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Advanced Imaging in Mucosa Disease: Do You See What I See

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The ability to enhance imaging in gastrointestinal mucosal disease has been sought after since the original description of the gastric camera in 1952 that was designed for detection of gastric neoplasia. This was a remarkable event as luminal imaging had never been accomplished previously without surgical assistance. Subsequently, the rapid advance of fiberoptic endoscopes and now CCD based imaging has greatly improved visualization of the mucosa surface and has evolved into digitally enhanced imaging of the mucosa.

As with the original imaging techniques, the goals of advanced imaging are still focused on detecting early neoplasia and the report in this issue of GIE from a leading research group in the Netherlands highlights the latest of advanced imaging endoscopes. The trimodal instrument represents a multi-modality endoscope capable of high-resolution white light, autofluorescence and narrow band imaging. Several excellent well-constructed studies by this group have demonstrated the remarkable capabilities of the instrument in the detection of dysplasia of Barrett's esophagus in tertiary care settings¹. Autofluorescence was found to be very sensitive but not very specific for dysplasia with narrow band imaging helping to increase the specificity for dysplasia. This is consistent with what is known about autofluorescence as it is generally accepted that the most abundant fluorophore is collagen and that areas of dysplasia generally have increased epithelial proliferation and the thickness of the mucosal layer thereby decreasing the fluorescence from the collagen in the lamina propria. Narrow band imaging has also been found in a number of studies to be very sensitive and specific for detection of dysplasia. In a recent meta-analysis of eight studies encompassing 446 patients found that the sensitivity of 0.96 (95 % confidence interval of 0.93–0.99) and specificity of 0.94 (95 % confidence interval of 0.84–1.0) for detection of high-grade dysplasia. In fact the likelihood ratio for detection of high-grade dysplasia was 342.49. These studies clearly establish the efficacy of this diagnostic modality.

However, efficacy does not translate into effectiveness which is defined as how trimodal imaging will perform in the community setting. Endoscopic research studies by their nature are usually performed by skilled and well-trained individuals who are committed to the advancement of technologies. This creates an inherent bias, as these individuals are likely to spend more time and commit more resources (time, training, ancillary personnel) than in everyday practice. A key point in translation into clinical practice is whether the differences in mucosal and vascular patterns in dysplasia can easily be detected by practicing gastroenterologists who are more likely to demand that these abnormalities are readily apparent and unequivocal.

An important question is does this study actually fulfill the requirement of an effectiveness study. There are eight defined criteria of effectiveness studies that have been proposed by

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the Agency for Healthcare Research and Quality (AHRQ) which include; 1) Populations in primary care; 2) Less stringent eligibility criteria; 3) Health outcomes; 4) Long study duration; 5) Clinically relevant treatment modalities; 6) Assessment of adverse events; 7) Adequate sample size to assess a minimally important difference from a patient perspective; 8) Intention-to-treat analysis (AHRQ Publication No. 06-0046, 2006). These criteria are established more for a therapy than a diagnostic test but the principles are similar.

The study population is not similar to that seen in community practices as they were restricted to individuals with confirmed low-grade dysplasia which certainly is not the general population and was selected because of the need to have adequate sample size to power this study statistically. The low-grade dysplasia was also confirmed by a pathology panel rather than a single pathologist that increases the likelihood that these patients are more likely to progress which is what was found in the study. The entry criteria were not less stringent neither for patients nor the performing physicians. The participating community physicians were trained with DVD's, attending a course, and had 5 cases of experience before entering the study. This makes a better efficacy study but a worse effectiveness study. Health outcomes and long study duration was also not included in this study. To truly assess the value of NBI in the community, the patient population who underwent this procedure should be compared to those that did not in terms of detection of early stage cancer and disease related mortality. Finally, adverse events such as missed cancers could not be assessed and the sample size was really not adequate for a true population based study.

How large would a study would have to be in order to demonstrate effectiveness? A rough estimate would be that using a trimodal endoscope that could detect every patient who did not have dysplasia who progresses to cancer over a 5-year study and is compared to a group that did not receive trimodal endoscopy and did not detect any of these progressors would require a total of 7788 patients to detect a difference at a significance level of 0.05 and a power of 0.80. This is because of the low progression rates found in Barrett's esophagus. However, even this theoretical study is still not sized appropriately for the clinically relevant endpoints of deaths from malignancy. It is clear that a true effectiveness study really cannot be practically performed in patients with Barrett's esophagus without dysplasia.

Even though this is not an effectiveness study, the study clearly demonstrates inability of community gastroenterologists to utilize this technology as well as has been demonstrated in the tertiary care setting. This occurred even though the trimodal endoscopy required significantly more time (a 50% increase). That the less than ideal performance occurred in an enhanced populations suggests that this may well be due to difficulties with the pattern recognition required .

Although the authors concluded that trimodal imaging really cannot be applied in the community to classify dysplasia, this may not be the case in the future. The difficulty with recognizing these patterns is that they are non-specific. Decreased fluorescence occurs in proportion to the distance from the endoscope. The GI lumen is not uniform and areas of decreased fluorescence can represent anatomically distorted lumen or areas of inflammation that will also increase the mucosa thickness. Vascular patterns associated with inflammation are also often irregular and difficult to differentiate from neoplastic lesions. Even in the most recent study on the trimodal system performed by expert centers found that the technology may not be as robust as initially reported ². Pattern recognition is also a problem in using the latest magnification techniques. Laser confocal endomicroscopy has also had problems in identifying dysplasia with a positive predictive value of only 46% in one recent study ³. However, imaging technology can be improved with the use of fluorescein bound probes that can be made specifically for recognition of areas of dysplasia. These probes have been

shown to bind to areas of dysplasia in colon polyps⁴. The same technology could make the detection of fluorescence in the mucosa much more specific and eliminate the need for pattern recognition. The probes can be made to be specific for molecular events that could help gastroenterologist identify areas of even pre-neoplasia. Different probes could be developed to detect early molecular events in different tissues to detect colonic, gastric, or esophageal dysplasia depending on need. Although autofluorescence may not help the community gastroenterologist detect dysplasia, it has the potential to allow the practitioner to see the light as well as anyone in tertiary referral centers with the use of specific molecular probes.

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