) and did not require further evaluation by QA 2. Of the 709 samples in which QA 1's diagnosis disagreed with that of the Site, QA 2 agreed with QA 1 51% of the time (365/709) and agreed with the Site 48% of the time (343/709). Three-way disagreements occurred for 2% (70/3,302) of the samples. For determining sensitivity and specificity of MHS, final diagnoses were based on the most severe disease for each of the 1,549 subjects in the study with available histopathology. For these cases, QA 1's diagnosis agreed with the Site 72% of the time (1,110/1,549) and did not require further evaluation by QA 2. Of the 439 cases in which QA 1's diagnosis disagreed with the Site, QA 2 agreed with QA 1 44% of the time (193/439) and agreed with the Site 46% of the time (200/439). Three-way disagreements occurred for 3% (46/1549) of the women. Of special interest in the evaluation of MHS were biopsies determined to be negative for CIN2+ disease by the Site pathologist and then subsequently found to be positive for CIN2+ disease by both QA histopathologists. For these 38 women, QA 1 was required to alert the Site in writing that a possible CIN2+ case had been under diagnosed. MHS prospectively identified 89% (34/38) of these cases as positive for CIN2+.

CONCLUSIONS: The histopathology QA procedure used in the evaluation of MHS as a new modality in the detection of cervical neoplasia offered several advantages, including blinded diagnoses by three independent histopathologists and a fully prospective method for determining disease outcome for each subject. The trade-off for this was the potential disadvantage that three way disagreements could not be resolved in a histopathology panel setting. However, histopathology agreement rates were high enough (over 70% between the Sites and QA 1 and approximately 50% for the remaining cases) that three-way disagreements leading to nonevaluable cases were kept to a minimum. The procedure also functioned as a method of follow up to determine how MHS performed on cases determined to be negative for CIN2+ by the site but positive for CIN+ upon QA histopathology review.

KEY WORDS: cervical histopathology review, dysplasia, spectroscopy