Ampullary Tumors Can Be Removed Endoscopically

OUTCOMES EXCELLENT FOR EARLY NEOPLASMS

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

NEW ORLEANS — Endoscopic ampullotomy had excellent results for early ampullary neoplasia, a 3-year multicenter prospective study has shown, and the procedure is now considered the first-line treatment for these early tumors.

The endoscopic procedure is an effective alternative to open surgery, which is quite complicated and often does not provide a complete resection, Dr. Thierry Ponchon said at the annual Digestive Disease Week. Ampullary tumors are very difficult to treat because of their location at the junction of the common bile duct and duodenum, said Dr. Ponchon, professor of medicine at the Centre Hospitalier Universitaire de Lyon, France. “You must remove the head of the pancreas and the distal part of the duodenum. . . . It’s a very complex process for a very small lesion.”

Dr. Ponchon reported 3-year outcomes for 93 consecutive patients with biopsy-proven ampullary neoplasia (including adenoma with low-grade dysplasia, adenoma with high-grade dysplasia, and adenocarcinoma) who were treated using endoscopic ampullotomy. The patients’ mean age was 57 years (range 13-83 years), and there were 49 females and 44 males. The lesion was considered sporadic in 71 patients, and was related to familial adenomatous polyposis in 22.

Eleven experienced endoscopists performed the operations using a side-viewing endoscope during the period 2003-2006. Follow-up biopsies were performed between 4 and 8 weeks, when a second procedure was considered necessary to ensure a complete resection. All the patients were followed for an additional 24 weeks after discontinuing treatment.

Ampullary tumors tend to be associated with familial adenomatous polyposis, hyperplastic polyps, and inflammatory bowel disease (IBD). Patients with diabetes were excluded from the trial to ensure that antidiabetic therapy wouldn’t confound the results. The primary outcome was a composite of histologic features: improvement in hepatocellular ballooning score, no increase in fibrosis score, and either a decrease in the activity score for nonalcoholic fatty liver disease to three or less or at least a two-point decrease in disease activity score that included improvement in inflammation or steatosis subscores.

Vitamin E therapy proved superior to placebo in improving nonalcoholic steatohepatitis by significantly reducing steatosis, lobular inflammation, and disease activity, according to a recent study published in the New England Journal of Medicine.

Pioglitazone also improved these factors as well as insulin resistance, but its histologic benefits did not reach the prespecified level of significance in the multicenter, phase III clinical trial, said Dr. Arun J. Sanyal of Virginia Commonwealth University, Richmond, and his associates.

The study findings are particularly important because this is the first time, to the authors’ knowledge, that a vitamin has been used to reverse a disease that is not a deficiency state, Dr. Sanyal said in an interview.

The investigators compared the two agents with placebo in 247 adults with biopsy-confirmed nonalcoholic steatohepatitis (NASH). Subjects were randomly assigned to receive oral vitamin E (800 IU daily, 84 patients), pioglitazone (30 mg daily, 80 patients), or placebo (83 patients) for 96 weeks. They were followed for an additional 24 weeks after discontinuing treatment.

Patients with diabetes were excluded from the trial to ensure that antidiabetic therapy wouldn’t confound the results. The primary outcome was a composite of histologic features: improvement in hepatocellular ballooning score, no increase in fibrosis score, and either a decrease in the activity score for nonalcoholic fatty liver disease to three or less or at least a two-point decrease in disease activity score that included improvement in inflammation or steatosis subscores.

Vitamin E was associated with a significantly higher rate of improvement in the primary outcome (45%) than was placebo (19%). Pioglitazone also was associated with a higher rate of improvement (34%) than placebo,

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Genes Explain Ribavirin-Induced Anemia

By Bruce Jancin
Elsevier Global Medical News

VIENNA — Genetic variants leading to inosine triphosphatase deficiency protect against ribavirin-induced hemolytic anemia in patients on antiviral therapy for chronic hepatitis C, according to a large pharmacogenomic study.

The clinical implication of this discovery is that a simple test for variants in the inosine triphosphatase (ITPA) gene identifies patients with chronic hepatitis C who are at either high risk or low risk for developing hemolytic anemia during long-term treatment with pegylated interferon-alpha plus ribavirin, the current standard of care, said Dr. Alexander J. Thompson at the annual International Liver Congress sponsored by the European Association for the Study of the Liver.

Ribavirin-induced anemia is a common complication that requires dose reduction in 15%-20% of patients, with correspondingly lower success rates in achieving sustained

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Thinking about a change? Interested in relocating? Go where the jobs are ...
Management of UGI Bleeding: New Consensus Recommendations

BY JAY CHERNIK
Elsive Global Medical News

A group of experts from 15 countries has updated and expanded recommendations for the management of upper gastrointestinal upper hemorrhage bleeding issued in 2003. The new guidelines, published in Annals of Internal Medicine, "emphasize early risk stratification, by using validated prognostic scales, and early endoscopy (within 24 hours)."

The group of 34 experts based its update on data sources including original and published systematic reviews and randomized controlled trials (Ann Intern Med. 2010;152:101-13). Of the 34 statements composing the recommendations, 22 are new or are revisions of statements in the 2003 guidelines, 10 were unchanged from the 2003 guidelines "because the majority of the group felt that they did not require revision at this time." The new and revised statements follow.

Resuscitation, Risk Assessment, and Pre-Endoscopy Management

- Prognostic scales are recommended for early stratification of patients into low- and high-risk categories for rebleeding and mortality.
- Blood transfusions should be administered to a patient with a hemoglobin level of 70 g/L or less.
- In patients receiving anticoagulants, correction of coagulopathy is recommended but should not delay endoscopy.
- Promotility agents should not be used routinely to avoid endoscopy to increase the diagnostic yield.
- Selected patients with acute ulcer bleeding who are at low risk for rebleeding on the basis of clinical and endoscopic criteria may be discharged promptly after endoscopy.
- Pre-endoscopic proton pump inhibitor (PPI) therapy may be considered to downstage the endoscopic lesion and decrease the need for endoscopic intervention, but should not delay endoscopy.

Endoscopic Management

- Early endoscopy (within 24 hours of presentation) is recommended for most patients with acute upper GI bleeding.
- A finding of a clot in an ulcer bed warrants targeted irrigation in an attempt to dislodge, with or without treatment of the underlying lesion.
- The role of endoscopic therapy for ulcers with adherent clots is controversial. Endoscopic therapy may be considered if a PPI therapy alone may be sufficient.
- Epinephrine injection alone provides suboptimal efficacy and should be used in combination with another method.
- Clips, thermocoagulation, or sclerosant injection should be used in patients with high-risk lesions, alone or in combination with epinephrine injection.
- Routine second-look endoscopy is not recommended.

Pharmacologic Management

- An intravenous bolus followed by continuous-infusion PPI therapy should be used to decrease rebleeding and mortality in patients with high-risk stigmata who have undergone successful endoscopic therapy.
- Patients should be discharged with a prescription for a single daily-dose oral PPI for a duration as dictated by the underlying etiology.

Nonendoscopic and Nonpharmacologic In-Hospital Management

- Most patients who have undergone endoscopic hemostasis for high-risk stigmata should be hospitalized for at least 72 hours thereafter.
- Where available, percutaneous embo- lization can be considered as an alternative to surgery for patients for whom endoscopic therapy has failed.
- Patients with bleeding peptic ulcers should be tested for Helicobacter pylori and should receive eradication therapy if the bacteria are present, with confirmation of eradication.
- Negative H. pylori diagnostic tests should be repeated.

Postdischarge ASA and NSAIDs

- In patients with previous ulcer bleeding, aspirin should be recognized that treatment with a traditional NSAID plus PPI or a cyclooxygenase-2 (COX-2) inhibitor is alone is still associated with a clinically important risk for recurrent ulcer bleeding.
- In patients with previous ulcer bleeding who require an NSAID, the combination of a PPI and a COX-2 inhibitor is recommended to reduce the risk for recurrent bleeding from that of COX-2 inhibitors alone.
- In patients who receive low-dose acetylsalicylic acid (ASA) and develop acute ulcer bleeding, ASA therapy should be restarted as soon as the risk for cardiovascular complications is thought to outweigh the risk for bleeding.
- In patients with previous ulcer bleeding who require cardiovascular prophylaxis, it should be recognized that clopidogrel alone has a higher risk for rebleeding than ASA combined with a PPI.

GI & HEPATOLOGY NEWS

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VIROLOGY

Ribavirin

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virologic response, added Dr. Thompson, a gastroenterologist at the Duke Clinical Research Institute, Durham, N.C.

Another implication of the new IFNA finding is that it may be useful to induce IFNA deficiency pharmacologically in order to protect against ribavirin-induced hemolytic anemia in patients not genetically so predisposed. This is a strategy that’s reasonable to pursue further because IFNA deficiency is thought to be a benign condition, according to Dr. Thompson.

He and his co-investigators conducted a genome-wide subset of 1,286 participants in the Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) study, whose primary outcomes have been published (N. Engl. J. Med. 2009;361:580-93). For this pharmacogenomic study, the authors tested nearly 600,000 single nucleotide polymorphisms. They determined that the occurrence of a greater than 3 g/dL drop in hemoglobin by week 4 was an end point that was entirely explained by variants in the IFNA gene. The minor alleles that cause IFNA deficiency were protective against ribavirin-induced hemolytic anemia in whites of European ancestry, blacks, and Hispanics.

Fifty-six percent of the 863 patients with a high-functioning IFPA gene had a greater than 3 g/dL drop in hemoglobin by week 4. In contrast, a significant decrease in hemoglobin occurred in only 20% of patients with mild IFNA deficiency. 4.6% of those with moderate deficiency, and no patients with severe IFNA deficiency.

The working hypothesis is that IFNA deficiency leads to accumulation of IFPA in red blood cells, hampering conversion of ribavirin monophosphate into the drug’s toxic metabolite, which is thought to cause hemolytic via oxidative stress.

This study was funded by the Schering-Plough Research Institute. Dr. Thompson’s research is funded by the National Health and Medical Research Council of Australia and the Gastroenterological Society of Australia.

February 2010 • GI & HEPATOLOGY NEWS
HalfLytely and Bisacodyl Tablets Bowel Prep Kit is a gastrointestinal lavage indicated for cleansing of the colon as a preparation for colonoscopy in adults. Most common adverse reactions (<3%) are abdominal pain/cramping, nausea, vomiting and headache. Use is contraindicated in the following conditions: known allergies to polyethylene glycol or other components of the kit, gastrointestinal (GI) obstruction, bowel perforation, toxic colitis, toxic megacolon. Use with caution in patients using concomitant medications (such as diuretics) that increase the risk of electrolyte abnormality, patients with known or suspected hyponatremia, patients with severe ulcerative colitis, ileus or gastric retention. There have been reports of ischemic colitis in patients with use of HalfLytely and 20 mg Bisacodyl Tablets Bowel Prep Kit. However, a causal relationship has not been established. If patients develop severe abdominal pain or rectal bleeding, patients should be evaluated as soon as possible. Patients with impaired water handling who experience severe vomiting should be closely monitored including measurement of electrolytes. Hives and skin rashes have been reported with PEG-based products which are suggestive of an allergic reaction.

Please see brief summary of prescribing information on adjacent page.
Use of High-Volume Centers Assessed for GI Cancers

BY DOUG BRUNK
Elsevier Global Medical News

ST. LOUIS — Nationwide, procedures for pancreatic and esophageal cancer are being centralized at high-volume centers, results from a long-term study of discharge data demonstrated.

At the same time, however, there has been no significant change in the patterns of care for colon and rectal cancer procedures, Dr. Karyn B. Stitzenberg reported at a symposium sponsored by the Society of Surgical Oncology.

“Specifically for GI malignancies, there are over 80 studies that support a relevant association between hospital procedure volume and clinical outcomes,” said Dr. Stitzenberg, of the division of surgical oncology at the University of North Carolina at Chapel Hill.

“Despite all these studies, until recently very little was known about how practice patterns have changed and if they’ve changed in response to these findings,” she explained.

In a previous study of cancer procedures performed in New York, New Jersey, and Pennsylvania between 1996 and 2006, Dr. Stitzenberg and her associates found extensive centralization of pancreatic and esophageal cancer procedures at higher-volume centers, but very little change in the practice patterns for colon and rectal procedures (J. Clin. Oncol. 2009;27:4671-8). On the basis of findings from this and other small, regional studies, they hypothesized that similar patterns have occurred nationwide.

To test that theory, the researchers analyzed data from the Healthcare Cost and Utilization Project National Inpatient Sample, examining trends in hospital procedure volume for all extirpative esophageal, pancreatic, and colorectal cancer procedures performed between 1999 and 2007.

Low-volume centers were defined as follows: colon, 1-43/year; esophagus, 1-3/year; pancreatic, 1-6/year; and rectal, 1-15/year. High-volume centers were defined as follows: colon, 80 or more/year; esophagus, 19 or more/year; pancreatic, 26 or more/year; and rectal, 35 or more/year.

A total of 351,164 cases were studied. Of these, 255,753 were colon, 6,345 were esophageal, 17,658 were pancreatic, and 71,408 were rectal. Pediatric cases were excluded from the analysis.

Dr. Stitzenberg reported that in 1999, 33% of colon and rectal cancer cases were performed at low-volume centers. By 2007, this proportion had decreased slightly to about 30%. In contrast, a significant proportion of esophageal and pancreatic cancer cases had shifted to high-volume centers during the same time period, with only 17%-18% remaining at low-volume centers.

High-volume centers were located predominately in urban areas, and those that treated esophageal and pancreatic cancer were located exclusively in academic centers.

The strongest predictor for having surgery in a low-volume center was being admitted to the hospital emergently rather than electively, with odd ratios that ranged from 1.13 for colon procedures to 1.38 for esophageal procedures, Dr. Stitzenberg said.

“For future directions, quality improvement efforts could potentially be directed at facilitating transfer of these emergency cases to high-volume centers,” Dr. Stitzenberg said.

Race also was associated with hospital procedure volume. Even after adjustment for payer, socioeconomic status, and admission type, black patients were 1.42-1.26 times more likely to be treated at a low-volume center, compared with other patients—unless they were undergoing colon cancer procedures, for which there were no significant differences.

“Meanwhile, we need to consider the impact of centralization on access to care,” he said.

In our previous study, we showed that, as esophageal and pancreatic cancer cases became centralized, there was a 40%-70% increase in patient travel distance. What we really don’t know at this point is, are there patients who are delaying or forgoing surgery due to this increasing travel burden and the access to care issues that are being imposed by centralization of these procedures?” For the more common malignancies such as colon cancer, “it’s impractical and probably not appropriate to move all patients to higher-volume centers,” Dr. Stitzenberg said.

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References: 1. IMS Health Inc, NPA Weekly Rx Audit, Jan 2008-Feb 2009. 2. In a clinical study of HalfLytely and Bisacodyl Tablets Bowl Prep Kits (10 mg vs 20 mg bisacodyl tablets) (See package insert, Table 3), Braintree, MA: Braintree Laboratories, Inc. 3. See package inserts: GoLYTELY® (PEG-3350 and Electrolytes for Oral Solution); 2001, NULYTIX® (PEG-3350, Sodium Chloride, Sodium Bicarbonate and Potassium Chloride for Oral Solution); 2008, HalfLytely and Bisacodyl Tablets Bowl Prep Kit; 2008, Braintree, MA: Braintree Laboratories Inc., MovPrep® (PEG-3350, Sodium Sulfate, Sodium Chloride, Potassium Chloride, Sodium Ascorbate and Ascorbic Acid for Oral Solution); 2006, Morrisville, NC: Salix Pharmaceuticals Inc.
Lawmakers Investigate Medical Radiation Excesses

Witnesses say strict measures needed to protect patients during treatment, imaging scans.

BY MONICA HOGAN

WASHINGTON — One congressional hearing on medical radiation safety may not be enough for the Health Subcommittee of the House Energy and Commerce Committee. “We probably will need an additional hearing because I just have so many questions that came out of this today,” chairman Frank Pallone Jr. (D-N.J.) observed during the Feb. 26 hearing.

Several witnesses called for the immediate passage of the CARE Act (Consistency, Accuracy, Responsibility, and Excellence in Medical Imaging and Radiation Therapy Act of 2009), which was introduced in the Energy and Commerce committee last September by Rep. John Barrow (D-Ga.). The CARE Act would mandate minimum education and training requirements, as well as state licensure, for personnel who plan or perform radiation oncology treatments or medical-imaging scans.

Subcommittee members and witnesses suggested that additional oversight may be needed as well, in the form of new regulatory agencies, quality standards, specialty practice guidelines, facility accreditation programs, and increased manufacturer participation in the process.

Industry Asked to Play Its Part

Manufacturers could move patient safety forward by immediately adopting agreed-upon standards for reporting radiation dose information from CT scans, said Dr. Rebecca Smith-Bindman, a radiology professor at the University of California, San Francisco, and a nuclear medicine accreditor.

“Industry has said that it supports an FDA plan to collect and track data on patient dose from CT scans. ‘If these standards were adopted by the manufacturers, we could quickly know what’s going on and then determine how closely different facilities abide by those guidelines that we have put out,’” Dr. Smith-Bindman said.

Manufacturers can also help ensure that patients receive the lowest possible dose from CT scans, she added, urging industry to draft and adopt guidelines on how device representatives set default settings as they install equipment and help establish treatment protocols with hospital physicians and physicists.

Doses for the most typical scans that patients undergo could be reduced by 50% without reducing image quality, Dr. Smith-Bindman said. CT scan vendors have recently developed software algorithms that work with existing equipment to help lower doses dramatically, she added.

News Report Led to Hearing

The Feb. 26 hearing was called largely in response to a Jan. 24 New York Times article that highlighted the adverse effects of too much medical radiation, including a fatal overexposure from image-modulated radiation therapy received by a patient named Scott Parks.

At the hearing, the patient’s father, James Parks, described how an error in equipment setup went unnoticed for 3 days of his son’s treatment, in part because the supervising physicist was off site. He asked manufacturers of such “deadly machines” to develop “fail-safe, interactive, expert systems that can interact with human technicians to reduce or eliminate human errors.”

“It is further recommended that such dangerous equipment never be operated by anyone not fully trained and qualified,” Mr. Parks stated. “Oncologists and supervising physicists must learn to micromanage every aspect of the radiology department. It is outrageous that any untrained and unskilled personnel can get anywhere near such dangerous equipment.”

Need For User Training Highlighted

Other witnesses supported the need for radiation therapists and physicists to be trained on new equipment as it is installed, and on an ongoing basis.

Kerneth Mirzaich, director of the Vet- ers Affairs New Jersey Health Care System, said his group decided to shut down its radiation oncology program in East Orange, N.J., after an internal investigation confirmed concerns over quality standards.

As the program was rebuilt, the facility established continuous education for all staff, with a major component dedicated to initial and ongoing training on new technology and equipment, Mr. Mirzaich said. Manufacturers were brought in to work with the staff and observe simulations in preparation for the facility’s reopening.

“We are conducting routine tests of our machines, simulating patient encounters, checking dose calculations, tracking patient outcomes, and instituting routine quality reviews of care, including peer review,” he said.

Eric Klein, Ph.D., professor of radiation oncology at Washington University in St. Louis, suggested that equipment vendors could send independent physicists to hospitals to help them become accustomed to new machines. Referring to a case in Florida in which 77 brain cancer patients were overdosed when a new machine was not properly set up, Dr. Klein noted that manufacturers do not typically have any direct control over the hospital personnel who determine the patients’ dose rate.

“If the manufacturer had said, ‘Okay, you’re buying this very expensive piece of equipment. It’s complex and is potentially dangerous. We are going to supply an expert physicist to come in from the outside to validate what you’re doing’ [that is] a very simple solution that would have caught what had happened,” he said.

Although radiation oncology equipment goes through much manufacturer testing, users could be trained better on exactly what “fault” messages mean, Dr. Klein continued.

Inconsistent Error Reporting

He added that there is wide variation among manufacturers in reporting machine errors and quality issues. Sometimes, malfunctions are reported anecdotally or via listserve, rather than by direct communication to all users of this equipment, Dr. Klein explained. “It might be better to do overkill communication. Right now, it’s just scant and irregular.”

In most states, hospitals are not required to report errors with linear accelerators as they occur, he noted.

Dr. Tim R. Williams, chair of the American Society for Radiation Oncology, said that ASTRO’s 6-point plan to improve patient safety and quality includes a recommendation to work closely with regulatory authorities to create a national database for the reporting of linear accelerator medical errors.

The ASTRO plan also attempts to ensure that radiation therapy technologies from different manufacturers can transfer treatment information seamlessly to help reduce medical errors.

CMS Could Foster Safety

Michael Herman, Ph.D., representing the American Association of Physicists in Medicine, called for rigorous minimum standards for accredited clinical practices, specifically including the oversight of dose and quality assurance for medical imaging and radiation therapy technology. He asked that reimbursement from the Centers for Medicare and Medicaid Services be directly tied to such accreditation.

The CMS could also help foster radiation safety by funding residencies for physicists in the field, as it does for physicians, said Dr. Klein. He noted that starting in 2014, the American Board of Radiology will allow only physicists who have completed a residency program to sit for board certification.

John Donahue, vice chairman of the radiology benefits management company Medicalis Inc., suggested that the CMS specify radiation safety among the appropriateness criteria it will test in its pilot program on advanced imaging.

MIPPAs (Medicare Improvement for Patients and Providers Act of 2008) calls for a 2-year demonstration project to test appropriateness criteria for CT scans and other advanced imaging technology.

The American College of Radiology wants accreditation requirements for advanced imaging centers to be extended to hospitals and all clinical settings that perform advanced imaging and radiation therapy procedures, according to Dr. E. Stephen Amis Jr., former ACR chair.

Patients, Keep Your Appointments

While deliberations go forward, health subcommittee members were quick to state that they did not want to scare the public away from using radiation therapy or medical imaging when appropriate.

“We are not suggesting that we don’t want people to proceed with CT scans or other diagnostic tools or other forms of radiation because we know how important that is,” Chairman Pallone said.

“There are just a lot of questions that need to be answered.”

Monica Hogan is with “The Gray Sheet.” This publication and “The Gray Sheet” are published by Elsevier.

NICE Favors Infliximab, Adalimumab for Crohn’s

BY JENNIE SMITH

Elsevier Global Medical News

The clinical effectiveness agency for England and Wales—known as the National Institute for Health and Clinical Excellence (NICE)—has recommended two medicines, infliximab and adalimumab, for the treatment of severe Crohn’s disease.

The agency, known as NICE, said it favored adding these two drugs, both TNF inhibitors, as treatment options for adults with severe active Crohn’s disease, for “good reason.” The INNIT trial compared these to conventional therapies (which include immunosuppressive and corticosteroid treatments) or who are unsuited to or intolerant of these therapies.

The NICE reviewers cited data from 11 randomized controlled trials and 1 study that used patient questionnaires to evaluate the clinical outcomes. NICE recommended that, given the lack of evidence establishing one drug’s effectiveness over the other, the cheaper drug, adalimumab, should be tried first, except in cases of fistulizing Crohn’s disease, in which case infliximab may be chosen first.

With either drug, NICE recommends that therapy continue for 1 year, after which additional assessment is warranted.
A 68-year-old man was admitted to the hospital with asthenia, anorexia, a 10 lb weight loss of 6 months’ duration, abdominal distention, and acute low back pain. His medical history included a successful surgical intervention during infancy for an imperforated anus and chronic constipation with several episodes of intestinal pseudo-obstruction over the last 10 years. Physical examination showed serious cachexia, a thin abdomen without signs of peritonitis, and reduced bowel sounds. Palpation did not reveal masses or visceromegaly. The rectal examination showed stools of medium consistency and normal anal sphincter tone.

The patient’s left thigh was swollen, tender, and erythematous. Laboratory studies only revealed hypoalbuminemia (2.8 g/dL) with high carcinoembryonic antigen (13.1 ng/mL). A radiograph of the abdomen was taken (Figure A), which showed an absence of intestinal gas with a heterogeneous mass filling the abdomen.

Computed tomography of the abdomen showed a large colorectal dilatation due to a giant mass containing calcification that occupied the entire abdominal cavity (Figure B), leading to displacement of visceral structures and severe compression of the inferior vena cava with dilatation of the right renal pelvis (Figure C, arrows) without signs of colon perforation. Doppler ultrasonography of the lower left limb revealed an intraluminal thrombus (Figure D, arrow) and noncompressibility of the common femoral vein with the ultrasound transducer probe (Figure D, arrowhead). What is the diagnosis, and how should this case be managed?

The diagnosis appears on page 17.
IOM Urges Overhaul of Cancer Clinical Trials Network

BY ALICIA AULT
Elsevier Global Medical News

Saying that the cancer clinical trials system is in a state of crisis, an expert panel of the Institute of Medicine (IOM) called for an overhaul to speed up trial design and execution, incorporate scientific discoveries more rapidly, and create a structure to reimburse physicians and cover patients’ costs for participation in studies.

In a report issued Apr. 15, the 17-member panel said the backbone of the system, the National Cancer Institute-supported Clinical Trials Cooperative Group Program, has become cumbersome and inefficient. According to the report, it takes an average of 2 years to design, approve, and start a trial. Only half of trials are ever completed, and the groups’ funding has decreased by 20% over the last 8 years.

Moreover, enrollment in trials is abysmal. The American Cancer Society estimates that only 3% of adults with cancer participate. “Cooperative group studies have steadily improved the care of cancer patients for more than 50 years, but the program is at a breaking point,” said the IOM panel’s chairman, Dr. John Mendelsohn, president of the University of Texas M.D. Anderson Cancer Center in Houston.

“The program urgently needs changes across the board, if it is going to continue producing the kind of studies necessary to answer crucial and fundamental questions about how to successfully treat and prevent cancer, which can’t be answered through other means,” Dr. Mendelsohn said.

The American Society of Clinical Oncologists (ASCO) applauded the IOM panel’s recommendations. “The Cooperative Clinical Research Program is the jewel in our nation’s cancer research system, and is critical to advancing progress against the disease,” said Dr. Richard L. Schilsky, immediate past president of ASCO, in a statement.

The Cooperative Group Program, which is supported by the NCI, comprises 10 groups that incorporate 3,100 institutions and 14,000 investigators. Some 25,000 patients participate in cooperative trials each year.

Because the program does have the potential to be more efficient and effective, “it is imperative to preserve and strengthen the unique capabilities of the Cooperative Group Program as a vital component in NCI’s translational continuum,” wrote the panelists in the report. It will be an uphill battle. Currently, funding for the groups makes up only 3% of the NCI’s budget.

Dr. Schilsky said that “the system is being starved of funding.” In real dollars, “the program receives less funding today than it did a decade ago,” he noted.

“ASCO calls on NCI to double its support for cooperative clinical research within 5 years,” said Dr. Schilsky, a professor of medicine and section chief, hematology/oncology at the University of Chicago Medical Center, who also served on the panel. The ability to recruit, train, and retain enough clinical investigators is also crucial to the rebuilding of the trial system, said the IOM panel.

It recommended that insurers, Medicare, and federal and state health programs cooperate to establish consistent payment policies to cover all patient care costs in a trial, except for the drugs, devices, or diagnostics, which should continue to be paid for by the manufacturers. Such policies might act as an incentive for patients to participate in trials, said the panel.

The experts also urged the American Medical Association to create new CPT codes that would create a payment pathway for offering, enrolling, managing, and following a patient through a clinical trial. The new codes would reflect the additional time that physicians put in to getting patients into a trial, and for managing potential adverse events.

And, they would likely be a powerful incentive for physicians to consider putting more of their patients in studies, said the panel.

Physicians, indeed, are not happy about reimbursement. A recent ASCO survey showed that one-third of Cooperative Group Sites said they planned to limit participation in those trials due to inadequate per-case reimbursement. Almost 40% of those who were going to limit cooperative studies said they would instead increase their participation in industry-sponsored trials.
laparoscopic surgery to treat diverticulitis is associated with half as many complications as open surgery, according to a study of nearly 7,000 surgeries performed over a 1-year period, reported Dr. Andrew Russ and his colleagues in the June issue of Gastroenterology.

Investigators at the University of Wisconsin, Madison, led by Dr. Gregory D. Kennedy, examined records from the American College of Surgeons' National Surgical Quality Improvement Program, a database of information on surgeries performed in participating U.S. hospitals.

The research team identified records from all patients who had undergone any of 11 coded surgical procedures for diverticular disease from 2005 to 2008. Patients who had undergone emergency surgeries were omitted from the analysis. Of the 6,970 patients remaining, 3,468 underwent an open resection procedure and 3,502 underwent a laparoscopic procedure.

The incidence of complications—including infections, pneumonia, deep vein thrombosis or pulmonary embolism, and postoperative sepsis or septic shock—was markedly lower in the laparoscopic group, with overall complications in the month after surgery reduced by nearly half, from 21.7% in the open group to 11.0% in the laparoscopic group. Hospital stays were reduced by more than a third, from an average of 7.8 days in the open group to 4.8 days for the laparoscopic patients.

However, the patients undergoing laparoscopic surgery also happened to be younger (mean age 55.6 vs. 59.2 years for open surgery) and had fewer comorbidities, and this “is the crux of the difficulty with this paper,” Dr. Kennedy said in an interview.

The nonrandomization of the study was another limitation, he said, as was the fact that most of the surg- eries were performed in academic hospitals with high-volume colorectal surgery centers.

In addition, the investigators wrote that poor wound condition was evident in more than 20% of the open surgeries. Although they did not include in their analysis any emergency surgeries (defined as those initiated within 12 hours of hospital admission), the fact that one-fifth of wounds in the open surgery group were classed as “dirty” or “infected,” compared with only 5.1% in the laparoscopic group, suggests that many of the open surgeries “could be considered on some level urgent,” Dr. Kennedy said.

But when the investigators employed statistical models to correct for complication risks, including a propensity score adjustment based on all available preoperative variables, such as wound condition, American Society of Anesthesiologists physical status classification, body mass index, and recent surgeries, they nonetheless found that the risk of developing complications was roughly 50% lower after a laparoscopic procedure, compared with an open procedure.

“What we saw was that laparoscopy at least correlated with an improved outcome,” Dr. Kennedy said. “It is at least contributing to a 50% reduction” in complications.

Dr. Kennedy and his colleagues noted that, despite a growing body of research suggesting laparoscopy to be the safer option, it remains far from surgeons’ first choice for colorectal surgery.

Currently, in the United States, Dr. Kennedy said, the availability of the procedure “depends largely on the market; if you’re in Chicago and go for a colon surgery, nearly every surgeon will offer it. In other states, and in many rural communities, people are not performing or even offering laparoscopy.”

One reason for the hesitation, the investigators speculated, could be that laparoscopic surgeries for diverticular disease had been previously associated with high rates of complications. But currently, they wrote, conversion rates are between 20% and 26%, “not dissimilar to current large series reports on conversion rates for neoplastic disease.” Another reason, they said, could be the longer operating times associated with laparoscopic surgery.

Resistance to broader adoption of laparoscopy “may be largely a technical thing,” Dr. Kennedy said. “Laparoscopy takes longer, may require retraining, and there are other technical issues. Personally, I’d like people to start thinking of laparoscopy not necessarily as a selective option, but as how we should approach patients.”

The study was funded by the University of Wisconsin. Neither Dr. Kennedy nor any of his coauthors cited competing interests.

Statins, NSAIDs Reduced Barrett’s Progression to Cancer

BY JENNIE SMITH

Elsevier Global Medical News

Patients with Barrett’s esophagus who took statin drugs had a 45% lower risk of developing esophageal adenocarcinoma than did similar patients not taking statins, and patients taking aspirin or nonsteroidal anti-inflammatory drugs also had a reduced risk, reported Dr. Hashem B. El-Serag and his colleagues in the June issue of Gastroenterology.

In an effort to learn more about the effect of statins, proton pump inhibitors, aspirin, and NSAIDs on the progression of Barrett’s esophagus (BE) into cancer, researchers at the Department of Veterans Affairs Medical Center and Baylor College of Medicine, both in Houston, used a national VA database to identify 11,823 records of people diagnosed with Barrett’s esophagus in 2000-2002. Among these records, they identified 116 cases of esophageal adenocarcinoma, along with 696 controls who had BE but not adenocarcinoma. The cases and controls were matched for age (within 5 years), race (78% of cases and 73% of controls were white), sex (97% of both cases and controls were men). Data were subsequently adjusted for frequency of outpatient visits and sociodemographic status.

All of the controls had been diagnosed with BE on the same date (plus or minus 14 days) as the cases. The researchers examined records of prescriptions filled by the cancer patients between their BE diagnosis and cancer diagnosis, and looked at prescriptions filled by controls for 2 years after BE diagnosis.

Filled prescriptions for statins and aspirin/NSAIDs were associated, to different degrees, with a decreased risk of the development of esophageal adenocarcinoma in people with BE.

A 36% decrease in cancer risk was found for aspirin/NSAIDs, and this “was largely expected although not previously shown in a cohort of BE patients,” Dr. El-Serag said in an interview. With the use of statins, however, a hypothesis of chemopreventive effects in esophageal adenocarcinoma was based on in vitro studies, “and we were surprised,” he said, about the 45% decrease in risk.

The investigators could not conclude anything about proton pump inhibitors, because use of those drugs was nearly universal among cases and controls. This, said Dr. El-Serag, was not necessarily a bad thing, as it removed a potential confounding factor.

“The key point of the study is that, unlike any previous studies that examined the effect of NSAIDs on esophageal cancer, all the subjects had BE,” Dr. El-Serag said. “Everyone started on an equal playing field. We had pooled data from 128 hospitals, so to my knowledge this is the largest cohort assembled to date.”

Dr. El-Serag and his coauthors wrote in their analysis that the study’s limitations included its relatively brief length, using only 2 years of prescribing data, and the fact that the records of prescriptions filled through the VA system likely presented only a partial picture of medications taken.

Also, since NSAIDs and aspirin are readily available over the counter, patients of lower socioeconomic status would likely be the only users of the VA prescriptions to obtain these, presenting another problem for the researchers. “One cannot capture OTC medication with a study like this,” Dr. El-Serag said.

The study was funded in part by a grant from the National Institutes of Health, none of the investigators declared conflicts of interest.
Bacterial Overgrowth Found in Half of Patients on PPIs

**BY JENNIE SMITH**

*Elsevier Global Medical News*

Fifty percent of people taking proton pump inhibitors to treat gastroesophageal reflux disease develop small intestinal bacterial overgrowth, compared with a quarter of patients with irritable bowel syndrome not taking PPIs, reported Dr. Lucio Lombardo and his colleagues in the June issue of Clinical Gastroenterology and Hepatology.

In the study, 450 consecutive patients underwent glucose hydrogen breath tests, which measure the metabolic activity of enteric bacteria. Two hundred of the patients had been diagnosed with gastroesophageal reflux disease and had been taking one of several PPIs for a median of 36 months, although some had taken the medication for as little as 2 months.

The investigators recruited an additional 200 study subjects who had been diagnosed with irritable bowel syndrome (IBS) and were not taking PPIs. Dr. Lombardo and his colleagues noted that the symptoms of IBS—including bloating, diarrhea, and constipation—frequently overlap with the symptoms of small intestinal bacterial overgrowth (SIBO). They also recruited 50 healthy controls who did not have symptoms of either IBS or SIBO and had not taken a PPI for at least 3 years.

Patients with other gastrointestinal diseases, who had recent gastric surgery, who were taking antibiotics, or who had potentially confounding factors were excluded from the study.

Evidence of SIBO was found in 50% of the patients on PPIs, 24.5% of patients with IBS, and only 6% of healthy controls, wrote Dr. Lombardo, of the gastroenterology department of Mauriziano U.I. Hospital, Turin, and his colleagues.

Moreover, the researchers found a correlation between the duration of PPI treatment and the detection of SIBO, with more than 70% of the PPI group testing positive for SIBO after 13 months of PPI use—more than triple the proportion of positives among those taking PPIs for a year or less.

Although several studies have used breath-based tests to assess the prevalence of SIBO in patients with IBS, few have been designed to assess the independent influence of PPIs, the investigators wrote. This, they said, is an "important oversight," as PPI use is widespread in patients with IBS.

The authors cited a recent report suggesting that IBS patients not taking PPIs and GERD patients on PPIs have roughly equal rates of SIBO, as assessed by lactulose breath tests. However, the researchers wrote that no mention was made in that study of the duration of PPI treatment, while their own study showed that PPI treatment increased the incidence of SIBO drastically after the first year.

Dr. Lombardo and his colleagues speculated that PPI-related SIBO might be frequently underdiagnosed or misdiagnosed as IBS because of the overlap of common symptoms.

Study patients with SIBO were treated with the antibiotic rifaximin 400 mg three times daily for 14 days. Eradication of SIBO, as confirmed by a glucose hydrogen breath test, occurred in 87% of the PPI group and 91% in the IBS group. In the PPI group, eradication was more successful among subjects who had taken PPIs for less than a year, which suggested "a more profound or qualitatively different alteration in enteric microbiota after a year of treatment," the authors wrote.

In both the PPI and IBS groups, symptom severity was reduced by more than 90% in subjects whose SIBO eradication had been confirmed by breath testing and to a lesser but measurable degree in those subjects whose SIBO had not been eradicated at the same dose of rifaximin.

The investigators did not seek to learn whether SIBO returned after eradication in patients who continued PPI therapy but cited another study suggesting that such an outcome was likely.

"She noted a few limitations of the study, which included a lack of distinction between specific PPIs taken by the patients, the observational open-label study design, and that fact that Helicobacter pylori was not investigated as an independent contributor (although all 450 patients were tested, with 68% found to be negative)," the authors wrote. The study was not funded by outside grants, and neither Dr. Lombardo nor his colleagues reported any competing interests.

**Viral DNA Level Predicted Decompensation in Hepatitis B**

**BY JENNIE SMITH**

*Elsevier Global Medical News*

High levels of hepatitis B virus DNA constitute a strong predictive factor for hepatic decompensation in chronic hepatitis B patients with acute hepatic flares, reported Dr. Yun-Fan Liaw and colleagues in the June issue of Clinical Gastroenterology and Hepatology.

The authors determined that a specific cutoff value for HBV-DNA can be used in patients with acute exacerbations of chronic HBV infection to assess decompensation risk, allowing for immediate treatment with antiviral medication to prevent decompensation in those patients above the cutoff, the researchers wrote.

For their investigation—part of an ongoing multiyear cohort study of more than 1,400 patients treated at Chang Gung Memorial Hospital in Taipei—Dr. Liaw and colleagues isolated 138 exacerbations, which is based on aminotransferase (ALT) elevation that occurred in 110 hepatitis B e antigen-positive patients with chronic disease of at least 6 months. Patients with simultaneous anti-HB e seropositivity, with evidence of cirrhosis or other liver disease, or who were taking antiviral medication, were excluded.

The 110 patients were monitored every 1-2 weeks at the hospital’s outpatient hepatitis clinic, in accordance with the clinic’s normal protocol for hepatitis B patients with chronic infections. Researchers recorded serum ALT and HBV-DNA levels, as well as bilirubin, albumin, prothrombin time, and the cause (spontaneous, or a relapse from antiviral treatment) at the first sign of the exacerbations.

The median patient age during the 138 exacerbations was 34.7 years (range, 16-58.3 years); 81.2% of flares occurred in males and 18% were in genotype B HBV-infected patients. Median value of ALT was 419 U/L at enrollment; bilirubin was 1.1 mg/dL, prothrombin time prolongation was 0.4 seconds, and HBV-DNA level was 5.657 x 10^8 copies/mL.

Of the 138 flares, 7 (5.1%) resulted in decompensation before the antiviral drug could be administered. And in all seven episodes, "serum HBV-DNA level was the only significant risk factor," Dr. Liaw and colleagues wrote, although ALT levels were marginally higher for the cases that developed decompensation.

The decompensation patients also had higher bilirubin levels and prothrombin time at enrollment than did those who did not subsequently develop decompensation (1.3 vs. 1.1 mg/dL and 0.9 vs. 0.4 seconds, respectively). No significant differences were noted with regard to sex, age, or albumin level at entry.

The investigators used a receiver operating characteristic (ROC) curve to determine the optimal cutoff point for serum HBV-DNA, and found 1.55 x 10^5 copies/mL to be the ideal value for use in predicting decompensation, with a sensitivity of 85.7%, a specificity of 85.5%, a negative predictive value of 99.1%, and a positive predictive value of 24.8%.

Although normal protocols for the treatment of hepatitis B flare in Asia generally consist of monitoring and awaiting an immune-mediated secon- version, the ability to predict the rare occurrence of decompensation and to administer antiviral drugs before its onset is important, the investigators wrote, as decompensation can result in liver damage and death.

By using the predictive value of 1.55 x 10^5 copies/mL for HBV-DNA, antiviral medicines can be administered in time to prevent onset of decompensation in patients with acute exacerbations, the researchers concluded. Patients with levels of less than 1.55 x 10^5 copies/mL are at low risk and can continue to be monitored for spontaneous HBV Ag seroconver- sion.

The research was carried out using funds from Taiwan’s Prosperous Foundation and Chang Gung University.

Neither Dr. Liaw nor colleagues reported any competing interests related to their research, although Dr. Liaw has served as a reviewer for Roche, Bristol-Myers Squibb, Novartis Pharmaceuticals Corp., and Gilead Sciences Inc.
The Foundation for Digestive Health and Nutrition has announced the 2010 American Gastroenterological Association (AGA) Foundation Research Scholars. The grants have been awarded to seven outstanding young gastroenterologists who promise to make significant strides in the field of gastrointestinal research.

The current economic times have introduced new funding challenges, and research funding remains elusive for all scientists, especially those just beginning their career, despite their tremendous promise,” said Dr. Nicholas P. LaRusso, AGAF, chairman of the Foundation for Digestive Health and Nutrition (FDHN).

“The AGA Foundation for Digestive Health and Nutrition remains committed to continuing to help fund these gifted scholars. The pace of discovery must be sustained, and it is up to those of us in the profession to make it happen. The 75 grants we give out to gifted researchers each year boldly represent our commitment to progress.” In addition to the Research Scholar Awards, the AGA Foundation provides a variety of other funding mechanisms to young investigators.

The prestigious Research Scholar Awards offer each scientist a total of $60,000 for 2 years (third year is contingent on available funds and research progress) to help support his or her research over a 3-year period. Donor-funded Research Scholar Awards from the Bernard L. Schwartz Foundation and General Mills Institute of Health and Nutrition provide a total of $75,000 for 3 years in research support.

The goal of the Research Scholar Awards is to guarantee the perpetuation of strong science through the encouragement of young physician investigators, and ultimately to improve patient care through digestive diseases research.

These extremely competitive awards ensure that bright, young physicians and scientists devote their careers to advancing the field of digestive health through research. Awards are based on the qualifications of the candidate, the quality of the candidate’s research proposal, and the commitment of the candidate’s institution to protect 70% of his or her time for research.

The Research Scholar Awards program was launched in 1984 to provide crucial early support to investigators who show promise in academic gastroenterological research. The program’s premise recognized that resources awarded early on could provide a stable platform from which future research funding would be derived. During and after their time as an AGA Research Scholar, recipients have made important contributions to the field of gastroenterology, and many former award recipients have gone on to hold distinguished appointments at major medical institutions throughout the United States and Canada.

Since 1984, the AGA and its foundation have awarded more than $24 million to fund some 168 research scholars and have provided a total of $18 million in grant funding. The 2010 scholars were chosen by a distinguished 11-person national advisory committee chaired by Dr. David Brenner, dean and vice chancellor for Health Sciences at University of California. Members of the committee include leading gastroenterologists from the Cincinnati Children’s Medical Center, Johns Hopkins University School of Medicine, University of Michigan, University of North Carolina, Chapel Hill; University of Texas Southwestern Medical Center; Vanderbilt University; and Washington University.

The AGA Research Scholar Awards program addresses the critical problem of lack of funding for entry-level researchers in gastroenterology. At a time of unparalleled scientific and clinical opportunity, the field of gastroenterology faces a significant decline in the number of gastroenterologists entering academic research careers. Although the National Institutes of Health (NIH) funds a significant amount of gastroenterology research, it rarely funds young investigators working independently without a research track record. Additionally, NIH gastroenterology research funding is proportionately much smaller than that for diseases with less, or similar, health impact (such as HIV/AIDS or breast cancer).

Holding Medicare/Medicaid Overpayments Can Put a Practice at Risk

Included in the Patient Protection and Affordable Care Act of 2010 is a provision that requires providers (hospitals, skilled nursing facilities, home health agencies, and others) and suppliers (physicians, ambulatory surgery centers, labs, and others) to report and refund any overpayment within 60 days of the date the overpayment is “identified.” Failure to do so could result in a False Claims Act (FCA) violation, a civil monetary penalty, or other penalties.

Prior to this change, providers and suppliers had advantages if they refunded overpayments promptly, including the possibility of limiting FCA damages to double rather than triple damages, as well as garnering favor with enforcement officials.

Now, however, this flexibility is constrained with the 60-day window being an outside date for refund. What is not yet clear is when the 60-day window is triggered. Is it when the overpayment is received, when it is suspected, or more likely, when it is confirmed? It is likely that CMS will publish guidance on how the provision will be implemented and enforced. However, if you are certain that you have received an overpayment from Medicare or Medicaid, returning the overpayment within 60 days is critical to avoiding severe penalties. Make copies of the refund check and the letter explaining the refund and keep it on file in your office. Send the letter and check via certified mail to your Medicare contractor or state Medicaid office.
AGA Launches Digestive Health Outcomes Registry

The American Gastroenterological Association (AGA) and MedAssurant Inc. announce the launch of the largest patient registry in the GI field, the AGA Digestive Health Outcomes Registry™.

The AGA Registry captures data and tracks outcomes related to inflammatory bowel disease (IBD) and colorectal cancer (CRC) prevention. Unique in the history of registry launches, the registry starts with a foundation of clinical data from more than 4.3 million patients who have IBD or who have had screening colonoscopies.

“The AGA Registry is a powerful tool that will help gastroenterologists improve quality of care by understanding what outcomes result from specific interventions,” says Dr. Gail A. Hecht, MS, AGAF, president of the AGA Institute.

‘THE REGISTRY IS FIRST AND FOREMOST A TOOL FOR QUALITY IMPROVEMENT, BUT IT WILL ALSO SUPPORT THE BUSINESS SIDE OF A MEDICAL PRACTICE.’

“The registry is first and foremost a tool for quality improvement, but it will also support the business side of a medical practice. We plan for the registry to help physicians participate in commercial and government programs that provide incentives for quality measurement.”

The AGA Registry will provide real-time feedback reports to practices about the care they provide. The feedback, at the provider and practice level, will allow physicians to benchmark services against data from gastroenterologists providing care to similar patients. At the patient level, the data can help practices monitor patient care and track interventions and outcomes.

“The ability to benchmark and understand where your practice is doing well, but especially where others appear to be doing better, is a critical component in quality improvement,” notes Dr. John I. Allen, MBA, AGAF, chair of the Registry Executive Management Board. “The registry will allow community and academic gastroenterologists to tap into ‘real-world’ observational data from similar practices.”

Largest GI Data Registry

The foundation of The AGA Registry is built from MedAssurant’s Medical Outcomes for Research on Economics and Effectiveness (MORE2) Registry™. Use of the MORE2 Registry™, one of the industry’s most sophisticated research data sets, has enabled the AGA Registry to launch with an unprecedented depth and breadth of clinical insight—already including extensive data on more than 4 million colonoscopy screenings and nearly 300,000 IBD cases.

These data allow for retrospective and prospective benchmarking, as well as a basis for immediate outcomes research. Practices that participate in the registry will be able to run comparative reports after 6 months of data entry.

Dr. Cary Sennett, chief medical officer at MedAssurant, added, “The AGA Registry brings great benefit by providing physicians with the information they can use to improve the quality and cost-effectiveness of care in an environment increasingly focusing on buying value. The potential to use data for CMS’ Physician Quality Reporting Initiative (PQRI) and Maintenance of Certification will also help them meet government and quality standards.”

The registry on IBD and CRC prevention is the first in a series, which will address the high-cost and high-variation aspects of care for patients with GI disease.

Possible future registries include upper endoscopy/gastroesophageal reflux/Barrett’s esophagitis/eosinophilic esophagitis, obesity, viral hepatitis, irritable bowel syndrome, ulcer disease/dyspepsia/Helicobacter pylori, GI motility, nutrition/enteral feeding/total parenteral nutrition, and advanced endoscopy procedures.

For more information about the registry or to enroll, go to http://www.agaregistry.org.
Trastuzumab Beneficial in HER2-Positive Gastric Ca

By Kerri Wachter

The addition of trastuzumab to standard chemotherapy for patients with HER2-positive advanced gastric cancer improves outcomes without reducing quality of life for patients, based on an analysis of data from a pivotal phase III study of nearly 650 patients.

Gastric cancer is one of the most common malignancies in the world, and it is the fourth leading cause of cancer death globally. While the overall 5-year survival rate is low, improvements in the treatment of advanced disease have been made. One of the key advances in the treatment of gastric cancer has been the targeting of the HER2 receptor, which is overexpressed in a subset of patients with gastric cancer.

The phase III trial, known as ToGA (Trastuzumab for Gastric Cancer), randomized 290 HER2-positive advanced gastric cancer patients to receive trastuzumab plus 5-FU and cisplatin, and another 294 patients to receive 5-FU and cisplatin alone. Overall survival, the primary end point of the study, was significantly longer in the trastuzumab arm (13.8 months), compared with the chemotherapy-alone arm (11.1 months), as reported at the 2009 ASCO annual meeting.

Importantly, this was the first trial to show a benefit from targeting HER2 with trastuzumab in HER2-positive gastric cancer. Up until now, the drug has been used exclusively in HER2-positive breast cancer.

Cisplatin was delivered at 80 mg/m² every 3 weeks for six cycles, and 5-FU was given in continuous IV infusion at 800 mg/m² on days 1-5 every 3 weeks for six cycles.

“Trastuzumab plus chemotherapy improves overall survival and progression-free survival vs. chemotherapy alone, without compromising quality of life,” said Dr. Satoh.

The researchers added that survival was significantly longer in the trastuzumab arm. “We strongly believe that this is because of the extension of progression-free survival with trastuzumab,” said Dr. Satoh.

The median EORTC QLQ-C30 global health status score improved over time for both arms, with no significant difference between the two arms. “Trastuzumab was comparable to, if not better than, the chemotherapy-alone arm,” Dr. Satoh commented.

However, these findings should be interpreted in light of diminishing patient completion of the quality-of-life questionnaire, said Dr. Cunningham. Although global health status scores for both groups of patients improved following discontinuation of chemother-apy, the number of patients who completed quality-of-life questionnaire at that time was relatively small: 36 (13%) in the chemotherapy-alone arm and 87 (30%) patients in the trastuzumab arm at week 34.

“This is a self-selected population,” said Dr. Cunningham, head of the gastrointestinal and lymphoma units at the Royal Marsden Hospital in London.

On the physical-functioning component, scores in both arms only began to improve after treatment was completed. Similar trends were seen for social and emotional function, Dr. Satoh explained. Nausea and vomiting symptom scores improved over time for both arms.

Similar trends occurred for pete-nique and constipation.

According to the EORTC QLQ-ST022 results, dysphagia scores in both arms started to improve during treatment, and continued to improve after treatment was stopped; no significant difference was seen between the two arms. Similar trends were seen for body image and hair loss scores.

There was no significant difference between the arms over time in VAS pain intensity scores. At baseline, 29% of patients used analgesic medications. During the course of the study, 2% in the trastuzumab arm and 6% in the chemotherapy-alone arm discontinued at least one medication.

Although 7% of those on trastuzumab and 6% of those receiving chemother-apy alone had no change in their medications, 20% and 17% of those groups, respectively, increased the dose or added at least one medication.

“Considering the prolongation of progression-free survival in the trastuzumab arm, this is quite important,” said Dr. Satoh. “We don’t have to compromise pain [control] of patients when we deliver trastuzumab,” he explained.

The study was sponsored by Hoff-man-La Roche. Herceptin is marketed in the United States by Genentech, in Japan by Chugai, and in Europe by Roche.

Dr. Satoh reported that he received travel support from Roche. He also has received consultancy fees from several pharmaceutical companies. Several coauthors are employed by Roche.

Dr. Cunningham reported that he is a consultant for several pharmaceutical companies and has received research funding from several pharmaceutical companies, including Roche.

GIST Relapsed Predicted by Mitotic Index and Tumor Size

By Kerri Wachter

Orlando — Mitotic index emerged as a leading predictor of relapse-free survival in a retrospective analysis of tumor tissue from a phase III study of more than 700 patients with localized primary gastrointestinal stromal tumors.

In multivariate analysis, high mitotic rate (hazard ratio 11.3, P less than .0001), tumor size (HR 2.0, P less than .0001), and location in the small bowel (HR 1.7, P = .02) were all significant prognostic factors and should be considered in making therapy choices, Dr. Martin E. Blackstein reported at a meeting on gastrointestinal cancers sponsored by the American Society of Clinical Oncology.

“These prognostic factors should be used to select patients who are at intermediate and high risk, for [adjuvant imatinib] therapy in the future,” said Dr. Blackstein, a professor of medical oncology at the University of Toronto.

The double-blind, placebo-controlled phase III American College of Surgeons Oncology Group (ACOSOG) Z9001 trial randomized patients with KIT-positive primary gastrointestinal stromal tumors (GIST) at least 3 cm in size to either adjuvant imatinib (Gleevec) or placebo for one year. Imatinib significantly improved recurrence-free survival, compared with placebo (Lancet 2009;373:1097-104).

In all, 354 patients received placebo, and 359 received imatinib. The groups were similar at baseline. Based on the results of three interim analyses, which showed 81% of patients were disease-free at 644 patients, the data monitoring committee recommended that the study be closed early.

Patients in the trial had been selected for the study by risk group, based on tumor size alone. But several studies have shown that tumor size, mitotic rate (greater than 5/50 HPF [high power field]), type of mutation (KIT vs. 11; KIT vs PDGFRA-alpha vs. wild type), and location in the GI tract (stomach vs. small bowel) influence the outcome of GIST at various stages, Dr. Blackstein noted.

In light of this, mitotic scoring was performed retrospectively by a central pathologist, who measured the mitotic rates from the tumors of 620 patients.

“In univariate analysis...it turns out that size and mitotic index are extremely important” predictors of relapse. Location within the GI tract was also an important predictor of relapse,” said Dr. Blackstein.

Using the Miettinen classification system (which includes tumor size and location and mitotic index), the researchers classified patients as being at low, medium, or high risk for relapse (Semin. Diagn. Pathol. 2006;23:70-81). Among 270 low-risk patients, relapse rates did not differ between imatinib and placebo. For 148 moderate-risk patients, the relapse rates showed a significant detrimental trend favoring imatinib (14% with placebo vs. 5% with imatinib; HR 3.2, P = .05).

“[For the high-risk [patients], there clearly is a very major benefit,” he said. In 201 patients, the relapse rate was 47% for those on placebo vs. 19% for those on imatinib (HR 3.4, P less than .0001).
Gastric Banding Achieves Durable Weight Loss in Teens

**Reviewal procedures were needed in 28%, and that rate could be higher in community practice.**

**BY MARY ANN MOON**
Elsvier Global Medical News

Gastric banding allowed severely obese adolescents to achieve a more substantial and durable weight loss than did an intensive lifestyle modification program, reported investigators regarding their prospective clinical trial of 50 adolescents.

The bariatric procedure improved overall health more effectively than the lifestyle intervention did, resolving all cases of metabolic syndrome and insulin resistance. It also improved the adolescents’ quality of life to a greater degree, according to an article published in JAMA.

Dr. Paul E. O’Brien of the Centre for Obesity Research and Education at Monash University, Melbourne, and his associates compared the two approaches in adolescents aged 14-18 years with a body mass index greater than 35 kg/m². All study subjects had related medical complications, including hypertension, metabolic syndrome, asthma, and back pain, as well as physical limitations such as inability to play sports and problems performing activities of daily living. They also reported psychosocial problems including isolation, low self-esteem, and victimization by bullies.

The subjects were randomly assigned to undergo laparoscopic adjustable gastric banding with follow-up education and guidance, or to participate in an intensive nonsurgical intervention program.

The intensive intervention program focused on achieving three goals: 1) reduced energy intake (800-2,000 kcal per day, depending on age and weight); 2) increased physical activity (more than 10,000 steps/day as measured by pedometer), which included structured exercise for at least 30 minutes per day; and 3) behavior modification.

The subjects were advised to limit time spent on sedentary pursuits such as computer or television to 2 hours per day, and to participate in bike rides, hiking trips, kickboxing events, and bowling parties with other patients. They received 6 weeks of instruction from a personal trainer and a physician, a dietician, or an exercise consultant every 6 weeks.

Twenty-four of the 25 subjects in the surgery group (96%) completed the full 2 years of follow-up, compared with 10 of the 25 participants in the lifestyle group (72%).

Twenty-one subjects in the surgery group (84%) but only three subjects in the lifestyle group (13%) achieved the primary outcome measure of losing at least 50% of their excess body weight. At 2 years, the surgery group subjects had lost a mean of 35 kg, which represents a mean loss of 28% of total body weight. In comparison, subjects in the lifestyle group lost a mean of 3 kg, which represents a mean loss of 3% of total body weight, according to the report by Dr. O’Brien and his colleagues (JAMA 2010;303:519-26).

At the inception of the study, 9 subjects in the surgery group and 10 in the intensive lifestyle group had metabolic syndrome. By the end of the study, metabolic syndrome had resolved in all 9 surgery subjects and in 6 of the 10 lifestyle subjects.

Similarly, insulin resistance was abated in more than half of the subjects at baseline. The problem resolved in all subjects in the surgery group but persisted in three subjects in the lifestyle group.

Those patients who underwent gastric banding also showed significant improvements in quality of life (QOL), specifically in the domains of physical functioning, general health, self-esteem, and family activities, whereas those who participated in the nonsurgical intervention did not show these gains.

There were no operative or postoperative complications, and the rates of adverse events were similar between the two groups.

Two girls in each group became pregnant during follow-up, an unexpectedly high rate that “suggests sexual counseling may be appropriate in association with weight-loss programs” in adolescents, the researchers said.

The authors also noted that compared with adults, adolescents may have more difficulty understanding and complying with instructions to eat only small meals and to eat very slowly in order to avoid the need for revisional procedures after gastric banding. Therefore, some additional education and supervision of eating may be helpful for this age group.

Seven patients in the surgery group (28%) required such revisions, but “the need for a revisional procedure did not compromise the weight loss outcome or lead to additional adverse events,” the investigators stated.

In an editorial comment accompanying the article, Dr. Edward H. Livingston, AGAF, of the University of Texas Southwestern Medical Center, Dallas, said that this study provides important data from a randomized, controlled trial comparing bariatric surgery with nonsurgical treatments, culminating in more level 1 evidence.

This is crucial, because the quality of the currently available evidence in support of bariatric surgery is “poor,” he said (JAMA 2010;303:559-60).

Dr. Livingston added that the 28% rate of revisional procedures in this study is particularly important “because O’Brien et al. are among the most experienced group in the world with these operations, suggesting that these complication rates will probably be higher in actual community practice.”

This study was supported in part by Allergan Inc., which provided the gastric bands.

Dr. O’Brien reported no potential conflicts of interest, but one of his associates is a consultant for Allergan, Bariatric Advantage, Scientific Intake Ltd., SP Health Co., Optifast, Abbott Australasia, Eli Lilly Australia, Merck Sharp & Dohme Australia, Nestle Australia, and Roche Products Australia. Dr. Livington reported no potential conflicts of interest.

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**Simple Device Helps Obese Adolescents Eat Less**

**BY JENNIE SMITH**
Elsvier Global Medical News

A computer device used to treat anorexic patients has been shown to be effective in treating adolescents with obesity, reducing patients’ body mass index and rate of food consumption even 6 months after completion of treatment and monitoring, researchers reported in BMJ.

The Mandometer, as the device is called, was developed at the Karolinska Institute in Stockholm. It consists of a scale placed beneath the plate of food, and a small monitor that helps patients compare and align their perceptions of satiety, in real time, with those of a normal eater.

Anorexic patients at Mandometer, in Stockholm, the United States, and Australia have used the device to retrain themselves to eat more food than would typically cause them feel full.

However, “with obesity it teaches patients to eat slower,” Per Södersten, Ph.D., one of the report’s authors and the inventor of the device, said in an interview. “Otherwise, the principles are identical.”

The report presents results from a randomized, controlled trial of 106 obese patients between the ages of 9 and 17 at the Bristol (England) Royal Hospital for Children. Dr. Julian P. H. Shield led the study along with Anna L. Ford, a research nurse trained at a Mandometer clinic in Sweden.

Approximately half of the participants (54 adolescents) were trained to use the device during evening meals at home, while the other 52 participants received standard care consisting mostly of advice on exercise and nutrition. The same advice was also provided to the Mandometer group (BMJ 2010;340:b5388).

After a year, the Mandometer group showed significant improvements in body mass index. For the 91 patients total in the two groups who were assessed at 12 months, the mean adjusted standard deviation score difference between the two groups was 0.27, the report said. Importantly, that difference was maintained at 18 months, which was 6 months after treatment and monitoring had ceased.

The authors noted that nine patients were lost to follow-up in the Mandometer group, six were lost in the standard-care group. Although their Mandometers had been taken away, the participants still tended to eat significantly smaller proportions than they had before beginning treatment.

The discovery of maintained weight loss and consumption of smaller portions 6 months after the end of treatment “was probably the best bit,” Dr. Shield said in an interview.

“We specifically chose adolescents because they’re a difficult group to persuade to eat better and exercise. But by doing this extra thing to help them eat more slowly, it allows them to curtail their portion sizes.”

Using a computer to track eating habits is not entirely novel, said Dr. Södersten, who cited research dating back to the 1960s in the United States, and the 1970s in Germany.

“We followed that tradition and realized the device could be used for clinical intervention,” he said.

The adolescent subjects in the Bristol study adapted well to using the device, Dr. Södersten said. “Young people like computers and they’re used to them. They comply better because it’s fun for them.”

Dr. Södersten and another coauthor own shares in the company that manufactures the Mandometer. The study was funded by the BUPA Foundation. The Mandometers were loaned to the research team at no cost.
Oncolytic Poxvirus Promising Against Advanced HCC

BY BRUCE JANCIN
Elsevier Global Medical News

VIENNA — A targeted oncolytic poxvirus designed as a novel, three-pronged therapy for advanced hepatocellular carcinoma drew responses from most patients in an interim analysis of a phase II study—and led to 1-year survival rates that were considerably higher than historical data for sorafenib or placebo.

Intratumoral injections of the genetically altered poxvirus, known as JX-594, resulted in an objective response at 8 weeks by RECIST (Response Evaluation Criteria in Solid Tumors) criteria in 15 of 17 patients in the phase II study, which continues to enroll patients, Caroline J. Breitbach, Ph.D., said at the International Liver Congress sponsored by the European Association for the Study of the Liver.

In all, 8 of 17 patients had an 8-week response by Choi criteria, developed at the University of Texas M.D. Anderson Cancer Center in Houston. These criteria rely on significant tumor necrosis, as reflected in at least a 15% reduction in average tumor density on dynamic contrast-enhanced MRI, noted Dr. Breitbach of Jennerex Biotherapeutics Inc., which is developing JX-594.

“Dr.-Breitbach said that Choi responses were reported to occur also in extrahepatic tumors that weren’t directly injected. This phenomenon is being systematically evaluated in a separate, ongoing phase II study,” she said.

The tumor vascular disruption is accomplished through direct injection of endothelial cells that are associated with the tumor vasculature, as well as by generation of an inflammatory response causing microvascular thrombosis within the tumor, Dr. Breitbach said.

The virus platform for JX-594 is a vaccinia virus strain used in the smallpox eradication program. “It’s been given to hundreds of millions of children worldwide,” she observed.

The virus has been engineered to selectively replicate in and destroy cancer cells that are distinguished by activation of the epidermal growth factor receptor pathway.

Thyroid Drug Linked to Severe Liver Injuries, Deaths

BY ELIZABETH MECHCATTIE
Elsevier Global Medical News

Severe liver injuries have been associated with use of the anti-thyroid drug propylthiouracil, and the Food and Drug Administration has added a boxed warning to the product’s label conveying this risk, the agency announced.

The warning for propylthiouracil (PTU) says that there have been reports of severe liver injury and acute liver failure—including fatalities—in adults and children who’ve been treated with the drug. Additionally, the agency said, for patients who are beginning treatment for hyperthyroidism, “it may be appropriate to reserve use of propylthiouracil for those who cannot tolerate other treatments such as methimazole, radioactive iodine, or surgery.”

PTU was approved in 1947 for the treatment of hyperthyroidism.

The warning also includes a statement concerning preferential prescribing of the drug for patients in early pregnancy. The warning notes that because birth defects have been associated with use of the anti-thyroid drug methimazole during the first trimester, “propylthiouracil may be the treatment of choice during and just before the first trimester of pregnancy.”

The FDA issued a warning to health care professionals about PTU’s hepatotoxicity in June 2009 and has added the boxed warning as part of the Risk Evaluation and Mitigation Strategy (REMS) for the drug—a result of the agency’s review of postmarketing reports of adverse events associated with PTU as well as meetings with various physician groups and the National Institute of Child Health and Human Development, according to the statement.

The FDA requires a REMS for a drug when it determines that a risk management strategy is needed to ensure that the benefits of a drug outweigh its associated risks.

Of the 34 cases of severe liver injury associated with PTU that were identified by the FDA, 23 were in adults (and included 13 deaths and 5 liver transplants), and 11 were in pediatric patients (and included 2 deaths and 5 liver transplants).

Although the 34 cases were reported between 1969 and 2009, the FDA added this information to a boxed warning now because of the severity of these cases “and to ensure that healthcare professionals are aware of this risk and are vigilant for the signs and symptoms of hepatic toxicity,” the statement added.

Information about PTU use during early pregnancy was based on a review of postmarketing data on PTU and methimazole. The review indicated that reports of congenital malformations were about threefold greater with methimazole than PTU, and there was a “distinct and consistent” pattern of congenital malformations associated with methimazole but not PTU.

More information is available at www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm209623.htm. Serious adverse events associated with PTU should be reported to the FDA at 800-332-1088 or www.fda.gov/medwatch/.
Progression-free survival doubled, but overall survival could not be assessed because of early termination.

By Kerri Wachter
Elsevier Global Medical News

Orlando — Treatment with sunitinib, an oral tyrosine kinase inhibitor, doubled median progression-free survival from 5.5 months to 11.4 months among patients with advanced pancreatic neuroendocrine tumors in a randomized, placebo-controlled, phase III trial.

A data-monitoring committee stopped the 171-patient study early after an analysis revealed that progression-free survival, the primary end point, was much longer in the active treatment arm. Dr. Eric Raymond reported at a meeting on gastrointestinal cancers sponsored by the American Society of Clinical Oncology. The hazard ratio for disease progression with sunitinib (Sercert) was 0.418, compared with placebo (P = .0001).

The findings are important for this small patient population, given that “there are a limited number of medical treatments that so far improve progression-free survival or overall survival in this disease,” he said.

It’s not completely clear, however, how important these results are, because of the early termination. “There were many events that were censored after 18 months,” because the study was stopped early, noted Dr. Raymond, a medical oncologist at Beaumont University Hospital in Glichy, France.

The researchers censored 56 patients in the sunitinib arm and 34 on placebo, meaning that the analysis of progression-free survival was based on 30 patients in the sunitinib arm and 51 in the placebo arm.

Although the results are impressive, they should be interpreted with some caution, Dr. Jennifer C. Obel commented in an interview. “Statistically significant results may not be clinically meaningful,” said Dr. Obel, a member of ASCO’s Cancer Communications Committee and an oncologist at NorthShore University HealthSystem in Illinois.

Early termination of trials, as in this case, is complicated by the following two issues, she suggested:

▸ Is the number of patients included in the analysis enough to change clinical practice? “Are we gathering the appropriate amount of information”?

▸ Is progression-free survival a legitimate early stopping point, or should we really be waiting for overall survival?”

Dr. Malcolm J. Moore, professor of medicine and pharmacology at Princess Margaret Hospital in Toronto, commented in an interview, “This is an important study because of the relative paucity of comparative trials in this area, and because it compares sunitinib to the current standard of care. The degree of difference that was seen—a doubling of progression-free survival—is significant.”

Although the trial was halted early before an overall survival benefit (if any) could be detected, it is reasonable to assume that a difference in progression-free survival of this magnitude will in time translate into an overall survival benefit. “I therefore think it was appropriate for the data-monitoring committee to stop the study, and announce the results,” Dr. Moore said.

The trial enrolled patients in Europe, Asia, the United States, and Australia between June 2007 and April 2009. Patients were eligible if they had well-differentiated, malignant pancreatic neuroendocrine tumors that had progressed during the previous 12 months.

The active treatment consisted of 37.5 mg/d of oral sunitinib. All patients were allowed to receive best supportive care and somatostatin analogs.

The two arms of the trial were not completely balanced. Most patients on sunitinib (62%) had a baseline ECOG (Eastern Cooperative Oncology Group) performance status score of 0; the other 38% had an ECOG score of 1. In the placebo arm, patients were more evenly mixed between an ECOG score of 0 (48%) and 1 (51%); one patient had an ECOG score of 2.

At baseline, roughly half of both arms (49% and 52% in the sunitinib and placebo arms, respectively) had functioning tumors, the investigators reported.

Functioning types included gastrinomas (11% of sunitinib patients, 12% of placebo patients), glucagonomas, (4% sunitinib, 2% placebo), insulinomas, (2% sunitinib, 2% placebo), VIPomas (0% sunitinib, 2% placebo), and other/multiple neuroendocrine tumors (13% sunitinib, 6% placebo). Tumor-functioning status was not available for 22% of patients in the sunitinib arm and 24% of those in the placebo arm.

Nearly all patients in each arm (95% in the sunitinib arm and 94% in the placebo arm) had distant metastases. The median time from diagnosis was 3.2 years for the placebo arm, but only 2.4 years for the sunitinib arm. The use of concomitant somatostatins was similar in both arms (21% for the sunitinib arm and 22% for the placebo arm).

The primary end point was progression-free survival. Secondary end points included overall survival, overall response rate, time to tumor response, safety, and patient-reported outcomes.

For the analysis of overall survival, 77 patients in the sunitinib arm and 64 on placebo were censored. Before the study was halted, 9 patients had died in the sunitinib arm at a median follow-up of 11.1 months, and 21 patients had died in the placebo arm with a median follow-up of 10.2 months. Median overall survival was not reached for either arm, said Dr. Raymond. The hazard ratio for overall survival favored sunitinib (HR, 0.409; P = .0204) vs. placebo.

This was a well-designed, phase III, randomized study, said Dr. Obel, adding that she would use this drug for her patients, based on the study results, with the caveat that patients need to be informed that sunitinib has been shown to lengthen survival without disease progression, but not necessarily to lengthen overall survival.

The objective response rate for the sunitinib arm was 9.3% by RECIST (Response Evaluation Criteria in Solid Tumors). The median duration of response was 8.1 months, and 35% of the patients on sunitinib had stable disease for at least 6 months, compared with 29% of patients on placebo.

“Adverse events observed with sunitinib continuous daily dosing were generally tolerable and [were] manageable by dosing interruption, dose reduction, and/or standard medical therapy,” Dr. Raymond noted.

The most common adverse event of any grade in both groups was diarrhea, followed by nausea and vomiting. The most common adverse events of grade 3 or greater for the sunitinib arm were neutropenia (12%) and hypertension (10%). There was one grade 3 or greater hypertension event in the placebo group, but no serious neutropenia.

“There has been significant debate among clinicians in specialty cancer centers about the appropriate treatment of rare pancreatic neuroendocrine tumors. It has been known for some time that these are highly vascular tumors, and it is therefore logical to test new antivascular therapies against them,” said Dr. Moore.

“Smaller studies have shown that agents such as bevacizumab and sunitinib have benefit in some patients with this tumor type, yet because many of these patients have very slow-growing tumors, it is often difficult to judge the value of specific therapies,” Dr. Moore added.
**Surgical Outcomes Appear Unaffected by Work Hours**

**San Antonio** — Surgical residents performing laparoscopic appendectomies or cholecystectomies achieved comparable outcomes during a 16-hour shift and from 16 to 30 hours in a retrospective study that may have implications for proposed surgery resident work hour restrictions.

“Despite contrary information, the Institute of Medicine is calling for new restrictions on resident work hours, such as a de facto 56 hours per week, elimination of 24+ hour call, and a 5-hour nap requirement during 30-hour shifts,” Dr. Arezou Yaghoubian said at the annual Academic Surgical Congress. The Accreditation Council on Graduate Medical Education has not yet adopted these recommendations.

In a multivariate analysis, Dr. Yaghoubian and her colleagues found that procedures performed by residents beyond a 16-hour shift had outcomes comparable to those performed during a regular 16-hour work day. “Instituting a 5-hour rest period at night is unlikely to improve outcomes of two of the most commonly performed operations in residency,” she said.

The researchers compared 875 daytime (6 a.m.-10 p.m.) and 708 nighttime laparoscopic appendectomies at Harbor UCLA Medical Center in Los Angeles, where Dr. Yaghoubian is a surgical resident. They also compared 2,512 daytime and 386 nighttime laparoscopic cholecystectomies. Residents admit and manage all such patients at Harbor UCLA, a level 1 trauma center that has a large volume of patients with biliary disease and acute appendicitis.

Procedures were performed between July 2003 and March 2009. Total complications, bile duct injury, conversion to an open operation, length of surgery, and overall mortality were the study outcomes. Mean patient age in both appendectomy groups was 24 years. The median length of laparoscopic appendectomy was 60 minutes during the daytime (within 16 hours of shift start) and 58 minutes at night (after 16 hours and up to 30 hours). The open conversion rate was 4% during the day and 5% at night, and the intraoperative complication rate was 0.3% during the day versus 0% at night. Overall complication rates were 2% vs. 1%, respectively.

The postoperative abscess rate was 2.5% in the daytime group versus 1.3% at night, the only significant difference. There was one patient death, in the nighttime group, Dr. Yaghoubian said. The median length of laparoscopic cholecystectomy was 94 minutes during the daytime and 95 minutes at night, and rates of conversion to open surgery were 10% and 11%, respectively.

“There was no [significant] difference in intraoperative complication rate or bile duct injury rate according to time of day or night,” Dr. Yaghoubian said. The intraoperative cholecystectomy complication rate was 0.7% during the day versus 0.5% at night, and the overall complication rate was 2.2% versus 2.3%.

The major bile duct injury rate was 0.2% in the daytime versus 0.5% at night. The overall bile duct injury rate was 0.6% during the day versus 0.3% at night. “There was one death, this time in the daytime group,” Dr. Yaghoubian said.

Meeting attendees asked about the role of attending physician involvement. For cholecystectomies, an attending is typically in the room looking at the critical view, she replied. For appendectomies, they are in the room but not necessarily scrubbed in. “My job as an attending is to contribute when residents appear tired. It could be attendings are a compensatory mechanism,” said Dr. Justin Dimick of the University of Michigan, Ann Arbor, who was not affiliated with the study.
Progress Seen in Endoscopy Capsule Technology

Capsules may prove most useful for patients who refuse colonoscopy, or for whom it is high risk.

BY DAVID MONAGAN
Elsevier Global Medical News

London — New generations of endoscopy capsules may soon yield enhanced imaging and perhaps even remote-controlled therapy of the entire GI tract, presented at the 13th World Congress of Gastroenterology.

“What are we striving for?” Dr. Rami Eliakim, chairman of medicine at Rambam Medical Center, Haifa, Israel, asked in an overview presentation. “We want new technologies and smaller pills; we want better controls; and we want better detection of pathology and expanded therapeutic options. We want to broaden our indications and motility.”

NEWLY RELEASED CAPSULES

Advances in diagnostic specificity have already been seen with Given Imaging’s new PillCam Colon 2 device—being released in Europe this year—which delivers 35 images/sec when in transit or 4 images/sec when stationary, Dr. Eliakim said. The 11 mm x 31 mm capsule incorporates bidirectional tracking and employs a built-in polyp size estimator and 172-degree-wide viewer angle when the capsule is stationary, allowing the operator to increase the image capture rate.

A five-center study of 98 patients with suspected colon pathology found the device had a sensitivity of 88% and a specificity of 89%, compared with colonoscopy, in detecting polyps 10 mm or greater. For polyps of 6 mm or more, specificity was 76%, Dr. Eliakim said.

The Colon 2 capsule may be a safe, minimally invasive option for patients who are unwilling to undergo colonoscopy, have undergone an incomplete examination, or those for whom colonoscopy is contraindicated, he said.

The size of the capsule devices will soon be cut by nearly half, alleviating the problem of retention. And the newly released EndoCapsule 1.02A software from Olympus Imaging America Inc. has improved overview and quick-viewing modes that should significantly speed up the slow work of polyp analysis.

In an interview, Dr. Douglas K. Rex commented, “The new capsule with higher frame speed shows promise, but the issue of poor preparation, despite a very aggressive preparation regimen that is challenging to patients, continues to loom over capsule colonoscopy. Intense effort to solve the preparation problem is needed.”

“Even effective capsule colonoscopy will probably seldom replace conventional colonoscopy, because the capsule is expensive and nontherapeutic. More likely, if the capsule can achieve adequate performance, it could be used when conventional colonoscopy is contraindicated or high risk,” said Dr. Rex, distinguished professor of medicine at Indiana University, Indianapolis, and director of endoscopy at Indiana University Hospital.

Even better, some patients who are afraid or unwilling to undergo conventional colonoscopy might do the capsule exam, leading to increased colorectal cancer screening adherence. In this instance, we would accept lower performance compared to conventional colonoscopy, but we need proof from clinical studies that the test will increase adherence before we make the test available for this purpose,” Dr. Rex noted.

Capsules in Progress

Advanced work is being done with electric-field propagation with the Korean MiRO capsule from IntroMedic Co., which aims to use the human body itself as a conductive medium for systemic data transmission.

Also promising, Dr. Eliakim said, is the 11 mm x 26 mm Pill from Koninklijke Philips Electronics NV, which contains a microprocessor with temperature and pH sensors designed to better detect suspicious lesions and control the release of steroids and other drugs at the target point where they are needed. “It contains an ultrafrequency wireless receiver that will activate the capsule at the right time and release the drug into the right place,” Dr. Eliakim noted.

Beetles and Joysticks

The push is on for capsules with the ability to orient and move up and down the gastrointestinal tract, while the clinician controls the movement externally with a joystick-like device.

In the Vector (Versatile Endoscopic Capsule for Gastrointestinal Tumor Recognition and Therapy) project, a European Union-funded group is continuing its development of a capsule with miniature ‘legs’ that allow the device to crawl like a beetle to the point where it can stop and deploy on-board tools for not only visualization but also to perform a biopsy or deliver drugs.

Researchers at Carnegie Mellon University, Pittsburgh, are working on related technology, using bioadhesives that will enable the capsule to anchor itself to the intestinal wall where needed. Meanwhile, German and English researchers have begun experimenting with using external magnet paddles in an attempt to better control and orient magnetized PillCam capsules.

Reporting on the pilot study of this approach, Dr. Jutta Keller of the University of Hamburg, Germany, said that his group tried this approach on 10 healthy volunteers (mean age 25) who agreed to undergo both conventional capsule endoscopy and the experimental modality (in randomized order, 1 week apart). External operators were able to make the test capsules rotate successfully during esophageal transit in 9 of 10 cases.

The results were mixed, although none of the experimental procedures resulted in pain or damage to the lining of the GI tract. In two cases, the magnetic capsules turned around when swallowed, leaving the camera pointing in the wrong direction. “The magnetic forces were not strong enough to fully hold the capsules where the operators desired, or satisfactorily counteract peristalsis,” Dr. Keller acknowledged.

In fact, the esophageal transit times in both arms of the experiments were highly variable, at anywhere from 111 to 1,514 seconds in the magnetically guided arm, and 47 to 1,474 seconds in the controls. Half of the test procedures also resulted in a sensation of uncomfortable retrosternal pressure during manipulation. Further, the test capsules yielded visualization that was inferior to that of the conventional capsules (4 vs. 16 frames/sec).

Dr. Keller said that the new magnetic capsules will be tested in the stomach next, although the ultimate goal for this technology will be to enhance the more difficult visualization of the small intestine. “At this point, we would have to say the new technology is not advanta-
geous,” he said.

Dr. Eliakim disclosed that he has served as a consultant for Given Imaging, but not in the past year.

CLINICAL CHALLENGES AND IMAGES

The Diagnosis

Answer to “What’s Your Diagnosis?” on page 6: Deep Venous Thrombosis due to Idiopathic Megarectum and Giant Fecaloma

The patient was diagnosed with deep vein thrombosis and intestinal pseudo-obstruction secondary to giant fecaloma. Anticoagulation was started. Although the fecal impaction was initially treated with laxatives, enemas, and manual extraction, these measures failed.

The patient suffered a progressive clinical deterioration and required surgery. Resection of the middle and lower mesocolon, manual extraction of the fecal impaction, proctectomy, and terminal colostomy were performed following Hartmann’s technique. The histopathologic study revealed hyperplasia of the muscularis mucosae, submucosal fibrosis, and minimal inflammatory infiltration with the presence of ganglion cells, compatible with idiopathic megarectum. The initial postoperative recovery was favorable.

Intestinal constipation with fecal impaction is a common and underestimated problem. When associated with persistent intestinal dilatation in the absence of an organic cause, it is called idiopathic megarectum. Depending on the segment affected, 3 types are distinguished: megacolonic, megarectum, or both. Symptoms may begin in infancy or adulthood, and recurrent fecal impaction is common (it is called fecaloma in extreme forms).

Fecal incontinence, abdominal pain, and distention or mass that may appear as an abdominal tumor are also noted (1). Abdominal computed tomography was the diagnostic procedure in our case, while other alternatives include a barium enema or flexible rectosigmoidoscopy (2). The initial management is conservative, including enemas with per- iodic disimpaction and manual evacuation. Occasionally, general anesthesia and intravenous or long-term polyethy- neneol are used (2).

Surgical intervention is indicated in cases of refractory constipation, intolerance to medical treatment, and secondary complications (3). Proctectomy with coloanal anastomosis and vertical reduction colopexy are the most commonly performed procedures (3).

The complications described include stenosis and ulcer, which may lead to spontaneous colonic perforation associated with high mortality, scatica caused by sacral nerve root compression, as well as recurrent volvulus and overt obstruction with secondary hydronephrosis (1). Our case involved an exceptional complication—compression of the inferior vena cava and deep vein thrombosis.

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High Intake of Animal Protein May Raise IBD Risk

BY KERRI WACHTER
Elsevier Global Medical News

O RLANDO — More attention needs to be paid to intermedi-
ate-risk factors for inflammatory bowel disease, according to inves-
tigators who demonstrated a significant relationship of tumor and node
categories to overall survival, relapse, and risk of IBD in a phase III chemoradiation
trial. Patients who had two risk factors—a high T category based on tumor size, and nodal
involvement (N3)—have the worst survival and highest re-

dapse rates, Dr. Leonard L. Gun
derson told attendees at a meeting on gastrointestinal can-
cer, sponsored by the American Society of Clinical Oncology.

Patients with T2 and T3 tu-
mors and zero lesions had the
best outcomes, he said, “and we
do have this interesting inter-
mediate group with T4 nodes negative and T2-2N3-3 that have inter-

deval grades in combination with chemotherapy, and not be
satisfied with the status quo.”

The Intergroup Radiation
Therapy Oncology Group (RTOG) 98-11 trial, Dr. Gun-
derson noted, “established” a new category, T3-4N0, for patients who were treated with
5-fluorouracil (5-FU) plus mitomycin concurrent with radiotherapy as a standard of care for anal cancer (JAMA 2008;299:1941-
21). In the new TN analysis, the investigators reviewed 311 pa-
tients who were treated with the mitomycin regimen and 104 patients who were treated with
5-FU, capcitabine, and radiation.

“T2-3N0 patients clearly do better with survival when compared to the moderately high-risk and high-risk groups,” Dr. Gunderson said, noting that overall survival and disease-free survival rates dropped contin-

uously with increasing T category in the node-negative patients.

The data on colostomy failure also showed a clear trend toward greater failure with in-
creasing T number among node-negative patients. “Interestingly, we see that colostomy
failure is related to T category, not TN category,” he said.

The same patterns appeared in the 5-year data on locore-
gional relapse, but not in the data on distant metastases. The locoregional recurrence rate was 20% with T2-3N0 disease, 42% with T2N+T4N0 disease, and 60% with T3N+T4N0 disease, reported Dr. Gunderson.

He reported that the 5-year overall survival rate was 80% for patients with T2-3N0 dis-

ease, 64% for those with T2N+T3N0, and 43% for those with T3N+T4N0 disease. Likewise, disease-free survival rates at 5 years showed a steady decline at 67%, 40%, and 29%, respecti-

ingly. These results were highly significant statistically.

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Athough patent law is not usually a topic that instills much passion, media outlets have recently covered a court ruling on DNA patenting that has the genomics world in a twist.

Superficially, it may seem absurd that a human gene should be patentable, any more than a toenail or an eyelash is patentable. The U.S. Patent and Trademark Office (USPTO), however, has for some time held that genes are patentable. In fact, many people may be surprised to learn that an estimated 20% of human genes are already patented. (Rest assured, though, that your genes are your own as long as the sequence stays in your body.)

The potential reach of gene patents is substantial. In some cases, an infringement can be claimed when the gene sequence is determined outside of an individual’s body for any purpose, even in the setting of research studies.

On March 29, 2010, in a case (Association for Molecular Pathology et al. v. USPTO et al.) involving Myriad Genetics and the American Civil Liberties Union (ACLU, U.S. District Court Judge Robert W. Sweet invalidated long-held patent claims of Myriad Genetics and the University of Utah regarding the BRCA1 and BRCA2 genes. Mutations in these genes are associated with highly increased risk for breast, ovarian, and other cancers in the approximately 1 in 500 individuals who are affected. The invalidation of these claims could signal the end of Myriad’s monopoly on a potentially life-saving genetic test that currently costs several thousand dollars.

The basis for gene patents rests in part on establishing the novelty, nonobviousness, and usefulness of the subject of the patent. A patent cannot be obtained for a natural product such as copper, and an animal species cannot be patented.

The convoluted but internally coherent logic underlying human gene patents rests largely on the methodology used to discover the gene sequence in question and not on the information content of the sequence. The ACLU directly challenged this logic, arguing that the content of the gene sequence is what matters, and not the method by which it is derived. Furthermore, the ACLU asserted that the information content itself is naturally occurring, and not patentable.

If the recent ruling, which is in agreement with the ACLU argument, is upheld, this case would set a precedent for other challenges to existing gene patents with potentially great consequences for the biotechnology industry. Myriad has stated that it is planning to appeal the ruling, and the case may eventually reach the Supreme Court.

The answer to whether gene patents are good or bad is not a simple one. Patents are intended to provide financial incentives for the research and development work necessary to bring a new product, such as a genetic test, to market by granting a temporary monopoly to the patent holder in exchange for public disclosure.

In fact, patents are an extremely important part of the foundation of our economy, and are provided for in Article I of the U.S. Constitution.

Clearly, an entity that is capable of investing millions of dollars to perform groundbreaking research to bring a new genetic testing method to market is entitled to protect its innovation from competitors. The invalidation of Myriad’s patent claims could signal the end of the current system for gene diagnostics.

The outcome of the appeal of the Myriad Genetics case will have consequences for biotechnology companies, insurers, researchers, health care providers, and patients who require genetic testing for years to come. Clinicians can expect to see more on the topic of gene patenting in the headlines over the next year as the Myriad Genetics case unfolds.

Dr. Feero is special adviser to the director of National Human Genome Research Institute and is also a faculty member of the Maine Dartmouth Family Medicine Residency Program in Fairfield.

GENOMIC MEDICINE
A New Twist in DNA

BY GREG FEERO, M.D., PH.D.
Data Don’t Support Isotretinoin-Colitis Connection

BY BRUCE JANCIN AND MICHELE G. SULLIVAN
Elsevier Global Medical News

WAIKIKI, HAWAII — Two studies—both conducted by gastroenterologists—refute the notion that isotretinoin causes inflammatory bowel disease. Neither study found a basis for allegations of an increased risk of inflammatory bowel disease (IBD) in patients who were treated with isotretinoin.

“There has been a lot of concern about this. You can’t say anything with certainty in life, but at least thus far, the data we have are very reassuring that there is no association,” Dr. Sheila Fallon Friedlander said at the annual Hawaii Dermatology Seminar sponsored by Skin Disease Education Foundation.

She cited a retrospective, nested case-control study by investigators at the University of Manitoba, Winnipeg, who used the comprehensive provincial IBD database to demonstrate that patients with IBD were no more likely to have used isotretinoin before diagnosis than those who had not been treated with the drug.16-21

“Although there may be anecdotes of isotretinoin causing ‘acute colitis,’ our data suggest that isotretinoin is not likely to cause chronic IBD,” the investigators concluded (Am. J. Gastroenterol. 2009; 104:2774-8).

Dr. J. Mark Jackson of the University of Louisville (Ky.) characterized the Manitoba study as “a really well-done study coming at a critical time,” conducted by physicians who deal with IBD and, therefore, have no stake in protecting a drug that could cause it.

The second study was a seven-country, systematic data search led by gastroenterologists at the University of North Carolina at Chapel Hill, who found “no clear relationship” between the use of isotretinoin and IBD. Unlike the earlier study, this analysis used the rigorous Chapel Hill criteria designed to weigh the strength, consistency, specificity, and plausibility of scientific evidence, and on that basis, the investigators determined no causal association had been established (Am. J. Gastroenterol. 2009; 104:2187-93).

“We now have some very good data reviews showing that IBD is not overrepresented in patients who take isotretinoin,” Dr. Jackson said in an interview. “When this issue comes up [in prescribing], we need to make people aware that this rumor has not been validated.”

Dr. Maria T. Abreu commented in an interview, “As gastroenterologists taking care of patients with IBD, the more common problem is that patients have severe, cystic acne for which nothing has worked. Acne can leave someone permanently scarred. Therefore, based on these studies, I would reassure my patients that if all other things have been tried and that to use retinoids, I would prescribe them.”

There has been a lot of concern. ‘At least thus far, the data we are very reassuring that there is no association.’

DR. FRIEDLANDER

Wider Waist Raises Risk of Rectal Ca Surgery Complications

BY HEIDI SPLETE
Elsevier Global Medical News

Wast circumference is more effective than body mass index at predicting complications after abdominal surgery, based on data from 150 rectal cancer patients.

“Our study is the first to use waist circumference to predict surgical complications,” Dr. David Berger of Baylor College of Medicine in Houston said in a teleconference in advance of the annual Digestive Disease Week. The findings were also presented during the meeting.

Previous research has shown that being overweight or obese can impede postsurgical recovery, but the specific impact of abdominal fat in particular on postoperative complications after abdominal surgery remains uncertain, Dr. Berger said.

Dr. Berger and his colleagues hypothesized that the use of BMI to assess patients for obesity does not accurately predict complications after abdominal surgery.

“It is our contention that BMI misses the nuances of obesity because it is un- able to demonstrate where the fat is distributed on the patient,” the corresponding author, Dr. Courtney Balentine, a fellow in surgical research at Baylor.

The investigators suggested that measuring waist circumference to estimate the amount of adipose tissue around the midsection would be a more accurate indicator than BMI of increased risk for complications after abdominal surgery.

In this study, the researchers reviewed data from 150 consecutive rectal cancer resection procedures performed in 2002-2009. The average patient age was 65 years, and the mean BMI was 28 kg/m2. Patients were divided into three groups based on waist circumference: less than 101.5 cm, 101.5-114 cm, and greater than 114 cm.

A larger waist circumference was a significant predictor of increased risk of complications after surgery. Specifically, the risk of superficial infection in patients with a waist circumference greater than 114 cm (approximately 4 inches) was 61%, compared with 28% in patients with a waist circumference less than 101.5 cm. The risk of surgical site infections was almost 50% in the largest-waist group, compared with 14% in the smallest-waist group.

Greater waist circumference was also associated with an increased risk of wound disruption, dehiscence, and re-operation, but these associations fell short of statistical significance.

In addition, the odds of infection doubled each time the waist circumference increased by 1 cm (approximately 4 inches), Dr. Berger noted.

The results remained significant after controlling for age, ethnicity, smoking, diabetes, hypertension, coronary artery disease, operative time, and the use of laparoscopic vs. open surgical technique.

BMI was not found to be a significant predictor of any type of postoperative complication.

Based on these findings, waist circumference might be useful to clinicians as a direct measure of central adiposity, and it can be used to identify abdominal surgery patients who may need more aggressive infection control, such as higher doses of antibiotics, Dr. Berger said.
Panitumumab Beneficial in Subset With Metastatic CRC

BY KERRI WACHTER
Elsevier Global Medical News

ORLANDO — The monoclonal antibody panitumumab extended progression-free survival and overall survival, each by a median of 2 months, when added to second-line treatment of metastatic colorectal cancer in patients with wild-type KRAS tumors, investigators reported.

Patients with KRAS mutations did not benefit from the addition of panitumumab ( Vectibix ) to a FOLFIRI regimen in the phase III trial, which enrolled more than 1,100 patients, Dr. Marc Peeters said at a meeting on gastrointestinal cancers sponsored by the American Society of Clinical Oncology.

Panitumumab targets the epidermal growth factor receptor (EGFR), and was approved in 2006 as a single agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. In July 2009, the Food and Drug Administration amended the panitumumab label to say it is not recommended “in patients whose tumors had KRAS mutations in codon 12 or 13.”

The current randomized, open-label study was planned as a comparison of panitumumab plus FOLFIRI (leucovorin, 5-fluorouracil, and irinotecan) with FOLFIRI alone in the entire randomized population, but the investigators amended the protocol to focus on testing the efficacy of panitumumab in the wild-type KRAS subset. Patients had to have documented disease progression within 6 months of fluoropyrimidine-based therapy to enter the trial.

In all, 591 patients were randomized to receive 1 mg/kg of panitumumab every 2 weeks plus FOLFIRI, and 395 patients to FOLFIRI alone. More than half the participants had wild-type KRAS status (56% of the panitumumab-FOLFIRI group and 54% of the FOLFIRI-alone group), said lead author Dr. Peeters of the University Hospital Ghent (Belgium).

Among patients with wild-type KRAS, he reported that median progression-free survival reached 5.9 months with panitumumab plus FOLFIRI, and 3.9 months with FOLFIRI alone (hazard ratio, 0.71; P = .004). Median overall survival was 14.5 months for those on panitumumab plus FOLFIRI vs. 12.5 months for those on FOLFIRI alone, but this was not statistically significant (HR, 0.85). Progression-free and overall survival were co-primary end points of the study.

The objective response rate (complete and partial responses) among patients with wild-type KRAS was 35% with panitumumab plus FOLFIRI vs. 10% with FOLFIRI alone (P less than .001). No patients had a complete response, and stable disease was achieved by 39% of the combination group but only 10% of those given FOLFIRI alone.

Among patients with mutant-type KRAS, the addition of panitumumab did not make a difference in any of these measures. Again, no patients had a complete response.

The findings highlight the need for therapies for patients with mutant KRAS, commented the invited discussant, Dr. Randolph Hecht. “In KRAS-mutant patients, this is clearly a place where there is an unmet need for new drugs and creative thinking,” he said.

The benefits of panitumumab came at the cost of increased toxicity, added Dr. Hecht, director of the gastrointestinal oncology program at the University of California, Los Angeles.

At least 90% of patients on panitumumab had some degree of skin toxicity, said Dr. Peeters. Grade 3/4 skin toxicity was reported in 37% of patients with wild-type KRAS, and 32% of patients with mutant-type KRAS. Panitumumab did not add to the rate of grade 3/4 diarrhea in patients with wild-type or mutant-type KRAS.

The researchers also evaluated patient-reported outcomes using the EQ-5D OHR (Overall Health Rating) and HSI (Health State Index) until disease progression. The HSI assesses mobility, self-care, anxiety/depression, usual activities, and pain/discomfort. Patient-reported outcomes and disease status were assessed. “In the wild-type KRAS subset, a significant and clinically meaningful difference in favor of panitumumab was observed in the EQ-5D OHR but not in the multidimensional HSI,” said Dr. Peeters.
MOC Process Expected to Be an Alternative to PQRI

BY ALICIA AULT
Elsevier Global Medical News

A little-noticed provision of the health reform law will let physicians use data collected and reported as part of the maintenance of certification process as an alternative to the Medicare Physician Quality Reporting Initiative.

The details have yet to be worked out, but it would mean that physicians likely would have at least one fewer process to do, to report their quality data, said Dr. Christine Cassel, president and CEO of the American Board of Internal Medicine.

The advantage of the maintenance of certification (MOC) process is that physicians are familiar with it, as more than 80% of all physicians participate, Dr. Cassel said in an interview.

Physicians have been eligible to receive bonuses for participation in the Medicare PQRI, but many view it as a redundant, burdensome, and confusing process, and have bemoaned botched or missing payments.

Even the Centers for Medicare and Medicaid Services has acknowledged problems with the program.

In a statement, Dr. Kevin Weiss, president and CEO of the American Board of Medical Specialties, said “MOC reporting would be even more comprehensive.”

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other key qualifications, including diagnostic acumen, clinical reasoning, and medical knowledge. This [law] is a significant step forward in recognizing the value of MOC in advancing health care quality for the benefit of patients.”

Under the Patient Protection and Affordable Care Act of 2010, the Health and Human Services secretary will decide how MOC will fit into the PQRI process. The hope is that this will be clarified within the year, Dr. Cassel said.

ABIM and other medical specialty boards seek to meet with CMS officials to help write the regulations for implementing the process, she said. “Our concept is that it would be kind of an alternative pathway … that it would include all the same conditions and measures as PQRI, but [would] be even more comprehensive,” said Dr. Cassel.

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Gastroenterologists Consider Health Reform Impact

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

After more than a year of heated debate over the merits of health reform, policymakers and physicians are switching gears, assessing the impact of the new law and considering how to improve it in the future.

There are many positive aspects to this legislation, like the increased access to colorectal cancer screenings, insurance reforms, and increased access to coverage,” said Dr. Joel Brill. AGAF immediate past chair of the practice management and economics committee for the American Gastroenterological Association, and the RUC and CPT Adviser for the AGA.

However, with much of the increased access to care coming from expanding Medicaid eligibility and coverage, this could present an access problem,” he added.

Many patients already have trouble finding specialists who will take Medicaid, and this problem could be compounded as the program expands without increased payments for specialty care, said Dr Brill, who is also the chief medical officer at Predictive Health, LLC, in Phoenix.

The law also involves some disappointments for physicians, he said, because Congress failed to include a permanent fix to the sustainable growth rate (SGR) formula and the law also does not include caps on noneconomic damages in medical liability claims.

President Obama signed the Patient Protection and Affordable Care Act, which contained most of the health reform provisions, into law on March 23. Later in the week, Congress passed a smaller bill known as the reconciliation bill—that included corrections to the original package, including additional subsidies for purchasing insurance, and removed some of the more controversial political deals from the law. The President signed that companion legislation on March 30.

The law clears the way for approximately 32 million previously uninsured Americans to have access to health insurance in the next few years. Health insurance exchanges, where individuals can shop for insurance that meets minimal coverage standards, will be created under the new law. It also requires individuals to obtain health coverage and bars insurers from discriminating against people based on preexisting medical conditions.

Beginning this year, private insurers are required to provide a minimum benefits package that includes coverage for colorectal cancer screening without cost sharing for patients. In 2011, Medicare and Medicaid will eliminate copayments for certain proven preventive screening tests, including colorectal cancer screening. The law also requires Medicare to waive the deductible for colorectal cancer screenings regardless of whether a polyp or lesion is found.

This new benefit has the potential to increase the uptake of screening. Dr. Brill said. However, physicians must still engage in outreach and education efforts to make patients aware of the coverage and why they should utilize it, he said.

Of special interest to gastroenterologists, the law gives new authority to the Secretary of Health and Human Services to adjust codes that are considered to be misvalued or overvalued. This provision, which goes into effect immediately, has the potential to affect many endoscopy codes since the law makes specific mention of codes that are high volume or have not been reviewed since the Resource Based Relative Value System was first implemented.

The HHS Secretary could make changes beginning with the 2011 Medicare physician fee schedule rule, which will be issued later this year. One concern, Dr. Brill explained, is if colorectal cancer screening codes increase dramatically because of the elimination of patient copays, the codes could become the subject of cuts for oversee. The AGA plans to monitor the process closely.

Another area of concern for the AGA is the creation of the Independent Payment Advisory Board (IPAB). The IPAB has been charged with presenting proposals to Congress that would slow the growth of Medicare and private health care spending and improve quality of care. The recommendations of the IPAB would take effect unless Congress votes to reject the proposal and approves its own plan that achieves the same level of savings. The IPAB is expected to submit its first recommendations to Congress in 2015. The AGA has pledged to advocate against the establishment of the board.

The IPAB will have negative consequences for physicians, Dr. Brill said.

“This board of unelected officials will have unprecedented authority over global Medicare budgetary decisions with little input from the public and greatly limits Congress’ authority over Medicare,” he said.

Currently, the Medicare Payment Advisory Commission (MedPAC) makes recommendations to Congress on Medicare payment rates in a variety of areas. However, while MedPAC is also an advisory board, its recommendations are not binding on Congress.

The new law also extended the Medicare Physician Quality Reporting Initiative (PQRI), which offers incentive payments for successful reporting of quality measures. Under the law, physicians can receive 1% bonus payments on Medicare charges in 2011 and 0.5% bonuses in 2012-2014. However, beginning in 2015, physicians who fail to report quality measures will receive a 1% cut in Medicare reimbursement. That penalty will rise to 2% in 2016. The AGA said it plans to advocate for the removal of penalties from the program.

The Affordable Care Act also addresses imaging payments. Effective immediately, the law would adjust the utilization rate assumption to 75% for advanced imaging equipment, including CT, PET, and MRI.

And starting in 2012, the law creates incentives for physicians to join accountable care organizations. Physicians in accountable care organizations would be eligible to receive enhanced payment incentives based on quality and efficiency improvement.

The AGA is working to identify the potential bonus criteria that gastroenterologists should be measured on within a shared savings model, and to include the AGA Digestive Health Outcomes Registry in the pilots for those gastroenterologists who choose to participate.

Finally, the law also aims to increase transparency in relationships between pharmaceutical companies and physicians and hospitals.

Health Reform Implementation Timeline

2010
Seniors whose prescription drug costs pushed them into the Medicare Part D doughnut hole receive a $250 rebate.
No new physician-owned hospitals may be built after Dec. 31.
Indoor tanning services are taxed at 10%, beginning as early as July.
Health plans are barred from excluding children due to pre-existing conditions, beginning as early as September.
Health plans are barred from dropping members due to illness.
Health plans that provide dependent coverage for children must cover them up to 26 years of age.

2011
A 10% Medicare bonus payment for primary care physicians begins and runs through the end of 2015.
A 10% Medicare bonus payment for general surgeons working in short-ages begins and runs through the end of 2015.
HHS awards 5-year grants to states to develop alternative medical liability reform initiatives.
Medicare and Medicaid programs eliminate outliers of-pocket costs for proven preventive services.
Unused specialty graduate medical education training slots can be used for primary care training.
Seniors whose prescription drug costs push them into the Medicare Part D doughnut hole receive a 50% discount on all brand-name drugs.

2012
Medicaid pilot tests bundled payments for episodes of care, including hospitalization.
Medicare provides incentives for physicians to form accountable care organizations.
Drug makers must report drug samples given to physicians if those drugs are covered by Medicare or Medicaid.

2013
Medicaid rates for primary care services are raised to at least Medicare rates, through 2014.
National pilot program tests bundled payment.
Health plans must adopt uniform standards for electronic submission of health information.
Drug and device makers must report any payments made to physicians and hospitals.

2014
Health insurance exchanges in each state open for individuals and small employers.
Health plans are barred from denying coverage based on pre-existing conditions.
Health plans are barred from charging higher fees based on health status or gender.
Health plans are barred from imposing annual limits on coverage.
Most individuals are required to obtain health insurance coverage or pay a fine.
Medicaid eligibility expands to individuals at 133% of poverty.
Independent Payment Advisory Board created.
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