Patients with long-standing and extensive inflammatory bowel disease have an increased risk of advanced neoplasia, but this risk appears to be ameliorated with thiopurine therapy.

Card 1 of 2.

**Background:** Investigators have proposed that thiopurine therapy could be (1) protective if it reduces an inflammatory process that predisposes the patient to neoplasia or (2) harmful if the immunosuppression facilitates neoplasia.

**Objective:** To assess the risk of high-grade dysplasia or cancer in patients with inflammatory bowel disease (IBD), and to determine the relationship between thiopurine therapy and neoplasia risk.

**Design:** Long-term multicenter prospective observational follow-up study.

**Methods:** Between May 2004 and May 2005, French gastroenterologists entered almost 20,000 IBD patients into the study. Approximately 60% had Crohn's disease, and the remainder had ulcerative or unclassified colitis. At inclusion, about 30% of patients were using thiopurine. The patients were followed up from entry until December 2007. All cases of cancer or high-grade dysplasia were reported.

**Results:** During follow-up, 36 cancers and 21 cases of high-grade dysplasia were identified. The standardized incidence ratio for cancer compared to the general French population was 2.0. Independent risk factors for advanced neoplasia included male gender and the extent and duration of disease. The hazard ratio of advanced neoplasia between those who were and were not taking thiopurine was 0.57, but the 95% confidence interval crossed the line of equivalence, indicating that this was only a trend for a protective association. In a subgroup analysis of 2800 colitis patients with long-standing (disease present for ≥10 years) extensive (>50% of the colon involved) disease, the standardized ratio for cancer was 6.3. In fact, the entire associated increased risk of cancer was found in this subgroup. The standardized incidence ratio for the remaining IBD patients was 1.0. When data were corrected for the risk factors, investigators were able to produce a statistically significant hazard ratio of 0.28 between thiopurine use and advanced neoplasia (95% CI, 0.1 to 0.9). No differences were seen when only Crohn's disease or ulcerative colitis was considered separately.

**Conclusions:** IBD patients with long-standing and extensive disease have an increased risk of advanced neoplasia, but this risk can be ameliorated with thiopurine therapy.

**Reviewer's Comments:** Please see next card in this series. (Reviewer-Ronald L. Koretz, MD).

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Keywords: Inflammatory Bowel Disease, Neoplasia Risk

Print Tag: Refer to original journal article
Because of various forms of bias seen in a study by Beaugerie and Seksik regarding the incidence of neoplasia in patients with inflammatory bowel disease, it is unclear if the conclusions are reliable.

Card 2 of 2. The results of a long-term follow-up study from France were presented on the previous card. In this study, the investigators assessed the risk of high-grade dysplasia or cancer in patients with inflammatory bowel disease (IBD) and attempted to determine the relationship between thiopurine therapy and the risk of neoplasia. The investigators concluded that IBD patients with long-standing and extensive disease have an increased risk of advanced neoplasia, but this risk can be ameliorated with thiopurine therapy. Important comments about possible problems with the study and its conclusions are presented below. 


**Reviewer's Comments:** I cannot stress too strongly that this was an observational study with inherent bias. Any screening or surveillance program will identify more cancers because one is looking more intensively for them. Lead time bias accounts for some of this. Some of these identified cancers may not become clinical problems because of the length time bias—such screening or surveillance preferentially identifies slower-growing tumors. The identification of high-grade dysplasia lesions is solely a phenomenon of looking for them. High-grade dysplasia was not observed in the control group because these lesions are not symptomatic problems. For this reason, these investigators could only calculate hazard ratios for cancer. There are also potential problems with selection bias. We do not know why these patients, but not other IBD patients, were entered into the prospective study. The thiopurine observation is also unreliable. Since this was not a randomized trial of thiopurine usage, there had to be some reason(s) why those who received the thiopurine did so. Those reasons confound any effort to try to establish a causative relationship, protective or otherwise. This calculation may also have represented a post hoc decision, but, in any event, it is only one of a number of analyses, so one must worry about type I errors. This observation may be only a random error and, at the very least, needs to be validated. Because this was a prospective study, investigators should have been aware of these limitations and incorporated some effort to deal with them or at least discuss them. However, as became obvious during the question phase of the investigator's presentation at Digestive Disease Week, no such considerations were addressed. Thus, it is not clear that we learned anything from this effort.

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**Keywords:** Inflammatory Bowel Disease, Neoplasia Risk

**Print Tag:** Refer to original journal article
After the diagnosis of colorectal cancer, regular aspirin use may reduce the risk of colon cancer mortality. However, because of design flaws in the study, these conclusions may not be reliable.

**Objective:** To determine the impact of aspirin therapy on survival after a diagnosis of colorectal cancer.

**Design:** Data were derived from 2 long-running observational studies. Data regarding the use of aspirin both before and after the cancer diagnosis were available for all participants. The median duration of follow-up was 11.8 years.

**Results:** Of the 1279 cases of colorectal cancer identified, 480 individuals died (280 died from colorectal cancer). No protective or harmful effect on survival was associated with the use of aspirin prior to diagnosis. Those who began or continued aspirin after the diagnosis had a significantly lower multivariate hazard ratio of dying from cancer (0.72; 95% CI, 0.54 to 0.97). Those who were taking aspirin after the cancer diagnosis had a strong trend for better overall survival (HR, 0.82; 95% CI, 0.67 to 1.00). Of the 719 patients who began aspirin after the cancer diagnosis, the hazard ratio was even lower for dying of colorectal cancer (0.55). Those who used aspirin before the diagnosis did not have any survival benefit associated with the continued use of aspirin after the diagnosis. The beneficial effect of post-diagnosis aspirin use was only seen in the patients with cancers positive for COX-2.

**Conclusions:** Regular aspirin use after the diagnosis of colorectal cancer may reduce the risk of colon cancer mortality, especially in those whose cancers express COX-2.

**Reviewer’s Comments:** In this study, some data suggest that aspirin may prevent the development of colonic neoplasia. Since only patients with cancer were considered, the study could not assess any role of prophylactic aspirin. Furthermore, why wouldn't aspirin use be effective in everyone who developed cancer rather than just in the subgroup that did not use it before the diagnosis? Is there something different about the cancers that arise in people who do or do not use aspirin, such as COX-2 expression? Another inexplicable issue is why only some patients began aspirin therapy after the diagnosis. During the question period at the authors’ presentation during Digestive Disease Week, the investigators noted that, in the smaller subset of patients for whom they knew why aspirin therapy was initiated, no correlation was seen between the various reasons. The investigators stated that they looked at the group who had not been taking aspirin to see if the same conditions existed. We cannot know if those who did not receive aspirin had some compelling contraindication to that medication, and whether that contraindication may have put them at higher risk of mortality. I again did not think that I learned anything useful from this study, other than the obvious fact that large numbers of subjects cannot overcome limited study design. (Reviewer-Ronald L. Koretz, MD).

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Keywords: Colorectal Cancer, Aspirin Therapy vs Survival

Print Tag: Refer to original journal article
In a recent trial, flexible sigmoidoscopy was not associated with a decrease in the incidence of colorectal cancer.

**Objective:** To determine the risk of colorectal cancer (CRC) after flexible sigmoidoscopy (FS) screening.

**Methods:** Eligible individuals were randomly invited to either one-time FS screening (n=13,823) or to no screening (n=41,913). Those undergoing FS were in turn randomly assigned to Hemoccult screening or no Hemoccult screening. Colonoscopy was performed if any adenoma or any polypoid lesion >1 cm was found on FS or if a positive Hemoccult was found.

**Results:** This report provided the 7-year follow-up for incidence and 6-year follow-up for mortality. The data for individuals undergoing FS screening who did or did not also have Hemoccult screening were not presented separately. Using an intention-to-screen analysis, no difference was seen in the 7-year incidence of cancer. Also, no significant difference was seen in the CRC mortality rate. While the hazard ratio was <1.0 (0.73), the 95% confidence interval of 0.47 to 1.13 overlapped the line of equivalence.

**Conclusions:** The risk of dying from CRC appears to be slightly lower in individuals undergoing FS screening, but the incidence of CRC does not appear to be reduced by FS screening.

**Reviewer's Comments:** Despite this paper's title, this is the second reported randomized trial of FS—these investigators published the first trial 10 years ago. That initial trial enrolled about 400 patients in each arm and demonstrated that significantly fewer CRCs were found in the FS group (FS was associated with reduced incidence). This finding was attributed to the polypectomies that were performed, and this finding is cited in the most recent CRC screening guidelines. The other significant difference in this first trial was that the all-cause mortality rate was higher in the screening group. This was initially attributed to random error and then to an alteration in behavior by the screened group who, encouraged by their negative cancer screen test, altered their health habits in an unfavorable manner. This latter finding is not mentioned in the guidelines. We already know that Hemoccult screening reduces the incidence of CRC mortality. Half of the study arm but none of the controls had this intervention. This will bias the trial in favor of FS even though the effect is actually due to a different intervention. The Hemoccult trials have not been able to show that any life years have been saved by such screening. In fact, the data are more consistent with an offsetting increase in non-CRC deaths than with a type II error. I asked Dr. Hoff about the all-cause mortality in the current trial. He stated that there was no significant difference, but he did not provide any actual mortality figures. (Reviewer-Ronald L. Koretz, MD.)

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Keywords: Flexible Sigmoidoscopy, Cancer Risk

Print Tag: Refer to original journal article
Endoscopist Critically Important in Altering Missed Cancer Rate

Colorectal Cancer Despite Colonoscopy: Critical Is the Endoscopist, Not the Withdrawal Time.


Gastroenterology 2009; 136 (May): A-55

The endoscopist rather than the withdrawal time is critically important in detecting colorectal cancer in patients undergoing colonoscopy.

**Objective:** To determine the effect of endoscopists and withdrawal times on the incidence of colorectal cancer (CRC) that develops despite colonoscopy.

**Design:** Retrospective study from the Mayo Clinic.

**Methods:** Records were searched to identify individuals who underwent colonoscopy between 1992 and 2002 and patients in whom CRC had developed between 1992 and 2004. In this study, CRCs were identified between 90 days and 3 years after the colonoscopy in group A (truly missed cancers) and between 3 years and 5 years in group B (possibly missed cancers). Most patients had no lesion removed at colonoscopy. Those who had lesions removed were labeled either as patients who had had a lesion removed and a cancer developed anyway or patients with recurrent cancers. Based on data collected between 2002 and 2006, each endoscopist at the Mayo Clinic had their average withdrawal time for screening colonoscopies calculated. Only endoscopists who had identified at least 10 cancers were considered for the analysis of withdrawal times.

**Results:** Among the 2692 patients who underwent colonoscopies, cancers were identified in 145 group A patients and 104 group B patients. CRC was identified in 82 group A patients (truly missed cancer) and in 54 group B patients (possibly missed cancer). An additional 95 patients had a lesion removed, but cancer developed anyway. The remaining patients were considered to have recurrent cancers. For any given time after colonoscopy, the average sizes of the cancers were similar in the 4 groups. The investigators concluded that all cancers were present at colonoscopy. Withdrawal times were calculated for 44 endoscopists. A rate of truly missed cancers (number of missed cancers divided by the total of the missed and diagnosed cancers) was calculated for each endoscopist. That rate ranged from 0% to almost 8%, which did not correlate with the withdrawal time.

**Conclusions:** The endoscopist rather than the withdrawal time is critically important in detecting cancer.

**Reviewer’s Comments:** The investigators speculated that the association between withdrawal time and the identification of neoplastic lesions may only reflect 1 of a number of characteristics that identify the quality of an endoscopist. Since the data were retrospectively gathered, the problem of missing data was probably a confounding issue. Furthermore, even if the investigators are wrong and withdrawal time is important, the association cannot prove causation. All of the data linking withdrawal time to the sensitivity of colonoscopy only show an association. As such, we should carefully think about the potential consequences before we, in a more dogmatic and mindless fashion, impose arbitrary restraints on colonoscopists. (Reviewer-Ronald L. Koretz, MD).

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Keywords: Missed Cancer Rate, Determining Factors

Print Tag: Refer to original journal article
Colonoscopy has a 95% sensitivity and a 5% miss rate for detecting colon cancer. Diverticular disease, in-office colonoscopy, and no prior polypectomy increase the risk for missed advanced polyps and cancers.

**Background:** Although colonoscopy remains the best method of preventing colon cancer, the procedure is not perfect.

**Objective:** To define the miss rate for colon polyps and to identify factors influencing the sensitivity of colonoscopy for detecting colon polyps.

**Methods:** Participants included a national sample of 5% of Medicare patients older than age 70 years who had undergone inpatient surgery for colon cancer between 2005 and 2006. Patients were only included in the analysis if they had a colonoscopy within the 3 years prior to surgery. The authors assumed that if a colonoscopy had been found to be negative within 3 years of a diagnosis of colon cancer, then the larger precursor adenoma would have been missed at the time of colonoscopy. Patients were excluded if they had a prior history of colon cancer, inflammatory bowel disease, or had a family history suggestive of a familial colon cancer syndrome.

**Results:** 1567 patients were identified who had undergone inpatient surgery for colon cancer between 2005 and 2006. The rate of missed cancer was 5.7% (n=89). The risk factors for missed cancer included a history of diverticular disease (OR, 8.45), colonoscopy performed in the office setting (OR, 2.35), and not having had a previous polypectomy (OR, 14.65). There was no difference found in the sensitivity for right proximal to splenic flexure and left sided colon cancers. No geographic findings were also identified. Age, gender, race, and the volume of procedures by the endoscopist did not influence the sensitivity of colonoscopy in this population.

**Conclusions:** Colonoscopy has a 95% sensitivity and a miss rate of only 5% for detecting colon cancer. The endoscopist's experience and lesion location (right vs left side) do not appear to affect the sensitivity. Clinicians must realize that patients most at risk for developing missed advanced polyps and cancers are those with diverticular disease, those undergoing office procedures, and those without a prior polypectomy.

**Reviewer's Comments:** A major limitation of this study is that it is based on 100% accepted adenoma-to-carcinoma sequence. It is likely that some of these patients actually developed malignancies not related to a limitation in the sensitivity of colonoscopy. (Reviewer-Scott Tenner, MD).

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Keywords: Miss Rates, Confounding Factors

Print Tag: Refer to original journal article
Is Endoscopic Biopsy Safe in Patients Receiving Anti-Platelet Agents?

Dikman AE, Sanyal S, et al:

Gastrointest Endosc 2009; 69 (April): AB135

Upper endoscopy and biopsy is safe in healthy adults taking anti-platelet agents. Further study is needed to assess the risk of bleeding in an older population on anti-platelet agents.

**Background:** Last year, I biopsied the antrum on a patient taking an anti-platelet medication who underwent endoscopy. I had routinely been taking biopsies of patients on anti-platelet drugs if needed. For the first time in my clinical experience, this particular patient presented with gastrointestinal bleeding later that evening and required transfusion and hospitalization. Despite guidelines to the contrary, most Western endoscopists withdraw anti-platelet agents prior to upper endoscopy and biopsy. However, based on the available data for patients receiving anti-platelet agents, bleeding complications are rare while the cardiac benefits are of greater importance. For this reason, guidelines from the American Society of Gastrointestinal Endoscopy recommend that anti-platelet agents be continued for patients scheduled to undergo upper endoscopy.

**Objective:** To prospectively assess the risk of bleeding in healthy adults undergoing upper endoscopy and biopsy while taking anti-platelet agents.

**Design/Methods:** In a single-center blinded trial, healthy patients were randomly assigned to naproxen, celecoxib, aspirin, clopidogrel, or placebo. Each patient underwent 2 upper endoscopies 8 days apart. At baseline, 4 antral and 2 duodenal biopsies were obtained utilizing a standard 7.3-mm forceps. At final upper endoscopy, 5 antral and 3 duodenal biopsies were taken. After biopsies were taken, all sites were visualized until complete hemostasis was observed.

**Results:** 1029 antral biopsies and 571 duodenal biopsies were performed in 235 upper endoscopies in 123 subjects. In this study population, 51% of patients were men, and the mean age was 40 years. No clinical bleeding complications and no significant biopsy site bleeding events were visualized on endoscopy.

**Conclusions:** Upper endoscopy and biopsy is safe in healthy adults taking anti-platelet agents.

**Reviewer's Comments:** The patient population in this study consisted of healthy adults with a mean age of 40 years. Age is a clear risk factor for complications. Most patients that I see on anti-platelet agents are older than age 60 years and often have multiple medical problems. It is actually this patient population with which I have my concerns. Another problem with this study was the sample size of only 122 patients. It took me almost 15 years of endoscopic biopsies before having a patient with a bleeding complication. Although endoscopic biopsy appears safe, when a bleeding complication occurs, the anti-platelet agent will be blamed partially and the clinician will probably question his or her clinical judgment. Further study is needed to assess the risk of bleeding in an older population on anti-platelet agents. (Reviewer-Scott Tenner, MD).

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Keywords: Upper Endoscopy & Biopsy, Anti-Platelet Agents

Print Tag: Refer to original journal article
Wire-guided cannulation appears to reduce both the risk of post-ERCP pancreatitis and the risk of needing pre-cut access.

**Background:** The incidence of pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP) has significantly decreased over the past decade. There are multiple reasons for this decrease, including better patient, operator, and procedure selection. Pancreatic duct contrast injection is a risk factor for post-ERCP pancreatitis. Inadvertently, pancreatic duct contrast injection occurs in about 50% of ERCP cases when a conventional cannulation technique is employed. Recently, several investigators have compared a wire-guided cannulation technique versus conventional contrast cannulation as a method of decreasing post-ERCP pancreatitis and improved cannulation success. Results have been quite promising, but mixed.

**Objective:** To better define the effectiveness of wire-guided cannulation in preventing post-ERCP pancreatitis.

**Design:** A meta-analysis of randomized trials to determine if wire-guided cannulation is superior to conventional cannulation for preventing post-ERCP pancreatitis.

**Methods:** After a careful search of the literature, 2 reviewers independently scored the studies. Both the relative risk estimates for post-ERCP pancreatitis and a random effects model were generated.

**Results:** Five studies involving 1745 patients were included in the final analysis. Among these patients, 5.9% (n=102) developed post-ERCP pancreatitis. Post-ERCP pancreatitis developed in 7.9% of patients assigned to conventional cannulation and in 3.8% of patients who underwent wire-guided cannulation. In the random effects model, wire-guided cannulation was associated with a 58% reduction in post-ERCP pancreatitis. There was also a significant decrease of 29% in pre-cut access when wire-guided cannulation was utilized.

**Conclusions:** Wire-guided cannulation appears to reduce both the risk of post-ERCP pancreatitis and the risk of needing pre-cut access.

**Reviewer’s Comments:** Wire-guided cannulation must be added to the list of methods that decrease the risk of post-ERCP pancreatitis and severe post-ERCP pancreatitis. (Reviewer-Scott Tenner, MD).

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Keywords: Post-ERCP Pancreatitis, Prevention

Print Tag: Refer to original journal article
Celiac Plexus Neurolysis Reduces Pancreatic Cancer Pain

Results of the First, Randomized, Double Blind, Sham-Controlled Trial of EUS-Guided Celiac Plexus Neurolysis (EUS-CPN) for Pain Due to Newly Diagnosed, Inoperable Pancreatic Cancer.

Wyse JM, Carone M, et al:
Gastrointest Endosc 2009; 69 (April): AB132

In patients with pain due to inoperable pancreatic cancer, celiac plexus neurolysis can be safely performed at the time of endoscopic ultrasound diagnosis, and it reduces abdominal pain scores in all patients.

**Background:** Patients with pancreatic cancer not only suffer from a disease with few treatment options, but they also suffer from pain as the tumor invades the celiac plexus.

**Objective:** To determine if early (at diagnosis) endoscopic ultrasound (EUS) with celiac plexus neurolysis (CPN) compared to conventional pain management is more effective in reducing pain, as defined by a decreased pain score, decreased narcotic use, and improvement in a quality of life score.

**Design:** The first randomized, double-blind, sham-controlled trial of EUS-CPN for the management of pain due to newly diagnosed inoperable pancreatic cancer.

**Methods:** Patients with newly suspected pancreatic cancer referred for EUS were eligible if they had tumor-related pain and CT demonstrating no metastases or ascites. If EUS provided on-site cytologic proof of pancreatic adenocarcinoma and demonstrated inoperable disease (defined as celiac artery, or portal vein/superior mesenteric vein involvement), patients were randomly assigned during the procedure to bilateral EUS-CPN (bupivacaine 0.5% 10 mL and absolute ethanol 20 mL) or to conventional pain management with no EUS-CPN. Patients were then managed as per their referring physicians’ directions. Both were blinded to the treatment arm. Pre-EUS and post-EUS questionnaires were administered by a single physician, who was also blinded to the treatment arm. Narcotic use was measured by milligram equivalent of morphine.

**Results:** Of the 98 patients enrolled, the mean patient age was 66 years, and 52% were women. Fifty-three patients who survived received chemotherapy. There were no complications. EUS-CPN resulted in significantly lower abdominal pain scores on Likert scales. EUS-CPN also reduced narcotic usage in the patients who did not undergo chemotherapy. There appeared to be no difference in the effect on the quality-of-life score.

**Conclusions:** In this first sham-controlled, randomized trial of EUS-CPN, the EUS-CPN reduced abdominal pain scores in all patients and reduced narcotic usage in patients who did not undergo chemotherapy.

(Reviewer-Scott Tenner, MD).

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Keywords: Inoperable Cancer, Neurolysis

Print Tag: Refer to original journal article
In patients with discordant results on CT colonography (CTC) and optical colonoscopy, a follow-up CTC or colonoscopy should be performed in 1 year to check for missed lesions.

**Background:** I am finding that many of my patients are willing to spend cash to undergo CT colonography (CTC) rather than optical colonoscopy for colorectal cancer screening. This willingness results mainly from a poor understanding of the risks and benefits of CTC. Patients are often referred to me after a polyp is found on CTC but no polyp is identified on optical colonoscopy.

**Methods:** 351 patients at a single center were referred for optical colonoscopy to remove polyps found on CTC. Of these patients, 29 (8.2%) had no definite polyp found on optical colonoscopy. Seventeen patients were referred for lesions thought to be >10 mm in size, and 12 were referred for polyps 6 to 9 mm in size. Four patients with polyps detected by CTC were found to have venous lakes, lipomas, or inverted diverticula. Only 2 patients underwent a follow-up second colonoscopy exam that was completed within the study period, and 1 of the 2 with the repeat optical colonoscopy was found to have a small polyp. One of 12 patients (8%) with a polyp on CTC was found to have a normal exam on optical colonoscopy. In addition, due to the finding of a polyp on a repeat optical colonoscopy exam, the authors recommended that a repeat colonoscopy occur 1 year later when conflicting results from CTC occur with optical colonoscopy.

**Conclusions:** In patients with discordant results on CTC and colonoscopy, a follow-up CTC or colonoscopy should be performed in 1 year to check for missed lesions. (Reviewer-Scott Tenner, MD).

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Keywords: CT Colonography, Conflicting Results

Print Tag: Refer to original journal article
Elevated ALT levels were found in 38% of adults in the NHANES study (2003 to 2004). Several organochlorine pesticides were linked in a dose-dependent manner with an increased risk of abnormal ALT levels.

**Background:** The long-term hepatic health effects of low-dose exposure to industrial pollutants, such as pesticides and heavy metals, are not well understood. For example, aminotransferase elevation has been reported in agricultural workers following spraying of pesticides. In 1984, Tamburro described a disorder resembling nonalcoholic steatohepatitis with insulin-resistance among 16 non-obese chemical workers exposed to vinyl chloride. However, population-based studies are not available.

**Objective:** To analyze the association between chemical pollutants and liver abnormalities using data from the National Health and Nutrition Examination Survey (NHANES) undertaken in 2003 to 2004.

**Methods:** Blood and urine levels of 196 pollutants were measured in the NHANES adult population. Individuals with hepatitis C, B, alcohol excess, or iron overload were excluded. Elevated serum ALT levels were defined as >30 units/L for a man and >19 units/L for a woman. Only those 116 pollutants found detectable in ≥60% of tested subjects were included in the analysis. Using logistic regression analysis, the association of pollutant levels in quintiles with elevated ALT levels was assessed after adjusting for age, gender, race, body mass index (BMI), and insulin resistance.

**Results:** 38% of the 4582 studied subjects had elevated ALT levels. Several organochlorine pesticides, most of which are no longer used, were linked in a dose-dependent manner with an increased risk of abnormal ALT levels. Similarly, mercury, lead, and thallium, but not cadmium, were associated with elevated ALT levels. Increasing age and BMI were associated with the highest quartiles for pesticides.

**Conclusions:** Further exploration of the role of these agents in non-alcoholic fatty liver disease is warranted.

**Reviewer's Comments:** This analysis has multiple limitations which bear a resemblance to a large fishing expedition in which a wide net is thrown looking for possible associations. These limitations include the fact that not all pollutants were measured in all subjects, no data were presented for a range of elevated ALT levels, results were based on a single ALT determination, and the interaction of pollutants with each other was not studied. Furthermore, the spectrum of liver disease responsible for the elevated ALT levels was not assessed histologically, and the found association may not be causal. Perhaps some chemicals are simply stored in fatty livers or perhaps a mildly impaired liver fails to remove them. If 38% of adults in the NHANES population have an abnormal ALT reflecting liver disease, then the prevalence of liver disease is far higher than previously believed. **Reference:** Tamburro CH, Mark L, Popper H. Early hepatic histologic alterations among chemical (vinyl monomer) workers. *Hepatology* 1984; 4: 413-418. (Reviewer-Raymond S. Koff, MD).

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Keywords: Nonalcoholic Steatohepatitis, Chemical Pollutants

Print Tag: Refer to original journal article
Patients with cirrhosis due to nonalcoholic steatohepatitis are at increased risk for the development of hepatocellular carcinoma. Older age and social alcohol consumption are independently related to this risk.

Background: In the United States, the incidence of hepatocellular carcinoma (HCC) doubled between 1983 and 2002. Also, nonalcoholic fatty liver disease has become more prevalent in the past few decades. In the subset of patients with nonalcoholic steatohepatitis (NASH), perhaps as many as 20% progressed to cirrhosis. In a recent study from Japan, the 5-year cumulative incidence of HCC was 7.6%, and nearly 90% of those affected had cirrhosis. Older age, low level of AST, low-grade histologic activity, and advanced fibrosis stage were identified as risk factors. In other studies, visceral fat accumulation and liver iron excess were identified as risk factors. In a comparative study from Australia, the risk of HCC in hepatitis C virus (HCV)-associated cirrhosis was considerably higher than in NASH-associated cirrhosis.

Objective: To identify risk factors for HCC in NASH-associated cirrhosis and to compare the incidence of HCC in patients with NASH-associated cirrhosis versus those with HCV-associated cirrhosis.

Participants: Patients evaluated for transplantation and followed up between 2003 and 2007.

Methods: Patients with HCC on their initial visit or a history of HCC were excluded, as were those with a history of >2 alcoholic drinks on weekdays or more than 3 to 6 drinks on the weekend. Patients who drank but did so at less than these levels were labeled as social drinkers. NASH-induced cirrhosis was defined by typical histology, or cryptogenic cirrhosis with a metabolic syndrome or no alcohol intake or just social drinking.

Results: After a median follow-up of 3.2 years, HCC developed in 13% of 195 NASH patients with cirrhosis and in 20% of 315 HCV patients with cirrhosis (difference not statistically significant). In both NASH and HCV cirrhotic patients, older age and social alcohol consumption increased the incidence of HCC and were independently related to its development.

Conclusions: Patients with cirrhosis due to NASH are at increased risk for the development of HCC. Even limited alcohol drinking can increase this risk.

Reviewer’s Comments: It is likely that alcohol consumption was underestimated in those labeled as social drinkers in this study. Nonetheless, for both the NASH and HCV groups, patients who denied any alcohol intake had a statistically significant reduction in the risk of HCC. Therefore, until contrary data are presented, it would be reasonable to recommend complete abstinence for patients with both NASH and chronic HCV. Furthermore, patients with NASH-associated cirrhosis should be regularly screened for HCC. Whether those with bridging fibrosis also should be screened remains to be studied. (Reviewer-Raymond S. Koff, MD).

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Keywords: Nonalcoholic Steatohepatitis, Cancer Risk

Print Tag: Refer to original journal article
In the model for end-stage liver disease (MELD) score, the use of serum creatinine underestimates the severity of kidney and liver failure in women. Substituting glomerular filtration rate for creatinine may improve MELD’s accuracy.

**Background:** Since 2002, the model for end-stage liver disease (MELD) score predicts the 3-month mortality in cirrhotic patients, but it does so imperfectly. Nonetheless, MELD scores have been used widely in prioritizing patients for liver transplantation. The 3 components utilized in the equation for determining the MELD score are serum bilirubin, serum creatinine, and INR.

**Objective:** To determine if women might be disadvantaged as liver transplant recipients because they have lower serum creatinine levels than men, even those with similar glomerular filtration rates (GFR).

**Design/Participants:** Retrospective analysis of data from the United Network for Organ Sharing for patients on the liver transplant waiting list between 2002 and 2008.

**Methods:** Mortality rates were compared for men and women. GFR was measured by the MDRD modification of diet and renal disease equation for GFR. Mortality was defined as death while on the waiting list or removal from the list as the patient's clinical condition deteriorated.

**Results:** >22,000 patients were included in this analysis. Of the patients on the waiting list, 66% were men and 34% were women. While 58% of the men were transplanted, only 50% of the women received a new liver (difference statistically significant). Among patients with serum creatinine levels of ≥1 mg/dL, the mortality rate was higher for women than for men despite similar MELD scores. Whether serum creatinine was <1 mg/dL or higher, women had lower GFRs. When GFR was used instead of serum creatinine in the MELD scoring, the gender disparity was reduced.

**Conclusions:** In patients awaiting a liver transplant, women with serum creatinine levels ≥1 mg/dL have significantly lower GFRs and higher mortality rates than do men with similar creatinine levels. The use of serum creatinine in the MELD score underestimates the severity of kidney and liver failure in women, and it may be appropriate to replace the creatinine with GFR in the MELD equation.

**Reviewer’s Comments:** Given the higher prevalence of alcoholic liver disease in chronic viral hepatitis in men, it is not surprising that more men than women are listed for transplantation. Evaluating disease severity using creatinine levels underestimates GFR in women, which may be one of the more important reasons women are disadvantaged on the waiting list, but other reasons surely exist. Perhaps the smaller size of the donor liver needed in women is another problem. It would seem reasonable that transplant centers begin collecting prospective data comparing priority listing when using both creatinine and GFR. If the data presented here are confirmed, it would be reasonable to make the appropriate change in the MELD equation. (Reviewer-Raymond S. Koff, MD).

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Keywords: Liver Transplantation, MELD Scores

Print Tag: Refer to original journal article
For pediatric cases, the incidence of acute graft rejection is significantly lower with living related donor liver transplants than with deceased donor liver transplants.

**Background:** Living related donor (LRD) liver transplantation (LT) for children with end-stage liver disease has potential advantages over deceased or cadaver donor (DD) LT. Rapid access to a living donor should permit LT prior to clinical deterioration (more optimal patient conditions), thereby reducing waiting time and mortality for these children.

**Objective:** To review the authors’ experiences with pediatric LT between 1998 and 2009.

**Design:** Single-center study from the Cincinnati Children's Hospital.

**Results:** During this study, 24 LRD LTs and 237 DD LTs were undertaken. The 24 patients with LRD transplants were matched by diagnosis, age, and pediatric UNOS score with 24 patients who received DD livers. About 50% of the patients in each group were transplanted before age 12 months. Priority scores were similar in both groups, and postoperative immunosuppression regimens were the same. Postoperative complication rates were similar in both groups, although biliary complications were more common in the LRD group than in the DD group. Follow-up time was longer in the LRD group. At a mean follow-up of 88 months after transplant, patient survival was 83% in the LRD group and 92% in the DD group (difference not significant). Cold ischemia time was significantly shorter in the LRD group than in the DD group. Even when status at transplant, waiting time, and graft type were considered, the graft survival rates were 71% in the LRD group and 87% in the DD group (difference not significant). Acute rejection was significantly less common in the LRD group (29%) than in the DD group (63%).

**Conclusions:** Pediatric living related donor liver transplantation results in a lower risk of acute rejection than does deceased donor liver transplantation. This lower risk in LRD LTs appears to be a major benefit.

**Reviewer’s Comments:** The limitations of this study include the single-center design and the small number of studied patients. Larger multicenter studies with longer follow-up will be needed. The highest mortality rate on the pediatric waiting list may be for children younger than 1 year of age, and long waits are avoided in LRD donations. However, donor body and liver sizes remain an issue. The risk for the donor, although clearly <1% in the adult experience, must not be ignored. (Reviewer-Raymond S. Koff, MD).

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Keywords: Liver Transplantation, Donors

Print Tag: Refer to original journal article
In patients with chronic HCV infection who previously failed treatment with any alpha-interferon plus ribavirin, low-dose maintenance therapy with pegylated interferon does not appear to prevent clinical events.

**Background:** There is no established highly effective treatment for patients with chronic hepatitis C virus (HCV) who are nonresponders to either standard or pegylated interferon (PEG-IFN) with ribavirin. Retreatment with PEG-IFN and ribavirin results in sustained virologic response rates of generally <15%. Three trials of so-called maintenance treatment of nonresponders have been undertaken. Two of these trials using either low-dose PEG-IFN alpha-2a or alpha-2b have been failures since no clinical benefits were found. **EPIC3 Trial:** The third trial, the EPIC3 trial, was designed as a low-dose PEG-IFN alpha-2b maintenance trial in the control of HCV cirrhosis. In the first part of EPIC3, nonresponder patients were retreated with 1.5 μg/kg per week of PEG-IFN alpha-2b and ribavirin. The sustained viral response rate was 14%. The maintenance trial was a multicenter study undertaken in 22 countries. Of 626 cirrhotic patients, 454 from the retreatment phase and 172 "direct enrollers" were randomly assigned to an observation group or to receive 0.5 μg/kg per week of PEG-IFN alpha-2b without ribavirin. The primary efficacy analysis was timed to the development of the first clinical event (variceal bleeding; Child-Pugh class C; grade 2 or higher encephalopathy; or ascites requiring treatment). Other clinical events included hepatocellular carcinoma, death, or liver transplantation. Secondary analyses were timed to disease progression as indicated by obtaining a Child-Pugh score of B, emergence of esophageal varices, and an enlargement of preexisting varices requiring treatment. **Results:** Of studied patients, 85% were genotype 1 and 70% had viral levels >600,000 IU/mL. The mean duration of treatment or observation was 31 to 32 months. Although clinical events were more common in the observation group, the difference was not statistically significant. Emergence or enlargement of varices was significantly more common in the observational group, and there were significantly more events and subjects with varices at baseline. Serious bacterial infections were more common in the PEG-IFN group. **Conclusions:** PEG-IFN does not prevent clinical events but may delay the progression of portal hypertension. **Reviewer's Comments:** I do not believe that one can recommend maintenance therapy with low doses of either form of PEG-IFN for nonresponders with histologically advanced disease. Because the evidence suggesting a potential benefit on progression of portal hypertension in the EPIC3 study is based on unconfirmed reports of varices seen on endoscopy, it is hard to give much credence to the notion that low-dose maintenance PEG-IFN was of any benefit. Maintenance treatment, in my view, is a dead issue, and resurrection is not indicated. (Reviewer-Raymond S. Koff, MD).

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Keywords: Cirrhosis, Treatment

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MP-PD Improves Survival for Advanced Pancreatic Cancer

*Margin Positive Pancreaticoduodenectomy Is Superior to Palliative Bypass in Advanced Stage Pancreatic Adenocarcinoma.*

Lavu H, Mascaro AA, et al:

Gastroenterology 2009; 136 (May): A-870

In highly selected patients with advanced pancreatic adenocarcinoma, the median and 1-year survival rates are improved with margin positive pancreaticoduodenectomy versus palliative gastric and biliary bypass.

**Background:** Surgical therapy with negative margins of resection (R0) remains the only chance for cure of pancreatic adenocarcinoma (PA). Patients with advanced disease may undergo a margin positive pancreaticoduodenectomy (MP-PD), a palliative biliary and enteric bypass to overcome gastric and biliary obstruction, or a celiac plexus neurolysis (CPN) for pain management.

**Objective:** To determine the difference in perioperative outcome and survival for patients who undergo MP-PD, palliative bypass, or CPN for the treatment of advanced PA.

**Design:** Retrospective review.

**Participants:** 127 patients underwent surgical therapy for PA, including R0 resection (n=57), MP-PD (n=37), palliative bypass (n=24), and CPN (n=9).

**Results:** Metastatic disease was present in 75% of the palliative bypass patients and in 100% of the CPN group. In the MP-PD group, positive margins were found in the uncinate process or posteriorly (57%), the pancreatic neck (11%), the bile duct (8%), and the circumference (5%). The patients who had pancreatic neck margins and bile duct margins were negative on intraoperative frozen section. The overall median follow-up of the entire group was 25.7 months. The 30-day perioperative mortality rate was 1.6% (n=2) in the R0 resection group. The complication rate was 54% for R0, 48% for MP-PD, 20% for palliative bypass, and 11% for CPN. A significant increase in complications, length of stay, and estimated blood loss was seen in the MP-PD group versus the palliative bypass group. Nonetheless, the median survival was 21.8 months for MP-PD and 11.8 months for palliative bypass. The 1-year survival was 84% for MP-PD group and 38% for palliative bypass.

**Conclusions:** In highly selected patients with advanced PA, MP-PD can be performed safely with an acceptable morbidity similar to that of curative resection. The median and 1-year survival rates are improved in patients who undergo MP-PD versus palliative gastric and biliary bypass.

**Reviewer’s Comments:** In this retrospective review, the patients did not receive uniform adjuvant therapy, so it is unknown whether the survival benefit was due to the different surgical therapies. Furthermore, metastatic disease was present in 75% of the palliative bypass group and in 0% of the MP-PD group at surgery. The results clump all palliative bypass patients together, regardless of metastasis, which may skew the difference appreciated between the 2 groups. Further subgroup analysis is needed. This study begins to shed light on outcomes of aggressive surgical therapy. Further investigation for the role of adjuvant treatment with long-term follow-up is required to assess the durability of MP-PD. (Reviewer-Khashayar Vaziri, MD).

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**Keywords:** Advanced Disease, Treatment Outcomes

**Print Tag:** Refer to original journal article
Further investigation is warranted to determine whether certain magnitudes of plasma hepatocyte growth factor elevation are specific to periampullary cancer as opposed to other gastrointestinal malignancies.

**Background:** Hepatocyte growth factor (HGF) plays a crucial role in the invasion and metastasis of tumor cells. However, the clinical significance of HGF as a tumor marker to diagnose periampullary cancer (PAC) is not clear.

**Objective:** To determine the sensitivity and specificity of plasma HGF in detecting PAC; to study the changes in HGF plasma levels following pancreaticoduodenectomy (PD); and to determine the prognostic value of HGF.

**Participants:** Patients with PAC (n=57), benign periampullary tumors (n=21), chronic pancreatitis (n=20), and healthy individuals (n=20; controls).

**Methods:** HGF plasma levels were determined preoperatively, after resection, and again at 1, 6, 12, 24, and 48 weeks postoperatively. The relationship between HGF levels and clinical and histopathological parameters was analyzed retrospectively.

**Results:** Preoperatively, patients with PAC had significantly higher levels of HGF than did controls and patients with benign periampullary tumors. Mean HGF values were 1574 pg/mL in PAC patients, 670 pg/mL in controls, 781 pg/mL in benign periampullary tumors, and 881 pg/mL for chronic pancreatitis. A cut-off value of 1120 pg/mL yielded a sensitivity of 84% and a specificity of 89%, with only 4 chronic pancreatitis patients exhibiting a false-positive result. False positives were not found in controls or in patients with benign periampullary tumors. Postoperative HGF levels were higher than preoperative levels at 1 and 6 weeks after curative resection. Baseline levels were seen between 6 and 12 weeks and normalized after 12 weeks. Patients experiencing early recurrence tended to have higher postoperative levels and did not show normalization of HGF. No correlation was found between plasma HGF levels versus clinical parameters or histological findings.

**Conclusions:** The high sensitivity and specificity of plasma HGF in patients with PAC suggests that preoperative levels can be useful in establishing a diagnosis. The increases in plasma levels postoperatively may also suggest that HGF is not directly secreted by tumor cells but could be related to the surgical stress response. Persistently elevated HGF levels may be associated with recurrence or metastatic disease.

**Reviewer's Comments:** Although the sensitivity and specificity are high, plasma HGF may not serve as a screening tool for PAC. Similar to other tumor markers, HGF is elevated in a variety of cancers. Further investigation is warranted to determine whether certain magnitudes of plasma HGF elevation are specific to PAC as opposed to other gastrointestinal malignancies. If HGF is not specific to PAC, then its use as a diagnostic or screening tool must be correlated to clinical suspicion. (Reviewer-Khashayar Vaziri, MD).
In patients with hepatic colorectal metastases, neither disease-free nor overall survival is improved with the use of neoadjuvant FOLFOX or FOLFIRI treatment.

**Background:** 25% to 30% of patients diagnosed with colon and rectal cancers will have metastatic disease, with the liver being the most common site of metastasis.

**Objective:** To determine if the use of neoadjuvant FOLFOX and FOLFIRI increases disease-free survival or overall survival in patients with hepatic colorectal metastases (CRM).

**Methods:** All patients who underwent hepatic resection for CRM during a 5-year study interval at the Mayo Clinic were subdivided into 2 groups based on the use of neoadjuvant FOLFOX and FOLFIRI. Disease-free and overall survival rates as well as the associations between treatment and survival were analyzed.

**Results:** The cohort included 58 men and 41 women (median age, 63 years). The size of hepatic metastases was significantly larger in the non-neoadjuvant therapy group (4 cm) than in the group receiving neoadjuvant therapy (3 cm). Disease-free survival for patients receiving neoadjuvant treatment was 52% at 1 year, 14% at 3 years, and 14% at 5 years, with a median disease-free survival of 1 year. The disease-free survival of patients not receiving neoadjuvant therapy was 52% at 1 year, 24% at 3 years, and 21% at 5 years, with a median disease-free survival of 1 year. Neoadjuvant FOLFOX and FOLFIRI was not significantly associated with improved disease-free survival (hazard ratio, 1.14; \( P = 0.58 \)). Overall survival for patients receiving neoadjuvant FOLFOX and FOLFIRI was 93% at 1 year, 62% at 3 years, and 48% at 5 years, with a median survival of 4.5 years. Overall survival for patients not receiving neoadjuvant treatment was 90% at 1 year, 63% at 3 years, and 45% at 5 years, with a median overall survival of 3.7 years. Neoadjuvant treatment was not significantly associated with an improved overall survival. The use of neoadjuvant FOLFOX and FOLFIRI did not improve the disease-free or overall survival in patients with synchronous and metachronous lesions.

**Conclusions:** The use of neoadjuvant treatment in patients with hepatic CRM is not associated with an improvement in disease-free or overall survival. However, the use of FOLFOX and FOLFIRI improves the resectability of the hepatic metastases and is applicable to a minority of patients.

**Reviewer’s Comments:** In this study, patients did not receive standardized adjuvant therapy with respect to duration and chemotherapeutic agent. CEA levels, both preoperatively and postoperatively, were not available. The selection of patients into the neoadjuvant group was not standardized. Further prospective randomized studies need to be performed with standardized neoadjuvant and adjuvant therapy protocols to truly discern the effect on disease-free and overall survival. (Reviewer-Khashayar Vaziri, MD).

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Keywords: Colorectal Metastases, Neoadjuvant Chemotherapy

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In patients with recurrent liver metastases after initial liver resection for colorectal metastases, repeat curative-intent surgery appears to be a safe and effective management tool.

**Background:** Although liver resection can be performed for hepatic colorectal metastases (CRMs), the 5-year survival rate approaches 55%. Approximately 60% of these patients will have recurrent disease, which is located in the liver in 40% of cases.

**Objective:** To determine the safety and efficacy of repeat curative-intent surgery (CIS) for recurrent hepatic CRMs and to identify any factors predictive of survival.

**Participants:** All patients in an international database who underwent curative-intent hepatic resection or radiofrequency (RF) ablation between 1985 and 2008.

**Results:** Of the original 1512 patients who underwent liver resection, 64% had recurrent hepatic CRMs. Of these, 209 underwent repeat CIS with a second liver resection or RF ablation, 35 underwent a third CIS, and 7 underwent a fourth. The tumor characteristics changed with each subsequent surgery. Hepatic CRMs were more likely to be solitary lesions and smaller than 5 cm with third and fourth CIS when compared to the second. The extent of hepatic resection also decreased, with fewer hemihepatectomies performed at third and fourth operations. There was no significant difference in the length of hospital stay and perioperative morbidity or mortality between patients undergoing initial resection and repeat resection or third and fourth resection. Similarly, the 5-year survival rate was not significantly different (second resection, 36%; third or fourth resection, 44%). Increasing tumor size, increasing tumor number, and the presence of extrahepatic disease predicted a poor survival rate in patients who underwent CIS for recurrent CRM.

**Conclusions:** After initial liver resection for colorectal metastases, repeat CIS is safe and effective in patients with recurrent liver metastases. Because recurrent metastases tend to be smaller and solitary, they require a less extensive resection or ablation. Patients undergoing resections for the third and fourth times had similar length of stay, morbidity, and mortality rates compared with those undergoing resection for the first and second time. In cases undergoing repeat resections, extrahepatic disease, larger tumors, and more numerous tumors were negative predictors of survival.

**Reviewer's Comments:** This is the largest cohort of repeat CIS for hepatic CRM. The authors have shown that repeat resection or RF ablation is a safe and useful tool in the treatment of recurrent disease. The study is limited by its retrospective design and lack of standardized adjuvant treatment. Although future studies will be useful to identify the true extent of benefit provided to these patients from resection or RF ablation, surgery remains a useful tool in the management of patients with recurrent liver metastases. (Reviewer-Khashayar Vaziri, MD).

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Keywords: Colorectal Metastases, Repeat Resections

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FDG-PET is not associated with histopathologic response or survival in patients with locally advanced gastric adenocarcinoma following neoadjuvant chemotherapy and gastrectomy.

**Background:** Gastric cancer remains a major cause of death in the United States, most likely due to the prevalence of advanced disease at presentation. Recent trials have shown that PET scan significantly correlates with histopathological response and survival in patients with gastroesophageal adenocarcinoma who have undergone neoadjuvant chemotherapy and surgical resection.

**Objective:** To evaluate the use of PET for the assessment of histopathological response and prognosis in patients undergoing neoadjuvant chemotherapy and surgical resection for locally advanced gastric cancer.

**Design:** Prospective clinical observational trial performed from 1997 to 2007.

**Participants:** 42 subjects with locally advanced gastric cancer (T3 or T4 gastric adenocarcinoma).

**Methods:** All patients received neoadjuvant chemotherapy according to the PLF-protocol (2 cycles of cisplatin, leucovorin, and 5-FU over 6 weeks followed by total gastrectomy). PET scan was performed before and at 2 weeks after the completion of neoadjuvant chemotherapy. Pretreatment and posttreatment standardized uptake values (SUVs) were measured. Major histopathologic response was defined as <10% residual tumor in the resected surgical specimen.

**Results:** All 42 patients received neoadjuvant chemotherapy, and 40 went on to total gastrectomy while 2 received definitive chemotherapy due to progression of disease. Neoadjuvant therapy led to a statistically significant reduction in FDG uptake between pretreatment and posttreatment SUVs. No significant correlation was found between histopathological response and pretreatment SUV, posttreatment SUV, or percentage change in SUV. Similarly, no significant correlation was found between SUV and prognosis. Histopathologic tumor regression was identified as a significant prognostic factor.

**Conclusions:** FDG-PET is not associated with histopathologic response or survival in patients with locally advanced gastric adenocarcinoma following neoadjuvant chemotherapy and gastrectomy.

**Reviewer's Comments:** This study does not confirm findings of previous investigations. However, the difference in clinical timing of PET may be an important factor, and it may have influenced these results. The results of this study suggest that future investigations need to be performed with a universal standardized approach. The lack of correlation between SUV and histopathologic response also begs the question as to whether PET is an appropriate diagnostic or clinical tool in gastric cancer. Investigations aimed at tumor biology with respect to glucose transport mechanisms and the difference in glucose affinity may be a more useful preliminary study to optimize the timing and use of PET in gastric cancer. Until further studies are performed, the clinical use of PET to gauge response of chemotherapy or to determine prognosis in gastric cancer remains questionable. (Reviewer-Khashayar Vaziri, MD).

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Keywords: Gastric Cancer, Chemotherapy Response

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