Quantitative biomarkers of colonic dysplasia based on intrinsic second-harmonic generation signal

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Abstract. Most colorectal cancers arise from dysplastic lesions, such as adenomatous polyps, and these lesions are difficult to be detected by the current endoscopic screening approaches. Here, we present the use of an intrinsic second-harmonic generation (SHG) signal as a novel means to differentiate between normal and dysplastic human colonic tissues. We find that the SHG signal can quantitatively identify collagen change associated with colonic dysplasia that is indiscernible by conventional pathologic techniques. By comparing normal with dysplastic mucosa, there were significant differences in collagen density and collagen fiber direction, providing substantial potential to become quantitative biomarkers for in vivo clinical diagnosis of colonic dysplasia. © 2011 SPIE. DOI: 10.1117/1.3659715

Keywords: collagen; colonic dysplasia; second-harmonic generation signal.

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the average SHG intensity of selected regions at each depth was then calculated and plotted as a function of depth. Decrease in SHG signal intensity with increasing depth can be approximated using a first-order model: \( I = Ae^{-kx} + C \), where \( I \) is the SHG intensity, \( x \) is the imaging depth, \( A \) is a pre-exponential scaling factor, \( C \) is an arbitrary constant that adjusts the lowest signal intensity to zero, and \( k \) is the DDD constant.\(^\text{15}\) Figure 3 shows a typical plot of the exponential fits from normal and dysplastic colonic tissues. Recently, Dunn et al. found that although scattering plays a role in DDD, absorption is the main factor responsible for DDD in turbid media at least to a depth of focus of 412 \( \mu \)m. Thus, although other factors, such as direction, distribution, and size of collagen fibers, may contribute to changes in the DDD value, it is a reasonable measure of collagen density.\(^\text{16}\) Moreover, the collagen fiber angle relative to the tangent of the interface of epithelium and stroma was measured every 5 \( \mu \)m using IMAGEJ software (National Institutes of Health), as reported previously.\(^\text{17}\) As shown in Table 1, the dysplastic colonic mucosa has a lower DDD constant and a bigger collagen fiber angle (\( p < 0.05 \)), indicating loss of the collagen density and the collagen fibers located at an angle to the interface of epithelium and stroma in dysplasia, consistent with the above-mentioned observations. Therefore, these differences in the collagen density and the collagen fiber direction may be used to quantitatively discriminate between normal and dysplastic colonic mucosa, and serve as quantitative intrinsic biomarkers for quantifying the diagnosis of colonic dysplasia.

In conclusion, this study demonstrates the potential of intrinsic SHG imaging to provide biochemical and morphological biomarkers, including the collagen density and the collagen fiber direction, which can be used to discriminate between normal and dysplastic colonic mucosa. With the advent of the SHG-based endoscopy,\(^\text{18}\) we expect that the analysis of collagen change using intrinsic SHG imaging may become an important noninvasive methodology that provides quantitative information about the collagen change for diagnosing colonic dysplasia.

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References