

Gastrointestinal Cancer Surveillance by Optical Sensing

□□ Commentary on Liu et al., p. 4392

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Will the practice of gastrointestinal cancer surveillance be revised by the advent of optical sensing?

This is not a facetious question. The article in this issue by Liu and associates (1) reports the first possible method for minimally invasive (and early) detection of pancreatic cancer. Although the reported experiments were performed on *ex vivo* tissue samples, the proposed method would entail minimally invasive endoscopic optical measurements of the epithelium in the periampullary duodenal mucosa, invoking a proposed field effect for pancreatic cancer. This follows on the heels of other recent reports by Backman and collaborators (2), of clinical studies showing that proximal colon cancers can be detected by less invasive optical measurements of the rectal mucosa. The putative deduction is that optical measurements in the rectum are sensitive to field effect changes corresponding to dysplasia elsewhere in the colon. In parallel, other groups have been conducting translational studies of optical methods for sensing cancer in a number of organ systems (3–6), and the emerging importance of optical methods for the diagnosis and treatment of cancer has been recognized by the National Cancer Institute, which, 3 years ago, funded the multi-center Network for Translational Research in Optical Imaging. The study reported in this issue is synergistic with the other studies, but is highly original in that the reported method is sensitive to early regional changes *prior* to the appearance of traditional histologic features.

The concept of a field effect for certain organs, although somewhat controversial, has been gaining acceptance as clinical evidence accumulates. Nonetheless, the common refrain of “tissue is the issue” will take some time to overcome, and only long-term outcome studies will yield general acceptance. Clearly, there is a need to diagnose pancreatic cancer earlier and better because the present survival rates are dismal regardless of detection or treatment. Such poor outcomes make “doing nothing” other than palliation the current standard of practice! Similarly, no widely accessible alternative to random biopsy exists for the

detection of endoscopically invisible precancer (e.g., in Barrett’s esophagus and ulcerative colitis). Optical guidance to the “right” spot for biopsy would improve sensitivity while reducing the number of excisions of “normal” tissue. In both cases, there is no downside to early adoption. The beauty of these optical approaches is that the standard of care need not be altered while the proof develops. The data can be collected, and it can be clearly determined what the statistical outcome would have been with an optically-guided biopsy protocol, as compared to random sampling (or doing nothing).

In the future, optical methods can be expected to enhance diagnostic testing and treatment monitoring, with benefits for both patients and the health care system. However, the potential impact of the study reported in this issue, in the case of pancreatic cancer, is one of a major breakthrough: there is simply no alternative surveillance diagnostic whose invasiveness can be justified for any but the highest risk patients. For the first time, there may be hope for the early detection of this insidious disease, which generally remains asymptomatic until it is too late for a reasonable prognosis.

An additional, beneficial, outcome of the clinical testing of these optical methods is that they can instigate the development of new, more quantitative methods of histopathology and ultrastructural analysis. Given that there are indeed micromorphologic changes underlying the optical scattering signatures, the fact that the samples, in this study, were histologically normal by standard analysis, begs for the development of more sensitive, objective, and quantitative methods of histopathology.

The caveat is that this preclinical investigation was performed *ex vivo* on excised tissue samples, and the excellent correlation statistics (sensitivity and specificity) are the results of retrospective correlation with a small data set. However, the authors clearly recognize the need, and are planning for a larger, age-matched, prospective clinical study. From the basic science viewpoint, it is also encouraging that the optical correlates are quantitative and are identified with underlying structural properties that are consistent with field effect changes. For example, chromatin granularity and cell clustering relate to the fractal dimension, which is estimated from the relationship between the optical angular measurement and the spatial mass-density variations.

There will be engineering challenges in designing a system for endoscopic application, but those are likely to be more easily dealt with than the eventual reworking of disease management protocols. The potential benefits are enormous, and we look forward to the larger-scale studies.

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