

EDITORIAL

Does Fundoplication Change the Risk of Esophageal Cancer in the Setting of GERD?

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The effect of a surgical antireflux procedure on the risk of cancer in those with GERD and Barrett's esophagus is unclear. Although some authorities have suggested that a surgical antireflux procedure might be superior to medical management for the prevention of cancer, the cumulative data do not demonstrate that those patients undergoing surgery have any decrement in cancer risk compared to those who receive medication. Most data available to assess the effect of surgery on cancer risk come from case series. These data are of very limited utility, because of differences in the baseline composition of groups undergoing medical and surgical therapy. Until more data are available, patients should not be advised to undergo surgical fundoplication as an antineoplastic measure.

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GERD causes Barrett's. Barrett's leads to cancer. Fundoplication decreases GERD. Ergo, fundoplication should stop cancer in GERD. Perhaps if fundoplication results in better acid control than medicine, it will also stop cancer better than medical management.

The simple logic of this reasoning is hard to deny, which may be the reason that it is so ubiquitous and persistent. Unfortunately, nature often does not listen to our attempts at reasoning, and instead follows its own course. This may be the case with the effect of surgery on cancer risk in GERD and Barrett's.

In this issue of *The American Journal of Gastroenterology*, Tran and colleagues present the results of their analysis of U.S. Veterans' Administration Medical Center Patient Treatment File (1). After matching 946 patients who underwent fundoplication with 1,842 patients with GERD treated medically and 5,676 patients with no GERD diagnosis, the investigators assessed the rate of progression to esophageal cancer in the three groups over a greater than 10-yr follow-up.

Cancer risk was actually highest in the group having undergone fundoplication, however, this risk was not statistically different from the medically treated GERD patients. Both of these groups had a higher risk than the non-GERD group, in which no cancers were noted. The adjusted hazard ratio for developing esophageal cancer in the fundoplication group was 1.88, with wide confidence intervals (0.7–5.0).

As the authors acknowledge, this study hardly provides definitive evidence about the effect of surgery in GERD. Although the study is large, the analysis is based on eight cancers in the fundoplication group and eight in the medical GERD group. The histology of these cancers is unknown, and given the past reported rates of alcohol use and smoking in VA cohorts, one certainly would not be surprised to find that one or

more were squamous cell cancers (2). Perhaps most importantly, the authors were unable to ascertain the prevalence of Barrett's esophagus in the two groups from the database. Certainly, if Barrett's was over-represented in the surgical group compared to the medical group (a very likely possibility), any beneficial effect of the surgery might be obscured. The authors do their best to consider these potential biases, and are to be congratulated on the extent of their efforts to consider the effect of comorbidity and other potential confounders on their data. Although the study by Tran and colleagues provides us with some of the best observational data yet with respect to this question, the study must be considered relatively weak evidence with which to address the question of the effect of fundoplication on esophageal cancer risk in GERD.

Does Fundoplication Change Cancer Risk?

Several previous investigators have attempted to answer the question that is addressed by Tran and colleagues. Spechler and colleagues assessed cancer risk in subjects with GERD more than a decade after their participation in a randomized controlled trial of medical *versus* surgical therapy (3). In their 239 person cohort, cancer risk was not significantly different between those treated with medical and surgical therapy. Of course, this cohort received H₂ receptor antagonist therapy *versus* open surgery, so extrapolating these data to the current situation may be difficult. Ortiz and colleagues asked a similar question specifically in a Barrett's esophagus population (4). Of the 59 patients randomized to either medical or surgical antireflux therapy and followed for a median of 4 and 5 yr, respectively, there was no significant difference in the risk of cancer between the groups. Each group demonstrated only one carcinoma *in situ*. However, there was more progression to mild dysplasia in the medical group, as well as a higher

proportion of subjects who demonstrated an increase in the length of their BE. The authors concluded that conservative management of BE might not be desirable.

Unfortunately, the majority of the data available to us with which to address the question of the effect of surgical antireflux procedures on cancer risk consists of case series of medically and surgically managed patients. Aside from obvious potential differences in severity of reflux disease and comorbidities, these series feature differences in methodology, disease definition, and follow-up protocol, which make them extremely hard to compare. Two efforts at metaanalysis of the cancer risk specifically in Barrett's patients have been made. The earlier of these, by Bammer *et al.*, demonstrated a decrease in cancer incidence in BE patients treated with surgery compared to medical therapy (5). A more recent publication, by Corey and colleagues, using more stringent entry criteria and encompassing a greater number of studies, demonstrated no difference between the reported incidences of cancer in medically and surgically treated patients (6).

Although the article by Tran and colleagues is yet another small piece in the puzzle, the issue of the effect of a surgical antireflux procedure on cancer risk is still quite unsettled. Studies such as the present work using nonrandomized patients to compare outcomes in medically- and surgically-treated patients tilt the field against surgery and toward medical management. Patients with GERD sent to surgery clearly have more severe disease in general, and to retrospectively compare their outcomes to those of medically treated patients provides little information regarding the effect of surgery on cancer risk. While long-term data from previous randomized controlled trials largely avoids this bias, the paucity of these data make a type II statistical error very possible. Also, much of the data on cancer risk in surgery patients does not provide information as to the long-term integrity of the wrap. Certainly, an ineffective wrap is not likely to convey much protection. Finally, the total number of cancers prospectively observed in the U.S. literature in GERD and Barrett's cohort is miniscule, with less than 50 in the most recent Barrett's metaanalysis, and 16 in the current study. Certainly, basing any firm conclusions about the effect of surgery on such scant data would be unwise.

Toward a Better Understanding of the Effect of Surgery on Cancer Risk

Where are the areas of future interest likely to be? The best answer to the question of surgery's effect on cancer risk would come from a multicenter, large study of medical *versus* surgical therapy. Follow-up would be standardized, and histologic interpretation would be centralized. Crossover would be minimized and well documented. Esophageal acid exposures in both groups would be assessed periodically to measure the effectiveness of therapy. While such a study is highly desirable, it would be logistically very difficult to perform. Pragmatically, a such a clinical trial study needs to focus on a Barrett's population, because cancer outcomes in non-Barrett's GERD

patients are so few that even a quite large study would be unlikely to have sufficient power to detect clinically important differences.

More generally, it is imperative to separate Barrett's esophagus from the general GERD population conceptually when considering the issue of the effect of surgery in cancer risk. It may be that the factors that cause normal mucosa to progress to Barrett's are different than the factors causing Barrett's to progress to cancer. If a surgical antireflux procedure stops GERD from progressing to Barrett's, but not Barrett's degenerating to cancer, no protective effect will be recognized in studies of Barrett's patients undergoing surgery. Such an effect would only be obvious in studies of non-Barrett's GERD patients. Because the risk of cancer in non-Barrett's GERD patients is so low, mixed populations of Barrett's and non-Barrett's GERD patients (such as in the present study) yield risk estimates that are difficult to interpret. Future studies will need to compulsively document the condition of the esophageal mucosa prior to therapy to better assess the cancer risk.

For the present, a few conclusions can be drawn. The risk of cancer in the GERD, non-Barrett's population is very low, and surgery should not be recommended in this group as an antineoplastic measure. Even with the safety of laparoscopic surgery (7–9), the complications and mortality of the surgery likely outweigh any benefit with respect to cancer risk. In subjects with Barrett's, surgery has not been convincingly demonstrated to lower cancer risk or change the natural history of the disease. Although it is certainly reasonable to present surgery as a treatment option to improve GERD symptoms or control erosive disease in the appropriately selected Barrett's patient, current data do not support the contention that an antireflux procedure is any better than medical management in preventing adenocarcinoma of the esophagus. The decision for an antireflux surgery should depend on the circumstances of the "here and now," not unsupported speculation of what could be.

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REFERENCES

1. Tran T, Spechler SJ, El Serag HB. Fundoplication does not reduce the incidence of esophageal cancer in gastroesophageal reflux disease: A cohort study. *Am J Gastroenterol* 2005;100:1002–8.
2. Hankin CS, Spiro A III, Miller DR, et al. Mental disorders and mental health treatment among U.S. Department of Veterans Affairs outpatients: The Veterans Health Study. *Am J Psychiatry* 1999;156(12):1924–30.
3. Spechler SJ, Lee E, Ahnen D, et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: Follow-up of a randomized controlled trial. *JAMA* 2001;285(18):2331–8.

4. Ortiz A, Martinez dHL, Parrilla P, et al. Conservative treatment versus antireflux surgery in Barrett's oesophagus: Long-term results of a prospective study. *Br J Surg* 1996;83(2):274–8.
5. Bammer T, Hinder RA, Klaus A, et al. Rationale for surgical therapy of Barrett esophagus. *Mayo Clinic Proc* 2001;76(3):335–42.
6. Corey KE, Schmitz SM, Shaheen NJ. Does a surgical anti-reflux procedure decrease the incidence of esophageal adenocarcinoma in Barrett's esophagus? A meta-analysis. *Am J Gastroenterol* 2003;98:2390–4.
7. Frantzides CT, Richards C. A study of 362 consecutive laparoscopic Nissen funduplications. *Surgery* 1998;124(4):651–4.
8. Coelho JC, Wiederkehr JC, Campos AC, et al. Conversions and complications of laparoscopic treatment of gastroesophageal reflux disease. *Am J Coll Surg* 1999;189(4):356–61.
9. Eshraghi N, Farahmand M, Soot SJ, et al. Comparison of outcomes of open versus laparoscopic Nissen fundoplication performed in a single practice. *Am J Surg* 1998;175(5):371–4.