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**Serrated Colorectal Neoplasia: From Sideshow to Center Stage**

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In 2011, *Clinical Gastroenterology and Hepatology* published our study “Prevalence and Variable Detection of Proximal Colon Serrated Polyps during Screening Colonoscopy”<sup>1</sup>. It is appropriate to first put this paper in context. At the time, there had been escalating concerns about colonoscopy’s imperfect protection against colorectal cancer (CRC), with observational studies suggesting that colonoscopy was significantly less effective in preventing deaths from right-sided colon cancer than left-sided CRC<sup>2,3</sup>. In parallel, the serrated neoplasia field was undergoing profound transformation, and emerging as an important factor in the CRC arena. Aiming to reorganize disparate and evolving histopathological criteria, the World Health Organization had just updated its classification of serrated colorectal neoplasms, grouping lesions under 3 major categories (hyperplastic, sessile serrated adenoma/polyp, and traditional serrated adenoma)<sup>4</sup>. In addition, progress was being made in elucidating the mechanisms involved in the serrated pathway to colorectal carcinogenesis<sup>5</sup>, including the observation that there was an overlap in the molecular features of post-colonoscopy CRCs and serrated neoplasms<sup>6,7</sup>. Serrated polyps are often located in the proximal colon and exhibit morphologic features which can render detection and complete resection challenging, even for experienced endoscopists. The effectiveness of colonoscopy as a screening modality depends on the quality of its performance, and variability in endoscopists’ adenoma detection rates (ADR) had been associated with the risk of post-colonoscopy CRC<sup>8</sup>. However, whether and to what extent this detection variability applied to proximal serrated polyps was uncertain.

Using the Indiana University endoscopy database, we identified 6681 screening colonoscopies performed by 15 attending gastroenterologists, and determined detection rates of adenomas and serrated polyps. The proportion of colonoscopies with at least one adenoma was 38% (range 17%-47%), and 13% for proximal serrated polyps (range 1%–18%). Adenoma and proximal serrated polyp detection rates per colonoscopy were strongly correlated ( $R = 0.76$ ,  $P =$

.0005). Endoscopist was associated with proximal serrated polyp detection ( $P < .0001$ ), but patient age ( $P = .76$ ) and gender ( $P = .95$ ) were not.

Ours was one of the first studies to demonstrate that detection of serrated lesions was even more variable than detection of conventional adenomas. One previous work reported variation in serrated polyp detection rates within the same group of endoscopists<sup>9</sup>. However, the 18-fold variability in proximal serrated polyp detection we observed in the study published in *CGH* was novel and striking, and indicated significant shortcomings in some endoscopists' ability to recognize these lesions. This was further supported by the observation that the endoscopist performing the procedure was a powerful predictor of proximal serrated polyp detection. Studies published subsequent to our work have confirmed that detection of proximal serrated polyps can be highly variable and endoscopist-dependent<sup>10,11</sup>.

The serrated neoplasia field has evolved considerably and in exciting new directions since 2011. One development is the realization that the prevalence of the most relevant subtype of serrated polyps, the sessile serrated polyp (SSP), was higher than originally thought. We conducted a study<sup>12</sup> including 1910 average-risk patients ( $\geq 50$  years old) who had undergone screening colonoscopy by one endoscopist with high adenoma and serrated lesion detection rates, combined with a review of all slides of serrated lesions proximal to the sigmoid colon and rectal-sigmoid serrated lesions  $> 5$  mm by one expert GI pathologist. The overall SSP prevalence in this study was 8.1%, of which about 7.4 % exhibited cytological dysplasia. A subsequent large Dutch study<sup>13</sup> yielded similar results. Another important development is the recognition that serrated polyps are associated with increased risk of synchronous<sup>14</sup> and metachronous<sup>15,16</sup> neoplasia, with one study<sup>15</sup> showing that the risk of subsequent CRC development in patients with SSP was comparable to that of patients with conventional adenomas. Considerable progress has also been made in elucidating the molecular and clinical bases of the serrated pathway to CRC, including the most extreme manifestation of the serrated

milieu, the serrated polyposis syndrome<sup>17</sup>. The role of image-enhanced endoscopy to allow differentiation of SSPs from non-neoplastic lesions has been the focus of recent research, with the development of reliable algorithms such as the WASP<sup>18</sup> optical diagnosis classification, which combines the NBI International Colorectal Endoscopic (NICE) algorithms with surface features associated with SSP (clouded surface, indistinctive border, irregular shape, and dark spots inside crypts). The optimal polypectomy techniques for serrated polyps are also being refined. The CARE study<sup>19</sup> found that large serrated polyps were at highest risk for incomplete resection using conventional methods, likely due to their indistinct borders. However, subsequent reports<sup>20,21</sup> showed that standardized dye-assisted endoscopic mucosal resection techniques could result in complete resection of SSPs which was at least as effective as for comparable-sized conventional adenomas.

Serrated polyps have “come a long way” from the status of relative histopathological oddity, to recognition as being CRC precursors, and a suitable target for screening on par with conventional adenomas. We believe our study was an important contribution along the way; it drew attention to the problem of variability in detection rates among endoscopists, and the need to increase efforts to educate providers to optimize recognition of serrated polyps. We are grateful to *CGH* and its Board of Editors for giving us the opportunity to share our findings with the medical community and increase awareness about the significance of serrated neoplasms.

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