Variants in APOE3 Gene Associated With NAFLD, Insulin Resistance

Apolipoprotein C3 Gene Variants in Nonalcoholic Fatty Liver Disease.

Petersen KF, Dufour S, et al:


Among healthy, but sedentary, men, the presence of variants in the apolipoprotein C3 gene is linked to nonalcoholic fatty liver disease and insulin resistance.

**Background:** Apolipoprotein C3 (APOC3) is a regulator of lipoprotein metabolism. It impairs lipolysis of triglyceride-rich lipoproteins. Whether genetic changes in the APOC3 gene are related to the development of nonalcoholic fatty liver disease (NAFLD) and insulin resistance is not known, although 2 single-nucleotide polymorphisms (SNPs) in APOC3 have been associated with elevated serum triglycerides.

**Objective:** To determine whether these polymorphisms are related to NAFLD and insulin resistance.

**Methods:** In healthy, but sedentary, Asian Indian men, dietary histories, measures of physical activity, fasting glucose and insulin levels, and plasma lipid and APOC3 levels were studied. Insulin sensitivity was assessed with an oral glucose tolerance test and hepatic triglyceride content was measured by proton magnetic resonance spectroscopy. Retinyl fatty acid ester absorption was studied after subjects had a high-fat meal and plasma triglycerides were studied after an intravenous fat tolerance test. A confirmatory study in non-Asian Indian men also was performed.

**Results:** Among the 95 Asian Indian men studied, 20% carried the wild-type alleles, and 80% carried ≥1 variants. Although those with the genetic variants were similar in age, weight, body mass index (BMI), and physical activity level to those without variants, plasma APOC3 levels were 30% higher and plasma triglycerides were 60% higher. Liver triglyceride levels were also significantly higher in the variant carriers even after adjustment for age and BMI; 38% of those with variants had hepatic triglycerides >5.5% versus none of those without variants, and those with variants also had marked insulin resistance. Clearance of triglycerides and retinyl fatty acid ester was slowed on oral fat tolerance tests in the variant patients. Similarly, plasma triglyceride clearance was decreased in the variant group after intravenous fat tolerance testing. In 7 insulin-resistant subjects with NAFLD who were placed on caloric restriction, weight loss resulted in reduced liver triglycerides and improved insulin sensitivity. In the confirmatory study, 9% of those with the variant had NAFLD versus none of those without the variants. Compared to men without NAFLD, those with the variants and NAFLD had striking insulin resistance.

**Conclusions:** Based on these observations, polymorphisms in the APOC3 gene appear to be associated with NAFLD and insulin resistance.

**Reviewer’s Comments:** The authors suggest that the mechanism of NAFLD in individuals with these genetic variants is elevation of APOC3 levels leading to delayed triglyceride clearance and enhanced hepatic uptake of circulating chylomicron-remnant particles. They also postulate that this increase in hepatic steatosis results in insulin resistance. It would have seemed reasonable to determine whether weight reduction in those with the variants and both NAFLD and insulin resistance was accompanied by a decrease in the elevated level of APOC3 described in this study. Of course, the relationship of APOC3 variants to the development of nonalcoholic steatohepatitis remains to be determined in future studies. (Reviewer-Raymond S. Koff, MD).

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Keywords: Apolipoprotein C3, Polymorphisms, NAFLD, Insulin Resistance

Print Tag: Refer to original journal article
Rifaximin Reduces Risk of Recurrent Hepatic Encephalopathy

Rifaximin Treatment in Hepatic Encephalopathy.

Bass NM, Mullen KD, et al:


The risk of a recurrent episode of hepatic encephalopathy in patients taking lactulose could be reduced by 52% with administration of rifaximin compared to placebo.

Background: Lactulose reduces the risk of recurrent hepatic encephalopathy (HE), but recurrent episodes nonetheless occur in approximately 20% to 30% of patients. The efficacy of rifaximin, an oral, minimally absorbed antibiotic in the prevention of recurrent HE, is uncertain.

Objective: To assess the efficacy of this antibiotic in the prevention of recurrent HE.

Participants/Methods: Eligible patients were recruited in multiple medical centers in the U.S., Canada, and Russia. Participants had to be ≥18 years of age, have experienced a minimum of 2 episodes of overt HE during the preceding 6 months, had to be in remission from HE at enrollment, and had to have a Model for End-Stage Liver Disease (MELD) score of ≤25. Previous episodes of HE associated with well-known precipitants were excluded. Patients were randomized to receive 550 mg of rifaximin or a placebo twice daily for 6 months. Lactulose use was permitted. On clinic visits on day 7, day 14, and every 2 weeks thereafter, the Conn score was utilized to assess mental impairment, and an asterixis severity scale was used to assess neuromotor impairment. The time from onset of treatment to the first breakthrough episode of HE was the primary efficacy point, defined as an increase in the Conn score to a level of 2 or an increase to a level of 1 plus a 1-unit increase in asterixis grade. The interval from onset of treatment to the first hospitalization for HE or to a hospitalization in which HE occurred was the secondary efficacy end point.

Results: Baseline features were similar in the 140 patients assigned to the rifaximin group and the 159 patients assigned to the placebo group; 91% of patients in both groups were receiving lactulose at baseline, and the mean daily doses were similar. In the rifaximin group, breakthrough episodes of HE occurred in 22% of patients versus 46% of those receiving placebo (HR, 0.42; P<0.001). Hospitalizations were also significantly less common in the rifaximin group at 14% versus 23% in the placebo group (P =0.01). The efficacy of rifaximin was unrelated to age, sex, geographic region, baseline MELD score, number of preceding HE episodes, lactulose use, or the presence of transjugular intrahepatic portosystemic shunts. Adverse events and serious adverse events were similar in the 2 treatment groups.

Conclusions: Treatment with rifaximin over a 6-month period reduced the risk of recurrent HE and hospitalization for HE when compared to placebo in patients with previous episodes of HE who were concomitantly receiving lactulose.

Reviewer's Comments: This report indicates that the addition of rifaximin to lactulose in patients who have recovered from recurrent HE is likely to reduce the risk of a subsequent recurrence by approximately 58% compared to placebo and concomitant lactulose. Clearly an improvement, but imperfect since breakthrough HE still occurred. (Reviewer-Raymond S. Koff, MD).

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Keywords: Recurrent Hepatic Encephalopathy, Rifaximin, Lactulose

Print Tag: Refer to original journal article
May Not Need to Cease Clopidogrel Before Colonoscopy/Polypectomy

Postpolypectomy Bleeding in Patients Undergoing Colonoscopy on Uninterrupted Clopidogrel Therapy.

Singh M, Mehta N, et al:

Gastrointest Endosc 2010; 71 (May): 998-1005

Cessation of clopidogrel may not be needed before colonoscopy and polypectomy.

**Background:** The American Society for Gastrointestinal Endoscopy (ASGE) guidelines recommends holding clopidogrel for 7 to 10 days before colonoscopy with possible polypectomy.

**Objective:** To evaluate the post-polypectomy bleeding rate (PPB) risk factors and outcomes in patients taking clopidogrel.

**Design:** Retrospective, single-center study.

**Participants:** Study participants were patients undergoing colonoscopy with polypectomy while on uninterrupted clopidogrel therapy. The control group consisted of patients not on clopidogrel and undergoing polypectomy. One hundred and forty two case patients were identified meeting entry criteria who underwent 375 polypectomies. The control group had 1243 patients who underwent 3226 polypectomies.

**Methods:** Veterans Affairs medical records, pharmacy records, and current procedural terminology (CPT) coding were used to identify cases and controls for this study from January 2002 to October 2007. Standard clinical and demographic data were mined from the charts. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin (ASA) were noted. Of note, these agents are not held prior to colonoscopy at this institution. Coumadin was held for 3 to 5 days. PPB was documented from several source documents.

**Interventions:** Colonoscopy with polypectomy.

**Results:** The groups were similar for polypectomy technique, number of polyps removed per patient, location, and adenoma rate. Interestingly, the largest polyp removed in the case group was 3 cm in size. The immediate PPB rates were similar, but delayed bleeding was higher in the clopidogrel group (3.5% vs 1.0%; *P*=0.02). Hospitalization and transfusion were also more common in the group on clopidogrel. Of most interest, the use of ASA/NSAIDs with clopidogrel and the number of polyps removed were the only significant risk factors associated with PPB. Clopidogrel itself was not an independent risk factor.

**Conclusions:** The PPB rate is higher in patients taking clopidogrel and concomitant ASA/NSAIDs, but the risk is small and outcomes good. Routine cessation of clopidogrel is unnecessary prior to colonoscopy/polypectomy.

**Reviewer’s Comments:** This interesting paper demonstrates how little we know about the interplay of clinical and pharmaceutical factors in increasing the risk of post-polypectomy bleeding. There was no statistical difference in bleeding rates between patients on clopidogrel and those not on clopidogrel until ASA or an NSAID was added to the equation. Stopping clopidogrel in patients with significant coronary or cerebrovascular disease may confer significant risk in and of itself and frequently requires clearance from the prescribing physician. Is this really necessary? Many questions are raised by this paper, such as simply holding the ASA or NSAID, whether clips should be applied to polypectomy sites, or since the immediate bleeding rates are not increased, would it make more sense to hold this medication after the polyp has been removed. This article was a great one to stir the pot so to speak, but we must await larger prospective trials to really know the optimal management for these patients. (Reviewer-J. Mark Lawson, MD).

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Keywords: Colonoscopy, Polypectomy, Clopidogrel

Print Tag: Refer to original journal article
In patients taking clopidogrel, the concomitant use of PPIs was associated with a lower incidence of upper GI bleeding without an associated increased incidence of cardiovascular events.

**Background:** Proton pump inhibitors (PPIs) may interfere with production of the antiplatelet metabolite of clopidogrel. Three observational studies have assessed the potential risk of concomitant PPI therapy in increasing the incidence of cardiovascular events. Two of those studies have suggested such an association.

**Objective:** To assess the benefit (prevention of upper GI bleeding) and risk (cardiovascular events) in patients who are taking clopidogrel and are, or are not, also taking PPIs.

**Design:** Retrospective, controlled cohort study.

**Participants:** Patients enrolled in the Tennessee Medicaid program, who were over the age of 30 years and were using clopidogrel, were included. Patients had to have assessable comorbidities (and thus have hospital diagnoses available) and be receiving all of their care from the Medicaid program (and thus to have been continuously enrolled in the program, including medication benefits, for at least 1 year before the hospitalization).

**Methods:** Identified patients were divided into 2 groups, those who had been given concomitant prescriptions for a PPI and those who had not. Information regarding a large number of potentially confounding variables was also collected and used to create a prognostic score, namely the likelihood that any combination of such variables would result in the use of PPIs. A variety of subgroup and sensitivity analyses were planned.

**Results:** Out of 26,315 users of clopidogrel, 20,596 met all of the entry criteria; 7593 of them were also using PPIs. After correcting for the various confounding variables, the hazard ratio (HR) of being hospitalized for gastroduodenal bleeding was 0.50 (95% CI, 0.39 to 0.65); the rate of such hospitalizations in those not taking PPIs was 12.2 per 1000 patient-years. For nonusers of PPIs, the risk of hospitalization for bleeding rose as the number of pre-existent risk factors for bleeding increased. The HR for a cardiovascular event was 0.99 (95% CI, 0.82 to 1.19). The various preplanned subanalyses did not change the conclusion. The tradeoff of benefit for risk was always in favor of the PPI users in the base-case (since there was no harm identified). When the extreme high end of the confidence interval was used for the risk of cardiovascular events (HR, 1.19), the risk outweighed the benefit for patients at high risk of cardiovascular events and low or moderate risk for GI bleeding.

**Conclusions:** While PPIs did appear to prevent bleeding without increasing the cardiovascular risk, the confidence interval did include a potentially important increased risk for the latter.

**Reviewer's Comments:** The editorial was a complicated critique of the prognostic scoring, but, when these editorialists did all of their statistical manipulating, the conclusions were still not changed. Uncommented upon in either the paper or the editorial was the issue of whether or not data from Medicaid recipients can be extrapolated to the general population. (Reviewer-Ronald L. Koretz, MD).

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Keywords: Clopidogrel, Proton Pump Inhibitors

Print Tag: Refer to original journal article
Step-Up Approach for Infected Necrotizing Pancreatitis May Be Preferable

A Step-Up Approach or Open Necrosectomy for Necrotizing Pancreatitis.

van Santvoort HC, Besselink MG, et al:


A step-up approach in patients with infected necrotizing pancreatitis is probably not inferior to open necrosectomy.

**Background:** Patients with infected necrotizing pancreatitis are typically treated with open laparotomy and resection of the necrotic tissue. Retrospective reports have suggested that percutaneous drainage, with minimally invasive retroperitoneal necrosectomy in nonresponders ("step-up approach") is also effective.

**Objective:** To compare a step-up approach to open necrosectomy.

**Design:** Randomized controlled trial.

**Participants:** Patients presenting with necrotizing pancreatitis who were known (or at least suspected) to have infection in the necrotic tissue and for whom a decision had been made to do some type of surgical intervention, were included.

**Methods:** Eligible patients were randomized (computer-generated with concealment of allocation) into 1 of 2 groups (step-up or open surgery) after the decision that some type of invasive therapy was needed was confirmed by an independent panel. The paper stated that the primary end point was the occurrence of at least 1 of the following events: death; multiple organ failure or systemic complication; enterocutaneous fistula or perforation of a visceral organ; or intraabdominal bleeding. The registered protocol indicated that each of these was to be analyzed separately, and no mention was made regarding combining all of these events. Any suspected complication was adjudicated by an independent and blinded panel. A sample size calculation indicated that 88 patients would be needed. (The registered protocol called for 94 patients.)

**Results:** 43 patients were randomized to the step-up approach and 45 to open necrosectomy. A total of 17 and 31 primary outcomes occurred in the step-up/open necrosectomy arms, respectively ($P=0.006$). With regard to the individual outcomes, a significant difference was seen only with regard to multiorgan failure/systemic complications (5 vs 19; $P<0.001$). There was no difference in mortality (8 vs 7 deaths). The open necrosectomy group had significantly higher incidences of subsequent ICU admissions, incisional hernias, new-onset diabetes, and use of pancreatic enzymes. The average costs in each group were $116,000 for the step-up approach and $132,000 for open necrosectomy (no $P$ value provided).

**Conclusions:** The step-up approach resulted in fewer primary outcomes.

**Reviewer’s Comments:** There were potential biases in this trial. There were acknowledged changes in some of the analyses as well as apparent unacknowledged changes in the sample size and the primary outcome. While the complications were assessed by a blinded panel, the only examples that the panel members saw were those that the investigators identified; bias may have led to different criteria for a complication in each arm. Thus, there was a real risk of bias in this trial, which, at the very least, may have exaggerated the size of the estimated effect. On the other hand, it would seem unlikely that the step-up approach is inferior to open necrosectomy; therefore, if a particular institution has the facilities to perform it, this approach could be considered. (Reviewer-Ronald L. Koretz, MD).

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Keywords: Necrotizing Pancreatitis, Open Necrosectomy, Step-Up Approach

Print Tag: Refer to original journal article
The safety and efficacy of balloon dilatation of strictures in Crohn's disease is independent of disease activity.

**Background:** Patients with Crohn's disease often develop symptomatic strictures that require intervention. Surgical resection was the treatment of choice in this situation, but more recently, stricturoplasty and endoscopic dilatation have been recommended to spare the loss of small bowel. The long-term efficacy and safety, as well as the influence of disease activity and medical therapy, have not been determined for this newest treatment option.

**Objective:** To retrospectively evaluate the long-term results of balloon dilatation in Crohn's disease and the effect of disease activity and medical treatment on the outcome of this procedure.

**Methods:** 237 dilatations were performed on 138 patients between 1995 and 2006. The patients mean age was 50.6 ± 13.4 years, and 56% were female. All strictures were symptomatic causing obstructive symptoms and <5 cms in length; 84% were anastomotic.

**Results:** 97% of the initial dilatations were immediately successful, with a 5% serious complication rate. During a median follow-up of 5.8 years (interquartile range, 3.0 to 8.4), recurrent obstructive symptoms led to the need for repeat dilatation in 46% and surgery in 24%. Neither endoscopic disease activity nor elevated levels of C-reactive protein predicted the need for new interventions. None of the medical therapies used influenced outcome.

**Conclusions:** The long-term efficacy of endoscopic balloon dilatation of symptomatic strictures in patients with Crohn's disease was confirmed by this, the largest study thus far presented in the literature. The efficacy of balloon dilatation in Crohn's disease outweighs the risk of this procedure. Neither disease activity at the time of dilatation nor medical therapy following dilatation predicts the development of recurrent symptomatic strictures.

**Reviewer's Comments:** This study is not only the largest series of Crohn's patients who have undergone balloon dilatation of strictures, but also, these patients have been followed for the longest period of time thus far reported. It would appear that balloon dilatation of strictures in Crohn's disease should be considered as primary therapy in any patient who has a stricture reachable by a colonoscope. This can be considered even in the face of active disease, and the benefit appears to clearly outweigh the risks in performing this procedure. (Reviewer-Michael M. Phillips, MD).

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**Keywords:** Strictures, Endoscopic Dilatation

Print Tag: Refer to original journal article
CRYO Safe, Effective for Eradicating HGD Associated With BE

Safety and Efficacy of Endoscopic Spray Cryotherapy for Barrett's Esophagus With High-Grade Dysplasia.

Shaheen NJ, Greenwald BD, et al:

Gastrointest Endosc 2010; 71 (April): 680-685

Cryotherapy is safe and effective in the treatment of high-grade dysplasia associated with Barrett's esophagus.

**Background:** Endoscopic ablation can effectively treat high-grade dysplasia (HGD) associated with Barrett's esophagus (BE).

**Objective:** To evaluate the safety and efficacy of cryotherapy (CRYO) to treat HGD associated with BE.

**Design:** Multicenter, retrospective cohort study.

**Participants:** Subjects had HGD confirmed by 2 separate pathologists.

**Methods:** A retrospective analysis was made of consecutive cases with BE and HGD who underwent CRYO at 9 different sites. The CSA cryotherapy system was used for noncontact application of liquid nitrogen. A dual lumen gastric decompression tube was used to remove nitrogen gas from the stomach. Follow-up ablations were performed at 2- to 3-month intervals until biopsies confirmed ablation of Barrett's lining or it was decided to stop therapy for clinical reasons or patients desire. Biopsies were done every 1 to 2 cm on follow-up endoscopy.

**Interventions:** Upper endoscopy with CRYO.

**Results:** 98 subjects (mean age, 65 years) had 333 treatments (mean, 3.4/patient). Strictures developed in 3 cases, and severe chest pain occurred in 2 cases requiring narcotic therapy. One patient had bleeding and was hospitalized. Sixty subjects completed all recommended treatments. Ninety-seven percent of cases had complete eradication of HGD, 87% had complete resolution of all dysplasia with persistent nondysplastic intestinal metaplasia, and 57% had complete eradication of all intestinal metaplasia. Two subjects were detected to have subsquamous BE.

**Conclusions:** CRYO is safe and effective in treating BE with HGD.

**Reviewer's Comments:** This interesting paper is limited due to its retrospective nature, lack of a control group, large drop out from the planned treatment protocol, and follow-up of only 10.5 months. We clearly need prospective studies that will determine whether the resolution of HGD is durable or not. If current estimates of a rate of 0.07cases/year of HGD evolving to cancer are correct, ablative therapy has significant appeal due to its low morbidity and mortality compared to esophagectomy. We anxiously await long-term prospective studies of cryoablation and radiofrequency ablation for the treatment of HGD in BE. (Reviewer-J. Mark Lawson, MD).

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Keywords: Barrett's Esophagus, High-Grade Dysplasia, Cryotherapy

Print Tag: Refer to original journal article
There is an association between having a negative colonoscopy performed in a hospital by a gastroenterologist and having a lower risk of subsequent cancer.

**Background:** Patients who have a negative colonoscopy can develop colon cancer subsequently. It is usually unclear if this represents the appearance of a new cancer or a technical failure of the colonoscopy itself. One proposed technical difficulty is the specialty of the endoscopist.

**Objective:** To look for an association between the specialty type of the colonoscopist and the subsequent development of colon cancer in those who have had negative colonoscopies.

**Design:** Retrospective observational study employing electronic database records.

**Participants:** Canadians living in Ontario, who had had a negative colonoscopy (one not associated with any biopsies or polypectomies and no second colonoscopy or diagnosis of cancer within the next 6 months) between 1992 and 1997, were included. Only patients without a previous cancer diagnosis or partial colectomy or a diagnosis of inflammatory bowel disease were considered. All of these patients had records of subsequent procedures and diagnoses, including diagnoses of cancer, available.

**Methods:** All of the patients initially identified were traced through their electronic records until December 31, 2006, unless they died, left the health-care system, or developed colorectal cancer. Patient demographics (age, gender, comorbidities), endoscopist characteristics (volume of colonoscopies performed annually as well as specialty, divided into gastroenterologist, general surgeon or other, who were largely internal medicine practitioners), and location of the colonoscopy (outpatient or hospital) were collected and entered into a multivariate analysis.

**Results:** 110,402 individuals with negative colonoscopies were identified; 86% of these procedures were performed in the hospital. Those who had outpatient procedures were younger, more likely to be male, had less comorbidity, and were more likely to have their colonoscopy performed by an individual with a high volume of procedures and/or a general surgeon. During the follow-up, 1596 new cancers were diagnosed. In those who had had the procedure as an outpatient, the multivariate analysis did not find any association between the type of specialist or volume of procedures and the subsequent development of cancer. However, among those who had the procedure done in the hospital, while there was no association with the volume of procedures, there was a significant increase in the hazard ratio (HR) for developing cancer if the procedure was done by a general surgeon (HR, 1.389) or by other non-gastroenterologists (HR, 1.275).

**Conclusions:** Being a gastroenterologist is an important determinant of the effectiveness of the colonoscopy.

**Reviewer's Comments:** This was an observational study that could only demonstrate association. It is difficult even to accept this association because there is no explanation as to why the patients had the colonoscopy in the first place. Given that so many were done in the hospital, it would appear that the procedures were not being done solely for screening. (Reviewer-Ronald L. Koretz, MD.)
Antireflux surgery does not prevent the occurrence of esophageal or cardia adenocarcinomas and should not be recommended as a means to prevent these cancers.

**Objective:** To determine whether there is a decrease in esophageal and cardia adenocarcinomas following antireflux surgery.

**Design/Participants:** Swedish population-based cohort study of 14,102 patients receiving antireflux surgery from January 1, 1965, through December 31, 2006.

**Methods:** Data extracted from this study included esophageal and cardia adenocarcinoma (EAC, CAC), cancers distal to the cardia and squamous cell cancer of the esophagus. Between 1965 and 1987, 65% to 85% of records could be extracted, but from 1985 through 2006, 100% of patient data were available through a national Swedish registry in which all Swedish patients are registered. Identification of EAC following surgery was 98% complete. The comparison cohort was age-, sex-, and calendar-year matched. The relative risk of developing adenocarcinoma was estimated as the standardized incidence ratio (SIR).

**Results:** The antireflux study cohort had 120,514 person-years of follow-up. The cancer group had more males and a higher mean age than the control cohort group. The risk of developing EAC following antireflux surgery was SIR, 12.3 (95% CI, 8.7 to 16.8), with no significant trend toward decreasing with time ($P=0.86$). The overall risk of developing CAC in the antireflux population was SIR, 4.4 (95% CI, 2.7 to 6.7), with no decrease in risk over time ($P=0.20$). There was no significant increase in other cancers (stomach and squamous cell) in the antireflux surgery population as compared with the comparison cohort.

**Conclusions:** Antireflux surgery does not prevent the occurrence of EAC or CAC. It should not be recommended as a means to prevent these cancers.

**Reviewer's Comments:** The major advantage of this study is that the entire Swedish population is enrolled in the health-care system, and follow-up is complete and accurate. Possible confounders could be that specialized centers would do a better antireflux procedure and possibly get better results. The fact that other cancers (gastric cancers of the stomach and squamous cell of the esophagus) had similar rates as the cohort population gives confidence that the results are accurate. (Reviewer-Roy K.H. Wong, MD).

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Keywords: Esophageal, Cardia, Adenocarcinoma, Antireflux Surgery

Print Tag: Refer to original journal article
Patients with pernicious anemia have an increased risk of developing hip fractures, and this increased risk persists after vitamin B-12 therapy.

Objective: To determine whether patients with pernicious anemia (PA) have an increased risk of hip fractures.

Design/Methods: This was a retrospective cohort study utilizing the United Kingdom’s General Practice Research Database (GPRD), which contains data on 98% of all patients in the U.K. seen by general practitioners who prospectively input data concerning their patients. PA patients (n=9506) were chosen from 9.4 million enrolled between 1987 and 2006, who were between 40 and 90 years of age. PA patients had to have received at least 1 year of vitamin B-12 therapy. Controls were matched 4:1 by age and sex. The primary outcome of the study was the time to the first hip fracture for both groups.

Results: 9506 PA patients were identified who received B-12 therapy for at least 1 year, with a control population of 38,848 individuals. PA patients were more likely to have potentially confounding medical diagnoses than were the control group. Following the diagnosis of PA and at least 1 year of B-12, the unadjusted Cox regression analysis had an increased risk of having a hip fracture of 1.73. When identifying PA cases 1 year after GPRD enrollment and 1 year of B-12 therapy (incident cases), the HR was higher at 2.63. To determine the effect of B-12 therapy on hip fractures, the risk of hip fractures was followed for 5 years. All hazard ratios were between 2.8 and 4.21, except for year 2.

Conclusions: Patients with PA have an increased risk of developing hip fractures. This increased risk persists after vitamin B-12 therapy. It is possible that chronic achlorhydria is one of the mechanisms resulting in increased hip fracture risk.

Reviewer's Comments: This study indicates that despite B-12 repletion, hip fracture risk persists, suggesting that achlorhydria may be the mechanism for increased hip fractures. However, some studies indicate that calcium absorption may not be affected by gastric acid suppression. An article in the March 2009 issue of Gastroenterology suggested that proton pump inhibitors are not associated with hip osteoporosis. Another possibility is the fact that hypergastrinemia is associated with hyperparathyroidism, which results in increased bone turnover. (Reviewer-Roy K.H. Wong, MD).

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Keywords: Pernicious Anemia, Hip Fracture Risk, Vitamin B-12, Achlorhydria

Print Tag: Refer to original journal article
Analyses of systematic reviews and their component randomized trials indicate that outcomes are frequently measured but not reported, and that this problem can materially influence the estimated effect of the meta-analysis.

**Background:** While randomized clinical trials (RCTs) eliminate confounding bias, other biases can exist. The frequency and influence of outcome reporting bias (an outcome is measured but not reported) is not known.

**Objective:** To assess the impact of outcome reporting bias.

**Design:** Descriptive analysis of systematic reviews.

**Methods:** A classification system was created in which a trial that failed to provide data regarding a particular outcome was assessed for the likelihood that the outcome was measured and analyzed. Trials were separated into those in which the outcome was clearly measured and analyzed, clearly measured but not analyzed, and clearly not measured, as well as those where it was unclear whether or not it was measured. For the first 2 categories, a judgment was made regarding the likelihood that the failure to report represented a high, low, or no risk of bias. A total of 283 new systematic reviews in the Cochrane Library, containing 2486 eligible RCTs, were identified. The primary outcome for each review was determined, and each RCT was classified. The investigators assessed whether or not all of the RCTs had contributed data to the meta-analysis for that outcome. If all of the identified RCTs were not used, the investigators undertook statistical corrections to account for the bias. For all of the RCTs for which the data for the primary outcome was not reported, the investigators contacted the primary trialists to find out what had happened.

**Results:** 712 (31%) of the RCTs did not completely report data for the primary outcome, and approximately 50% of them were labeled as high risk of bias. About one-third of the systematic reviews were missing primary outcome data from at least 1 of the trials with high risk of bias. Only 12% of the trialists responded to the request for clarification; the classification system identified 92% of the trials in which the outcome had been measured (sensitivity) and 77% of those in which it had not (specificity). The judgment regarding the degree of bias was 88% sensitive and 80% specific. When the statistical corrections were done, significant differences were rendered insignificant approximately one-third of the time. Among all of the trials with significant estimates of efficacy, the median percentage change in the size of the effect fell by 20%.

**Conclusions:** Outcome reporting bias has an effect on the conclusions of a substantial number of systematic reviews.

**Reviewer's Comments:** When we read reports of RCTs, we should consider what information should have been measured. If that information is not reported, we should worry about how methodologically sound that particular trial is. Similarly, when we read systematic reviews, we should look for an effort by those authors to account for outcome reporting bias. (Reviewer-Ronald L. Koretz, MD).
SNPs at IL28B Locus Associated With Spontaneous, Treatment-Induced HCV Clearance

Genetic Variation in IL28B Is Associated With Chronic Hepatitis C and Treatment Failure: A Genome-Wide Association Study.

Rauch A, Kutalik Z, et al:

Gastroenterology 2010; 138 (April): 1338-1345

In patients who spontaneously clear HCV infection or respond to treatment, a low frequency of the G allele of the rs8099917 SNP at the IL28B locus is found.

**Background:** Recent studies have reported that genetic factors may play an important role in spontaneous clearance following hepatitis C virus (HCV) infection and may also be predictive of the response to treatment in chronic hepatitis C. In this regard, single nucleotide polymorphisms (SNPs) in the IL28B gene, which encodes interferon lambda, have been identified as important host factors.

**Objective/Design:** To use a genome-wide association study to identify genetic determinants of spontaneous or treatment-induced HCV clearance.

**Participants/Methods:** In 347 Swiss Caucasians who had spontaneously cleared HCV but were anti-HCV positive and in 1015 with chronic HCV infection including those with HIV/HCV coinfection, a genome-wide analysis of >500,000 SNPs was undertaken. Response to treatment was defined as a sustained viral response following pegylated interferon and ribavirin.

**Results:** A genome-wide significant association for chronic versus spontaneously cleared infection was found solely on chromosome 19 and mapped to the IL28B locus. The top hit was the rs8099917 SNP, and T and G alleles were assessed. Individuals with the GG or GT alleles had a higher risk of chronicity than those with the TT allele. Neither sex nor HCV RNA level were associated with rs8099917. In the analysis of treatment-induced response versus treatment failure in HCV genotype 1 and 4 patients, GG and GT patients had a higher risk of treatment failure than patients who were genotyped as TT. In both assessments, the G allele was designated the risk allele. The G allele was less frequent in spontaneous clearance at 24%, more frequent among responders to treatment at 32%, and most frequent in nonresponders at 58%. However, there was no association of IL28B variants and response to treatment in patients with HCV genotypes 2 or 3. Resequencing of the rs8099917 revealed several SNPs that may be responsible for the action of IL28B.

**Conclusions:** IL28B is associated with both spontaneous clearance of HCV and treatment-induced recovery from chronic hepatitis C.

**Reviewer's Comments:** The major limitation of this analysis is that only Caucasian patients were studied. Because other studies have linked the frequency of the rs12979860 SNP near the IL28B locus with response to treatment in Caucasians, African Americans, and Latinos, it will be important to assess both SNPs in future studies. Taken together, all of the recent studies implicating IL28B in clearance and treatment response suggest a possible role for interferon lambda in treatment, and Phase 1 trials are promising. (Reviewer-Raymond S. Koff, MD).

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Keywords: Single Nucleotide Polymorphisms, IL28B, Spontaneous HCV Clearance, Tx Response

Print Tag: Refer to original journal article
Trunk Fat Independently Associated With Serum ALT Elevation

Trunk Fat Is Associated With Increased Levels of Alanine Aminotransferase in the United States.

Ruhl CE, Everhart JE:
Gastroenterology 2010; 138 (April): 1346-1356

Measurement of trunk fat is a better indicator of liver injury than the waist-to-hip ratio or waist circumference.

Background: High body mass index (BMI) and waist circumference, correlates of obesity that have been associated with liver injury, may reflect both body fat and lean mass. In previous studies, using the waist-to-hip ratio and waist circumference as surrogates for abdominal fat, the ratio was utilized to predict elevated serum alanine aminotransferase (ALT) levels in the population-based National Health and Nutrition Examination Survey (NHANES) III studies. A more sophisticated method to assess abdominal fat, namely dual-energy x-ray absorptiometry (DXA), has now been utilized in on-going NHANES studies.

Objective: To determine the relationships of body composition as measured by DXA and elevated ALT levels in the NHANES population, which represents the U.S. population but over-samples individuals >60 years old, African Americans, and Hispanics.

Methods: ALT was measured in a single serum sample from individuals in the NHANES population. Abnormal ALT was set at 44 U/L for men and 31 U/L for women, since these cutoffs reflected levels above the 95th percentile for individuals without risk factors for liver injury. DXA was used to determine trunk fat and lean mass and extremity fat and lean mass, and these were, with waist circumference, categorized into quintiles.

Results: 11,821 subjects participated in this analysis. Elevated ALT levels were found in 11% of men and 10% of women, and all body composition measures were higher in these subjects. DXA analysis revealed that trunk fat was most strongly associated with elevated ALT levels in men and women. Extremity fat in women was inversely related to elevated ALT levels. After multivariate adjustments, high trunk fat remained independently associated with elevated ALT levels, but BMI and waist circumference were not, and the presence of insulin resistance or the metabolic syndrome did not reduce the correlations significantly. The relationship between trunk fat and elevated ALT levels also was unrelated to underlying renal disease or use of prescription drugs.

Conclusions: Trunk fat is associated with elevated serum ALT levels and appears to be a better indicator of liver injury than the waist-to-hip ratio or waist circumference.

Reviewer's Comments: Unfortunately, DXA does not distinguish between subcutaneous trunk fat and visceral abdominal fat. It is the latter that is believed to be responsible for the liver injury identified by elevations of serum ALT. Thus, the current study confirms the importance of trunk fat but cannot identify the responsible metabolic tissue. (Reviewer-Raymond S. Koff, MD).

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Keywords: Elevated ALT, Body Composition, Trunk Fat, Extremity Fat, DXA

Print Tag: Refer to original journal article
Crohn's Proctitis Recognized as Distinct Clinical Entity

Crohn's Proctitis: A Distinct Entity.
Korelitz BI, Aronoff J:

Inflamm Bowel Dis 2010; 16 (May): 721-722

Crohn's proctitis may represent a distinct clinical entity characterized by large anorectal skin tags, severe inflammation with deep ulcerations, strictures, perirectal abscesses, and fistulas.

**Background:** Crohn's disease (CD) may involve any portion of the GI tract from mouth to anus, but is most commonly found on the right side in the ileum, cecum, or contiguous ascending colon. CD limited to the rectum (proctitis) in the absence of disease proximal to the rectum is extremely unusual. In contrast, ulcerative colitis (UC) more commonly involves the left colon, and in 80% of cases does not extend proximal to the splenic flexure. The rectum is involved in almost 100% of UC cases and is limited only to the rectum (proctitis) in 25% of UC cases. Sparing of the rectum in the presence of proximal disease strongly supports a diagnosis of CD.

**Objective:** To describe an independent disease entity, Crohn's proctitis.

**Participants:** 3 patients with strong features of CD limited to the rectum. **Case Reports:** Case 1 was that of a 48-year-old male with a 5-year history of ulcerative proctitis resistant to oral and rectal mesalamine, steroids, and flagyl. He had large anorectal skin tags, rectal stricture, and colonoscopic disease limited to the distal 1 inch of rectum, with edema, induration, and exudate. Biopsies showed severe inflammation but no granulomas. He responded dramatically to 6-mercaptopurine (6-MP) and infliximab. In addition, the patient's brother also had CD. Case 2 was that of a 23-year-old man with severe chronic proctitis complicated by rectal stricture and perirectal abscess, aphthous sores in the mouth, and erythema nodosum. Colonoscopy revealed friable cobblestoned mucosa limited to the rectum, with rectal biopsies showing dysplasia. Small bowel x-rays were normal. Case 3 involved a 61-year-old man who had large anorectal skin tags, rectal stricture, and perirectal abscess. Examination revealed inflammation with longitudinal ulcers limited to the distal 8 cm of rectum with normal mucosa proximal to 8 cm. Small bowel x-rays were normal.

**Conclusions:** 3 patients with Crohn's proctitis characterized by large anorectal skin tags, severe inflammation with deep ulcerations, strictures, perirectal abscesses, and fistulas are described. In all cases, disease was limited to the rectum. It is suggested that these cases are representative of an independent distinct clinical entity—Crohn's proctitis.

**Reviewer's Comments:** The recognition of Crohn's proctitis as a distinct independent clinical phenotypic entity is likely to soon lead to identification of specific genetic mutations associated with Crohn's proctitis. It would be of interest to know if this entity is, or is not, associated with NOD-2/CARD-15 mutations or other gene mutations that are being linked to inflammatory bowel disease. (Reviewer-Allen L. Ginsberg, MD).

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Keywords: Crohn's Disease, Proctitis

Print Tag: Refer to original journal article
Risk factors for kidney stones are found in many Roux-en-Y gastric bypass patients who do not have stones; these metabolic risk factors appear to differ from those found in comparably obese subjects who have not undergone surgery.

**Background:** Roux-en-Y gastric bypass (RYGB) surgery is associated with risks for kidney stones, oxalate nephropathy, and renal failure. Obesity itself increases the risk for kidney stones secondary to several metabolic risk factors including low urine pH, hyperoxaluria, and hypercalciuria. A prior examination of morbidly obese individuals prior to gastric bypass found that 98% had at least 1 risk factor for kidney stone formation and 80% had ≥3.

**Objective:** To assess the mechanisms by which RYGB increases nephrolithiasis risk.

**Design:** Comparative, cohort physiology study.

**Participants:** 19 non-RYGB subjects without a history of kidney stones compared with 19 gender-, age-, and body mass index-matched controls also without a history of kidney stones.

**Methods:** Fasting biochemical serum and 24-hour urine analyses were obtained.

**Results:** RYGB subjects compared with the nonsurgical obese controls had significantly higher (mean ± SD) urinary oxalate (45 ± 21 vs 30 ± 13 mg daily; \( P = 0.01 \)), significantly lower urinary citrate (358 ± 357 vs 767 ± 307 mg daily; \( P < 0.01 \)), and significantly lower urinary calcium (115 ± 93 vs 196 ± 123 mg daily; \( P = 0.03 \)). The urinary oxalate was greater in any individual RYGB subject than in a control with a comparable body mass index. The prevalence of hyperoxaluria was significantly higher in the RYGB subjects than controls (47% vs 10.5%; \( P = 0.03 \)), and the prevalence of hypocraturia was significantly lower in the RYGB subjects compared with controls (63% vs 5%; \( P < 0.01 \)). The prevalence of hypercalcuria was nonsignificantly lower in the RYGB group (5% vs 32%; \( P = 0.08 \)).

**Conclusions:** Risk factors for kidney stones are found in many RYGB patients who do not have stones. These metabolic risk factors appear to differ from the risk factors found in comparably obese subjects who have not undergone surgery.

**Reviewer’s Comments:** This study provides some insight into metabolic factors inducing stone formation in obese individuals who have undergone roux-en-Y bariatric surgery for obesity. It does not give us any information as to relative risks of stone formation between obese individuals who have, or have not, undergone surgery. The authors also note that we do not know the true incidence of nephrolithiasis in this population or the optimal treatment, if any is indicated, for the lithogenic risk factors found. (Reviewer-Timothy O. Lipman, MD).

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Keywords: Obesity, Gastric Bypass, Risk, Kidney Calculi

Print Tag: Refer to original journal article
Gluten-Free Diet May Help Patients With Endomysial Antibodies and Normal Villi

Gastrointestinal Symptoms, Quality of Life and Bone Mineral Density in Mild Enteropathic Coeliac Disease: A Prospective Clinical Trial.

Kurppa K, Collin P, et al:

Scand J Gastroenterol 2010; 45 (March): 305-314

Gastrointestinal symptoms and decreased bone mineral density in mild enteropathy may improve with adherence to a gluten-free diet.

**Background:** In order to make the diagnosis of celiac disease, a small bowel biopsy demonstrating villous atrophy and crypt hyperplasia is needed. Patients with structurally normal small bowel villi, but who have endomysial antibodies, may suffer from a disorder similar to those who have villous atrophy.

**Objective:** To evaluate GI symptoms, quality of life, and bone mineral density (BMD) in patients with mild enteropathy and the effect on them of a gluten-free diet.

**Design/Participants:** Prospective trial of 73 adults who had endomysial antibodies with normal villous morphology (Marsh I-II, mild enteropathy) who were treated with a gluten-free diet. GI symptoms and quality of life were ascertained by means of structured questionnaires. BMD was determined by x-ray absorptiometry. A total of 110 subjects who did not have celiac disease served as controls.

**Results:** At the onset of the study, those with mild enteropathy had more GI symptoms than those in the control group, but no differences in quality of life were noted between the 2 groups. After 1 year of a gluten-free diet, indigestion and depression were significantly alleviated in the mild enteropathy group. Osteopenia or osteoporosis was found in 58% of the patients in the mild enteropathy group, and there was a trend toward improved BMD after treatment.

**Conclusions:** Patients, who are endomysial antibody positive but have normal villous architecture, may suffer from GI symptoms and have poor bone health. This group appears to benefit from a gluten-free diet as do patients with overt villous atrophy.

**Reviewer's Comments:** This study was interesting but not completely convincing. Although there was an objective improvement in villous and crypt morphology in the subjects with mild enteropathy, their improvement in symptoms were somewhat subjective. There was a trend toward improvement in BMD with treatment with a gluten free-diet, but there was no statistical improvement. It was also disappointing that the BMD of individuals in the control group were not given. Perhaps with further follow-up, a statistically significant improvement in BMD will be demonstrated in the group with mild enteropathy. (Reviewer-Michael M. Phillips, MD).

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Keywords: Mild Enteropathy, GI Symptoms, Quality of Life, Bone Mineral Density

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High Folate Intake Associated With Reduced Pancreatic Ca Risk in Women

Folate Intake, Post-Folic Acid Grain Fortification, and Pancreatic Cancer Risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

Oaks BM, Dodd KW, et al:

Am J Clin Nutr 2010; 91 (February): 449-455

Secondary analysis of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial found that high folate intake is associated with reduced pancreatic cancer risk in women, but not men, and that folic acid supplements are not associated with pancreatic cancer risk.

**Background:** Pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States. The most consistently observed risk factors for pancreatic cancer are smoking, obesity, and family history. Folate plays a critical role in DNA synthesis, methylation, and repair. Folic acid is the synthetic form of folate used in supplements; some recent data suggest that folic acid effects and pathophysiology may differ from folate. Folate and folic acid intake have been associated with colorectal cancer risk; fewer data are available regarding folate, folic acid, and pancreatic cancer risk. The few available studies have come to varying conclusions; however, with mandatory food fortification with folic acid in the U.S., many have been concerned about potential unintended consequences.

**Objective:** To assess the relationship between dietary folate and folic acid supplements on pancreatic cancer risk.

**Design:** Secondary data analysis of a large prospective randomized trial.

**Participants:** Subjects from both arms of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial were included.

**Methods:** 51,988 male and 57,187 female participants, aged 55 to 74 years at baseline, were followed from 1998 through 2001. A self-administered food-frequency questionnaire was administered at baseline. Multiple Cox proportional hazards regressions were used to calculate hazard ratios (HRs).

**Results:** 266 pancreatic cancers developed over a median of 6.5 years. A significant interaction was found between total folate intake and sex, so that data were stratified by sex. Women in the highest quartile of dietary folate intake showed a significant (53%) decreased risk of pancreatic cancer compared with women in the lowest quartile (HR, 0.47; 95% CI, 0.23 to 0.94; \(P\) for trend: 0.09). There was no association between dietary folate intake and pancreatic cancer risk in men, and there was no association between folic acid supplement intake and pancreatic cancer risk in men or women.

**Conclusions:** High dietary folate intake in women, but not men, is associated with decreased pancreatic cancer risk. Folic acid supplement intake is not associated with pancreatic cancer risk in men or women.

**Reviewer's Comments:** Since these data represent secondary analysis of a large screening intervention trial, the findings can only be taken as associations, not causality. The authors do not provide any biologically plausible explanations for the differences between men and women with respect to dietary folate association with pancreatic cancer; they note the reason is unclear, with no further comment. At worst, these findings might be a statistical fluke; at best, they should stimulate future analyses of other available prospective cohorts and randomized trials. (Reviewer-Timothy O. Lipman, MD).

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Keywords: Pancreatic Ca Risk, Dietary Folate, Folic Acid Supplements

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Does HDC Identify More Polyps Than SWLC?

High-Definition Colonoscopy Detects Colorectal Polyps at a Higher Rate Than Standard White-Light Colonoscopy.

Buchner AM, Shahid MW, et al:
Clin Gastroenterol Hepatol 2010; 8 (April): 364-370

In comparison to standard white-light colonoscopy, high-definition colonoscopy identifies significantly more polyps, both hyperplastic and adenomatous polyps, especially in the left colon.

Objective: To determine whether high-definition colonoscopy (HDC) identifies more adenomas and polyps when compared with standard white-light colonoscopy (SWLC).

Materials/Methods: Computerized charts of patients undergoing average-risk screening colonoscopy between September 2006 and December 2007 were identified. Data obtained included demographics, adequacy of bowel preparation, indication, endoscopist and training, location, size of polyp, and histopathology. Exclusion criteria were incomplete and multiple colonoscopies and patients with polyposis syndromes. Colonoscopies were performed by 18 board-certified gastroenterologists; each had performed >5000 colonoscopies, using 6 GI suites (3 HDC [Olympus CF 180] and 3 SWLC [Olympus 140-160]). Patients were assigned to a room as it became available, and the GI physicians did not know that the detection adenoma rate was under study. Narrow band imaging (NBI) could be used to further define a polyp with HDC but was not the primary method of examination.

Results: 1204 HDC and 1226 SWLC patients were entered into the analysis after exclusions. Aspirin and screening cases were slightly more common in the HDC group. There was a 4.5% higher adenoma polyp detection rate in the HDC (28.8%) versus SWLC (24.3%) group (OR, 1.26; P =0.012). After a sensitivity analysis adjusting for bowel preparation, HDC still identified more polyps (OR, 1.34; 95% CI, 1.04 to 1.73; P =0.022). When comparing size, higher detection rates were noted for HDC versus SWLC in polyps 1 to 5 mm (19.9% vs 16.9%; OR, 1.31; P =0.024), 6 to 9 mm (8.4% vs 5.9%; OR, 1.47; P =0.031), and in the left colon (15.1% vs 12.2%; OR, 1.28; P =0.039). The overall polyp detection rate was higher with HDC versus SWLC (42.2% vs 37.8%; OR, 1.20; P =0.029) and also with hyperplastic polyps (20.1% vs 16.8%; OR, 1.25; P =0.036). These differences were most evident with small hyperplastic polyps and on the left side of the colon.

Conclusions: HDC identifies significantly more polyps than SWLC. This includes the identification of both hyperplastic and adenomatous polyps, especially in the left colon. The majority of these polyps were between 1 and 5 mm in size.

Reviewer’s Comments: Studies comparing HDC versus SWLC found more polyps with HDC but were underpowered and showed no significance. The view with HD colonoscopes is 170° versus 140° (Olympus 140 and 160 colonoscopes), which may result in greater polyp detection; however, other studies show no advantage. Previous studies indicate that wider viewing endoscopes do not improve the polyp detection rate. Finally, this was a retrospective study, so certain aspects of data collection were uncontrolled. The study did, however, reflect clinical practice. (Reviewer-Roy K.H. Wong, MD).

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Keywords: Colonoscopy, High-Definition, Standard, Detection Rate, Polyps

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Patients with sm1 esophageal carcinoma have significant rates of metastatic lymphadenopathy; therefore, endoscopic treatment should not be advised for these patients.

**Objective:** To determine the degree of lymph node metastasis and survival in relation to the depth of submucosal invasion of esophageal adenocarcinaoma (EAC).

**Methods:** All pathology reports from esophagectomies with lymphadenectomies between 1997 and 2007 for EAC were reviewed. Patients with submucosal invasion were re-reviewed by GI pathologist. Recurrence was either histologically confirmed or the appearance of lymph node metastasis noted on subsequent imaging. Survival status was checked using a Web service, and patients were called concerning their present status. The cause of death was extracted from the medical records. Pathologically, this study looked only at submucosal extension of EAC. This is the area located just below the muscularis mucosa and above the muscularis propria. The submucosa was divided into thirds (sm1, sm2, and sm3). Intramucosal tumors (mucosa, lamina propria, and muscularis mucosa) and tumors extending into the muscularis propria and deeper were not included in the study.

**Results:** 80 of the 1260 patients (6.3%) undergoing esophagectomy with no chemoradiotherapy had submucosal disease with slides available for study. There were no significant demographic, clinical, and histopathologic differences between sm1, sm2, and sm3 patients. The distribution of submucosal invasion was Sm1 (39%), sm2 (29%), and sm3 (33%), with a mean tumor size of 2.8 cm and similar mean number of lymph nodes resected in each group (13 to 15). Mean lymph node metastasis was 17.5% (sm1, 12.9%; sm2, 22%; sm3, 19%; NS). Patients with lymphovascular invasion had significantly more metastatic lymphadenopathy compared to those without lymphovascular invasion (30% vs 11%; \( P < 0.047 \)), but positive lymph nodes were not related to the depth of submucosal invasion. Recurrent disease was noted in 9% of patients, with no difference between submucosal invasion sm1 versus sm2/sm3 lesions. Multivariate analysis revealed that lower survival was related to the presence of metastatic lymph nodes (HR, 2.89; \( P < 0.02 \)) and recurrence of EAC (HR, 6.39; \( P < 0.001 \)).

**Conclusions:** Patients with sm1 superficial tumors have high rates of metastatic lymphadenopathy. Hence, endoscopic therapy of sm1 should not be advised if these patients are good candidates for surgery.

**Reviewer’s Comments:** There is controversy in the literature concerning the feasibility of mucosally resecting sm1 EAC because some would contend that lymph node metastasis is low. In this study, 81% of patients with HGD in the preoperative surveillance biopsies had submucosal EAC disease. This is an extremely important issue as RFA is now considered reasonable for the treatment of patients with HGD. In a younger patient who could undergo esophagectomy, missing submucosal adenocarcinaoma could be a significant error and should be searched for diligently. (Reviewer-Roy K.H. Wong, MD).

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Keywords: Metastasis, Submucosal Invasion, Esophageal Carcinoma, Survival

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