

# GASTROENTEROLOGY NEWSLETTER

## CONSIDERING COLONOSCOPY:

*An Interview with Anil K. Rustgi, MD*



ANIL K. RUSTGI, MD

T. Grier Miller Professor of Medicine & Genetics  
Chief, Division of Gastroenterology

This edition of the Penn Gastroenterology Division Newsletter features an interview with Anil K Rustgi, MD, Chief of Gastroenterology, Penn Medicine, and the T. Grier Miller Professor of Medicine and Genetics at the Hospital of the University of Pennsylvania. Dr. Rustgi received his training at Massachusetts General Hospital at Harvard Medical School and came to the University of Pennsylvania in 1998. His particular expertise is in the molecular genetics of GI cancers, especially those originating from the aero-upper digestive tract.

■ *Dr Rustgi, a recent report from Canada suggests that colonoscopies are an ineffective modality for diagnosing cancers of the right colon. What has been the reception in the GI community to this study?*

**DR RUSTGI:** First, let me say that colonoscopy remains the most accurate means of diagnosing colon cancer at a single application—more effective than flexible sigmoidoscopy and much more effective than fecal occult blood testing—and that the authors of this report do not suggest otherwise. That being said, the report from Canada has caused some controversy and its conclusions have been misunderstood by the public and exaggerated somewhat in the media. Unlike the public and the media, gastroenterologists and researchers tend to view this report from a methodological viewpoint. From this perspective, the report has many limitations, including its retrospective nature; the lack of information about incomplete examinations (those in which the examiners did not get to the cecum); the office-based nature of the exams; the failure to account for critical factors like family history and hereditary forms of colon cancer in their inclusion/exclusion criteria; and finally, the fact that the follow-up period was limited. These issues call some of the report's conclusions into question.

LOCATIONS

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*“Colonoscopy remains the most accurate means of diagnosing colon cancer at a single application—more effective than flexible sigmoidoscopy and much more effective than fecal occult blood testing...” —ANIL K. RUSTGI, MD*

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“Personally—and this may be the bias of a gastroenterologist—I think that only individuals who have had the rigorous training to do colonoscopies should be performing these procedures in any setting. —ANIL K. RUSTGI, MD

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■ *Are right-sided colon cancers different in some way than cancers at other sites in the colon? Are these cancers harder to detect via colonoscopy than left-sided cancers?*

**DR. RUSTGI:** We know that there are differences in colon cancers predicated upon their location, left-sided or right-sided, and biological studies suggest that right-sided cancers behave differently than left-sided cancers. The most compelling example is an inherited colon cancer called Lynch syndrome, which is associated with right-sided colon cancers. When family history and age are factors, the lifetime risk of colon cancer rises to about 20%; the risk rises to 100% when you start to look at hereditary colon cancers. We see a lot of these patients and families here at Penn. Outside of the inherited cancers, however, it's not entirely clear what leads to right- vs. left-sided differences in colon cancer. There are genetic differences between cancers from different sites in the colon, but we don't know what causes this. The question of whether these right-sided cancers are harder to detect is complicated because so much of the efficacy of a colonoscopy is operator-dependent.

■ *Among the potential influences on the efficacy of colonoscopy cited in the Canadian report are operator experience and competence, particularly in the community setting.*

**DR. RUSTGI:** High-quality colonoscopy remains the key to any effective screening program. A number of the important

determinants of efficacy in colonoscopy procedures, including thoroughness of preparation and completeness of the examination, are a reflection, ultimately, of the experience and training of the operator. Colonoscopies can be challenging, and skill is acquired by doing many procedures over time. Experience alone will not prepare an operator to recognize and appreciate the nuances of the colon, though. Personally—and this may be the bias of a gastroenterologist—I think that only individuals who have had the rigorous training to do colonoscopies should be performing these procedures in any setting. At Penn, we're very rigorous in that our fellows do more than the required number of colonoscopies each year so that they can experience the sorts of nuances that affect procedure efficacy. This is necessary so that when they do go out into the community, they're fully prepared to do the procedures on an independent basis. In addition, quality criteria and standards for colonoscopies—some of which were established by Penn gastroenterologists and researchers—should always be followed by physicians performing the procedure in the community setting.

■ *It's been reported that gastroenterologists are increasingly choosing to practice in urban settings. What does this mean to patients living in rural or community settings?*

**DR. RUSTGI:** We do have an over-saturation of gastroenterologists in urban areas in the US. To counter this trend, somewhat, Penn has established a practice base in Radnor, a community 18 miles outside of Philadelphia. We chose this site for its accessibility to

better serve the large population living to the west of Philadelphia. In the several years since its opening, Penn Medicine at Radnor has become a major site for colonoscopy referrals from towns throughout southeastern Pennsylvania. Now, this could be happening for a variety of reasons, but certainly one of them is the knowledge that patients having colonoscopies at Radnor are receiving high quality care from gastroenterologists associated with Penn. The message here is that quality, competent care can be extended from urban academic medical centers into the community, and is well received there.

■ *Recent reports from Japan suggest that nonpolypoid, or flat, adenomas and polyps are being missed during colonoscopy in spite of clean prep and getting to the cecum. Do these lesions present a concern to patients receiving colonoscopies in the United States?*

**DR. RUSTGI:** Several papers have reported that nonpolypoid colorectal neoplasms, or NP-CRNs, are an issue here in the US, though whether there is a predominance of these lesions in the distal colon here (as there is in Japan) is not yet clear. NP-CRNs are a matter of some concern because these lesions are highly cancerous and can be difficult to distinguish from the normal mucosa during colonoscopy or computed tomography colonography. Unfortunately, the optical colonoscopic magnification equipment required to detect NP-CRNs is very expensive and few gastroenterologists in the United States have been trained to use these modalities. Obviously, with time, this should change.

■ *Finally, should these reports be a concern for the patients considering colonoscopy?*

**DR. RUSTGI:** I hope not. Since the nation's public health agencies began recommending colonoscopies for colorectal cancer screenings, the percentage of patients receiving colonoscopies has doubled from about 25% of patients to about 50%, which is a significant advance. It would be a tragedy if that percentage began to recede after so much positive progress.

## RESOURCES

- Penn GI division patient website: [pennteam.org/GI](http://pennteam.org/GI)
- Penn GI division academic website: [www.uphs.upenn.edu/gastro](http://www.uphs.upenn.edu/gastro)
- Penn Abramson Cancer Center website: [pennteam.org/abramson](http://pennteam.org/abramson)
- Penn cancer information: [www.oncolink.org](http://www.oncolink.org)
- NCI program project on esophageal cancer at Penn: [www.uphs.upenn.edu/gastro/nci\\_project](http://www.uphs.upenn.edu/gastro/nci_project)

## CLINICAL INVESTIGATIONS *of* ENDOSCOPIC ULTRASOUND *at Penn*

Researchers with Penn's Division of Gastroenterology created an endoscopic ultrasound (EUS) database in 1993, and over the last decade, have established the value of EUS as the most accurate medical imaging technology for the diagnosis and staging of most GI cancers. This report offers a brief overview of clinical studies at Penn that examined EUS in the diagnosis of esophageal carcinoma and Barrett's esophagus.

### EUS as a Predictor of Long-Term Survival in Esophageal Carcinoma

The rising incidence of adenocarcinoma of the esophagus and the poor prognosis for patients with advanced adenocarcinoma have reinforced efforts to detect cancerous transformation in its earliest stages. Currently, EUS is the most accurate means for staging esophageal carcinoma, offering detailed images of the esophageal wall with effective resolution of up to 200 nm.

To predict outcomes and determine which EUS features predict survival in patients with esophageal cancer, Gregory Ginsberg, MD, and Michael Kochman, MD, of the Penn Division of Gastroenterology and members of the Center for Clinical Epidemiology and Biostatistics at the Hospital of the University of Pennsylvania (HUP) performed a retrospective examination of patients undergoing EUS for esophageal cancer staging.

Data on 203 patients undergoing EUS for the staging of esophageal cancer and cancer of the gastroesophageal junction over a 66-month period were entered into an endoscopic database to document EUS staging and patient demographics. A multivariate analysis with Cox regression was performed to examine the relative importance of the EUS T-stage, EUS N-stage, and presence or absence of celiac axis lymph nodes in predicting survival. Type of treatment, patient age and gender, and tumor histology (adenocarcinoma vs. squamous cell carcinoma) were also considered.

**Results:** The log-rank test showed a statistically significant difference in median survival based upon EUS T-stage ( $p = 0.0005$ ). Patients with lower EUS-T stages lived significantly longer than patients with higher EUS T-stages, with patients with EUS T0 stage having the longest median survival (>26.7 months) and patients staged as T4 by EUS having the shortest median survival (6.5 months). Patients with malignant-appearing lymph nodes on initial EUS had a significantly shorter survival time (13.5 months) compared with patients who were judged not to have malignant-appearing lymph nodes at EUS (>25 months). The detection of these malignant-appearing locoregional lymph nodes at EUS was a predictor of survival independent of the EUS T-stage, M-stage, type of treatment, patient age and gender and tumor histology. Median survival for patients with celiac axis lymph nodes present was significantly shorter than patients without celiac nodes on EUS: 11.8 months versus 23.8 months ( $p = 0.0049$ ).



Gary Ginsberg, MD, performs an endoscopic ultrasound (EUS) at the Hospital of the University of Pennsylvania.

These findings suggest that pretreatment EUS can predict survival in esophageal cancer based on initial T-stage, N-stage, and the presence of CAx nodes, and that lymphadenopathy at EUS is an important predictor of survival. The authors concluded that EUS should be performed in all patients with esophageal cancer, not only for staging patients before therapy, but also as a valuable method of determining prognosis.

### Accuracy of Evaluation of Barrett's Esophagus and High-Grade Dysplasia or Intramucosal Carcinoma

Endoscopic surveillance in patients with Barrett's esophagus is advocated because adenocarcinoma arising in this disorder progresses through grades of cellular dysplasia that predate or coincide with the development of carcinoma. A team of investigators from the GI division, the Department of Pathology, and the Department of Surgery at Penn participated in an investigation to determine the potential of EUS to preclude advanced esophageal carcinoma as a precedent to nonsurgical treatment of Barrett's esophagus and high-grade dysplasia or intramucosal carcinoma.

EUS was performed in 22 patients (mean age  $64 \pm 8.7$  years) with Barrett's esophagus and high-grade dysplasia or intramucosal carcinoma based on endoscopy, endoscopic biopsies, and CT before esophagectomy. EUS findings were compared with surgical/pathologic evaluation.

Following EUS, submucosal invasion was identified in six patients and lymph node involvement in five patients. By surgical/pathologic evaluation, five of 22 patients (23%) had unsuspected submucosal invasion and 1 had lymph node involvement. EUS detected all five instances of submucosal invasion and the single instance of lymph node involvement. False-positive ascription of advanced disease (i.e., submucosal invasion or lymph nodal involvement) by EUS occurred in only 3 of 17 cases (18%). For submucosal invasion, the sensitivity and negative predictive values of preoperative EUS were 100%; specificity was 94%.

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# CHIEF'S CORNER

The sensitivity, specificity, and negative predictive values of preoperative EUS for lymph node involvement were 100%, 81%, and 100%, respectively. Nodules or strictures noted by endoscopy were associated with an increased likelihood of submucosal invasion. Because EUS detected otherwise unsuspected submucosal invasion and lymph node involvement, this study supports the use of EUS when non-operative therapy is being considered in patients with Barrett's esophagus and high-grade dysplasia or intramucosal carcinoma.

### Defining the Earliest Stages of Barrett's Esophagus

A number of genes increase in expression in Barrett's when compared to normal esophageal epithelium, including the Cdx transcription factors and C-myc, a classic proto-oncogene. Recently, researchers with the GI division, in collaboration with investigators from the Abramson Cancer Center and the Center for Bioinformatics at Penn, completed a study to identify the genetic changes that induce the transdifferentiation of normal esophageal keratinocytes toward Barrett's. The Penn researchers compared tissue from Barrett's esophagus to normal stratified squamous epithelium of the esophagus and small intestine via microarray analysis. This comparison and its accompanying validation determined that both transcription factors cooperated to induce the production of mucin in goblet cells, among the earliest stages in transdifferentiation towards Barrett's esophagus and one of the hallmark morphologic features of the condition.

**GREGORY G. GINSBERG, MD:** Director of Endoscopy, has been elected President-Elect of the American Society of Gastrointestinal Endoscopy (ASGE).

**MICHAEL L. KOCHMAN, MD:** Co-Director of GI Oncology, Endoscopy Training Director, has been elected Councilor to the ASGE governing board.

**KYONG-MI CHANG, MD:** has received an NIH consortium grant on hepatitis B virus (HBV); her lab and program will serve as a national HBV immunology center. Readers are encouraged to contact her at [kmchang@mail.med.upenn.edu](mailto:kmchang@mail.med.upenn.edu) for their patients with HBV.

**RAJ REDDY, MD:** Director of Hepatology, Medical Director of Liver Transplantation, has received an NIH consortium grant on drug-induced liver injury. Readers are encouraged to contact him at [rajender.reddy@uphs.upenn.edu](mailto:rajender.reddy@uphs.upenn.edu) for their patients with drug-induced liver diseases.

**BEN STANGER, MD, PhD:** is the recipient of two NIH grants. The first is on pancreatic development and insulin producing cells, and the second is on liver development.

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