The Incidence of Duodenal Ulcer Disease in Patients with Gastric Adenocarcinoma

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A. Study Purpose and Rationale

Despite a decline in incidence of gastric adenocarcinoma, it still remains a formidable health problem. In the United States, gastric adenocarcinoma (GCa) ranks the eleventh most common malignancy and fourteenth most common cause of cancer death. Worldwide, it ranks second among all cancers in both categories with the highest incidence primarily in East Asia, South America, and Eastern Europe.

As is the case with many malignancies, many risk factors are found to be associated with GCa in the absence of a definitive etiology. These include Barrett's Esophagus, chronic atrophic gastritis, Familial Polyposis, H.Pylori positivity, pernicious anemia, gastrectomy, and a diet rich in nitrosamines (used to preserve and pickle foods). Some other associations seen in GCa are low socioeconomic status, tobacco, and heavy alcohol use.

Eighty percent of patients with GCa are asymptomatic. In those with symptoms, GCa most commonly resembles the presentation of peptic ulcer. This clearly makes diagnosis at a treatable stage difficult. In areas of high incidence, such as Japan, population screening programs have helped to increase the detection rate of earlier stages of GCa with such interventions as early upper endoscopy.

As research into risk factors for GCa accumulated it was found that, as mentioned previously, H.Pylori infection was felt to be a cause. This made a compelling argument for a link between gastric and duodenal ulcer (both well known to be associated with high rates of H.Pylori infection) and GCa. There exist many attempts in the literature to establish such a relationship. Most of these studies consist of case reports or poorly designed observational studies. The two best studies employ a prospective cohort design using a national registry in both cases as a control group. Hansson L. et al in the NEJM in 1996 looked at a large cohort in Sweden with the diagnosis of either gastric or peptic ulcers. They were followed with the primary endpoint of development of gastric cancer. It was found that when using a standardized incidence ratio (compared to expected number of developing gastric cancers in the population) patients with duodenal ulcers had actually a reduced rate of progression to GCa. A similar study done in Japan by Lee S. et al in 1990 looking at patients in a Japanese registry also found a significant decrease in the development of GCa in patients with duodenal ulcer as compared to the expected.

These results were explained as being related to the gastric acid secretion characteristics in duodenal ulcer. Since achlorhydria (increased gastric pH) is seen as a risk factor and possible pathophysiological antecedent substrate for development of GCa, the high levels of gastric acid in patients with duodenal ulcer might be protective. This is counterintuitive to the observation that H.Pylori infection, seen in nearly 100% of patients with duodenal ulcer, is also a documented risk factor for GCa. Although these are the two best studies documenting the relationship of both duodenal ulcer and gastric cancer, the lack of a matched control group, the variability in diagnostic methods, and different demographic make for difficulties when extrapolating this data to fit our patient population. It is in this setting that we propose a study looking at the association of gastric cancer and duodenal ulcer in patients diagnosed at CPMC in a retrospective fashion. If a correlation can be seen when controlling for risk factors and matching for various population differences, this can support further investigation in the form of a multicenter prospective cohort study to further establish the relationship between the two gastrointestinal diseases. In the future, this may be able to help in risk-stratifying patients according to presence or absence of duodenal ulcer which is of utmost importance given the indolent nature of the clinical presentation of GCa.

B. Study Design, Methods, and Statistical Analysis

This study will take place at Columbia Presbyterian Medical Center and will consist of a retrospective chart review of data from a pool of patients diagnosed with gastric cancer from 1990 to present as well as a matched control group. All subjects will be older than age 18. The gastric cancer group will be defined as having been diagnosed via upper endoscopy and confirmed with positive biopsy for adenocarcinoma histology regardless of stage at diagnosis. The control group will be selected such that the mean age, gender proportions of both groups as well as non-steroidal anti-inflammatory drug, tobacco use resemble that of the cohort with GCa. Both groups will include patients who were hospitalized as well as those who have been treated as an outpatient.

Patients will be excluded from the study if they have a history of ZollingerEllison syndrome, cirrhosis, Crohn's disease, or HIV/AIDS (to exclude the possibility of other gastrointestinal ulcerative conditions such as Cytornegalovirus infection, Herpes Simplex infection). In addition, patients having had total or partial gastrectomy prior to diagnosis of gastric cancer will be ineligible.

The primary end point will be the development of duodenal ulcer diagnosed on the basis of typical symptoms (epigastric burning pain diminished with meals, bloating, nausea) plus positive visualization by endoscopy and confirmation by biopsy. We will gather this data both on the basis of endoscopy reports and the medical records of the subjects and also in a questionnaire given to each subject. Secondary endpoints will also be assessed and these include the rates of use of alcohol in each group, *Helicobacter pylori* positivity in biopsy samples, and percentages of various ethnic groups involved in the study.

The study is designed to have 80% power to detect the incidence of duodenal ulcer in each cohort with a two-sided P value <0.05. Based on these criteria, the number needed in each arm is 435. The calculation of study size in the control arm is based on an estimate of 10% incidence of duodenal ulcer in the general US population *(Harrison's Principles of Internal Medicine.* Isselbacher K, et al. New York: McGraw-Hill Inc. 1994; 13th ed: 1366). The projected incidence of duodenal ulcer in stomach cancer was estimated based on data from the NEJM study which found a standardized incidence ratio of 0.5 compared to that of the general population (Hansson LE, et al. The Risk of Stomach Cancer in Patients With Gastric Or Duodenal Ulcer Disease. *N Engl J Med.* 1996; 335: 242-249). Therefore, we are assuming approximately half the incidence rate in the control group or 5%.

Data will be evaluated by using chi-square analysis to determine statistically significant differences in the incidence of duodenal ulcer disease in the GCa group versus the control group. The secondary endpoints as described above will be, subject to logistic regression analysis.

C. Study Procedures

Due to the retrospective nature of this study, no subjects will be undergoing any procedure that wasn't already done as part of their diagnostic workup or treatment to date.

D. Study Drugs

None

E. Medical Devices

None

F. Study Questionnaires

There will be a brief questionnaire given to each subject in both arms that will assess the occurrence of substance use, medications, past medical history, and symptoms. This will be completed at the beginning of the study.

G. Confidentiality of Study Data

In order to maintain the privacy of study subjects, each patient will be assigned a number (other than a medical record number or other such identifiable marker) and referred to that number throughout the data gathering process. These numbers will only be known by the primary investigators.

H. Potential Conflict of Interest

None

I. Location of Study

Columbia Presbyterian Medical Center and the Allen Pavilion

J. Potential Risks

None

K. Potential Benefits

The benefits will be obtained indirectly from knowledge gained during the trial since no persons will be directly subject to any medical intervention

L. CompensationlCosts to Subjects

None

M. Minors

None

N. Radiation or Radioactive Substances

None