

Biomarker May Help Predict Esophageal Cancer

Survivin gene expression in biopsy specimens may identify Barrett's patients at higher risk for cancer.

BY JEFF EVANS
Senior Writer

TUCSON, ARIZ. — High levels of survivin gene expression may identify patients with Barrett's esophagus who are at risk for developing precancerous dysplasia, Daniel Vallböhmer, M.D., reported at the annual meeting of the Central Surgical Association.

The development of adenocarcinoma associated with Barrett's esophagus is thought to be a "multistep process" following a sequence of reflux, metaplasia, dysplasia, and then adenocarcinoma.

Researchers know that acid reflux damage to the esophagus and genetic factors initiate the replacement of squamous epithelium with cardiac mucosa, and then the intestinal metaplasia characteristic of Barrett's esophagus, said Dr. Vallböhmer of the division of thoracic and foregut surgery at the University of Southern California, Los Angeles.

Clinicians are often unable to classify patients by the steps in the sequence, he said, even after endoscopy or histology has

been performed. "The major goal is to develop markers that can predict which patients with intestinal metaplasia or low-grade dysplasia will develop cancer" and which ones will not, although he noted that "we are far" from being able to do that.

Dr. Vallböhmer and his colleagues targeted their research on survivin, a member of the inhibitor-of-apoptosis family of proteins.

Avoidance of apoptosis is one of six major pathways described as necessary for the development of adenocarcinoma. The others are growth self-sufficiency, insensitivity to antigrowth signals, limitless replicative potential, sustained angiogenesis, and invasion (Lancet 2002;360:1587-9).

The investigators obtained endoscopic biopsies from 17 control patients with nonacid reflux and no esophagitis, 16 control patients with acid reflux and esophagitis, 12 patients with low- or high-grade

dysplasia, and 45 patients with esophageal adenocarcinoma. They used a laser to microdissect tissue of interest from each biopsy specimen.

All patients stopped taking proton pump inhibitors 2 weeks before they underwent endoscopic biopsies.

The levels of survivin expressed in esophageal biopsies increased with the severity of histopathology in the biopsies.

The control groups and patients with

Barrett's metaplasia had similar, low levels of survivin expression. But the expression of survivin significantly increased in a stepwise manner from patients with Barrett's intestinal metaplasia to patients with dysplasia

and then to patients with adenocarcinoma.

"Survivin gene expression might be used in the future to distinguish Barrett's metaplasia from dysplasia," Dr. Vallböhmer said.

The investigators were not able to find any clinicopathological factors that were significantly associated with the expression of survivin in adenocarcinomas, leading

them to think that survivin expression "may not be a useful marker in determining the prognosis of esophageal adenocarcinoma," he said.

But the findings lead us further into an understanding of the molecular biologic mechanisms related to the progression from an irritated, injured esophageal epithelium to precancerous lesions and frank esophageal cancer, Rodney Landreneau, M.D., told this newspaper. He agreed with the investigators that "these findings alone do not give us insight into relative cancer risk or prognosis for patients with histologic evidence of mucosal dysplasia and survivin expression."

According to Dr. Landreneau, professor of cardiothoracic surgery at the University of Pittsburgh, the findings may be an event related to repeated acid reflux injury and a marker of ongoing repair or the patients' response to the injurious effects of chronic reflux.

"Certainly this interesting finding should be explored further to determine the prognostic significance and possible means of reversing these molecular changes if they are involved in the evolutionary pathway toward the development of esophageal cancer," Dr. Landreneau said. ■

'The major goal is to develop markers that can predict which patients with intestinal metaplasia or low-grade dysplasia will develop cancer.'

Does Preop Induction Therapy Work for Esophageal Cancer?

BY MARK S. LESNEY
Associate Editor

SAN FRANCISCO — Between 20% and 30% of patients given preoperative induction therapy for cancer of the esophagus show a complete pathologic response. The remaining patients have a median survival time of 12–24 months and are subject to treatment known to considerably lower quality of life, according to paired presentations debating the value of induction therapy at the annual meeting of the American Association for Thoracic Surgery.

Despite anecdotal fears that preoperative chemoradiation increases operative mortality and morbidity, a metaanalysis of six published randomized clinical trials showed an improved 3-year survival rate and reduced locoregional tumor recurrence, compared with surgery alone. The mortality for preoperative chemoradiation therapy was 1.2%, compared with an overall complete pathologic response rate of 21%, according to Mark B. Orringer, M.D., director of the thoracic oncology program at the University of Michigan Medical Center, Ann Arbor.

Dr. Orringer saw additional "secondary benefits" of neoadjuvant chemoradiation therapy, including easier to enforce abstinence from alcohol and smoking, and a weight loss of 20–30 pounds before surgery in patients who had a tendency to be markedly obese as a class.

In contrast, citing the same metaanaly-

sis, Gail Darling, M.D., a researcher at Toronto General Hospital, indicated there was no significant improvement in survival at 1 or 2 years and that the 3-year results "are heavily influenced by the single positive trial report" of the six randomized trials studied.

In a disease that is rarely cured, quality of life is an important outcome measure, according to Dr. Darling, and at least 70%–75% of patients treated with induction chemoradiation will not be cured.

"Such patients might have preferred improved quality of life with immediate esophagectomy resulting in the ability to eat until the end of their days, spending the remaining months with family or friends," she said.

While disagreeing on whether preoperative induction therapy should become the standard of care, both Dr. Orringer and Dr. Darling agreed on the critical requirement for stage-specific decision making.

"Most patients with resectable stage II and III esophageal carcinomas should be offered this treatment," Dr. Orringer said. Esophagectomy alone is the best course in those with stage I tumors, other contraindicating medical problems, or age greater than 75 years, he noted.

Similarly, citing 5-year survival rates of 76% in stage I patients and 90% in stage 0 patients receiving surgery alone, Dr. Darling concluded, "Such patients do not derive benefit from induction therapy. Stage-specific therapy should be developed as it has for most other cancers."

Few GERD Patients Find Full Relief, Even With Prescription

BY TIMOTHY F. KIRN
Sacramento Bureau

CHICAGO — Individuals with gastroesophageal reflux fare better when they see a doctor than when they treat themselves with over-the-counter medications, but for the majority of those patients, symptoms are not totally resolved, Roger Jones, M.D., said at the annual Digestive Disease Week.

In a multinational survey of 1,908 individuals with gastroesophageal reflux disease (GERD), 81% of those who had never seen a doctor for the condition but who took over-the-counter medications continued to have unresolved symptoms.

That compared with 68% of patients with a formal diagnosis taking a prescription medicine, Dr. Jones, a professor of general practice at the Guy's, King's, and St. Thomas' School of Medicine, London, said.

The researchers surveyed persons who had previously been identified by a larger telephone survey conducted in the United States and three European countries. Half of the people in the group had been given a formal diagnosis of GERD, and the other half were individuals who reported two or more

episodes of heartburn in the week prior to being contacted, but who had never consulted a physician.

Of those without a diagnosis, 78% (721) reported taking over-the-counter medications. About two-thirds (65%) of those who had taken over-the-counter medications said their symptoms were improved since first taking medication. Still, 81% had residual symptoms.

Of those with a diagnosis, 74% (727 patients) had a prescription, and 80% of those had some improvement since first taking their prescribed medication. Eighty-seven percent of 537 patients receiving a proton pump inhibitor either alone or in combination reported improvement. Ninety-one percent of those taking only a proton pump inhibitor reported some improvement. Still, 68% of those taking a prescription drug continued to have residual symptoms.

The investigators had no trouble finding individuals with heartburn for their survey, Dr. Jones noted. Previous surveys have suggested that as many as one-third of adults experience symptoms.

Previous studies have also noted that the most common reason proton pump inhibitors do not work as well as they might is a lack of full compliance with a daily regimen, he said. ■

Of the patients with a formal diagnosis of GERD, 74% had a prescription, and 80% of those had some improvement since first taking their medication.