

## Commented Summaries from Current Medical Literature

### *Reducing Gastric Cancer Mortality in Developing Countries: Learning from the Experience in Japan*

#### **D2 Lymphadenectomy Alone or with Para-Aortic Nodal Dissection for Gastric Cancer**

**Summary:** Gastrectomy with D2 lymphadenectomy is the standard treatment for curable gastric cancer in eastern Asia. Whether the addition of para-aortic nodal dissection (PAND) to D2 lymphadenectomy for stage T2, T3, or T4 tumors improves survival is controversial. We conducted a randomized, controlled trial at 24 hospitals in Japan to compare D2 lymphadenectomy alone with D2 lymphadenectomy plus PAND in patients undergoing gastrectomy for curable gastric cancer. Between July 1995 and April 2001, 523 patients with curable stage T2b, T3, or T4 gastric cancer were randomly assigned during surgery to D2 lymphadenectomy alone (263 patients) or to D2 lymphadenectomy plus PAND (260 patients). We did not permit any adjuvant therapy before the recurrence of cancer. The primary end point was overall survival.

The rates of surgery-related complications among patients assigned to D2 lymphadenectomy alone and those assigned to D2 lymphadenectomy plus PAND were 20.9% and 28.1%, respectively ( $P = 0.07$ ). There were no significant differences between the two groups in the frequencies of anastomotic leakage, pancreatic fistula, abdominal abscess, pneumonia, or death from any cause within 30 days after surgery (the rate of death was 0.8% in each group). The median operation time was 63 minutes longer and the median blood loss was 230 ml greater in the group assigned to D2 lymphadenectomy plus PAND. The 5-year overall survival rate was 69.2% for the group assigned to D2 lymphadenectomy alone and 70.3% for the group assigned to D2 lymphadenectomy plus PAND; the hazard ratio for death was 1.03 (95% confidence interval [CI], 0.77 to 1.37;  $P=0.85$ ). There were no significant differences in recurrence-free survival between the two groups; the hazard ratio for recurrence was 1.08 (95%CI, 0.83 to 1.42;  $P=0.56$ ). As compared with D2 lymphadenectomy alone, treatment with D2 lymphadenectomy plus PAND does not improve the survival rate in curable gastric cancer. (ClinicalTrials.gov number, NCT00149279.)

**Source:** M. Sasako, et al. *N Eng J Med*. 2008; **359**: 453 – 462.

**Comment:** Gastric cancer is the second leading cause of cancer death worldwide, killing about one million people each year. It is the most common cause of cancer mortality in Iran with about 10,000 new cases diagnosed and 8000 deaths occurring from this cancer each year in Iran.<sup>1</sup>

Sasako and colleagues<sup>2</sup> present their results from a randomized trial of two surgical modalities for curable gastric cancer conducted in 24 specialized hospitals in Japan with comparable 5-year survival rates of 70%. Their results clearly shows that a more radical surgery for this cancer just increases the complication rates without adding to the overall efficacy of the surgery in regard of patient survival. Therefore, careful D2 lymphadenectomy seems to be as good as the more complex surgery of para-aortic node dissection in terms of patient survival. A very important point in this study is not only the comparison of the two techniques of surgery, but the rather fascinating five year survival of about 70% for a deadly cancer. Comparing to most reported experiences outside Japan it is a real success in treating a disease with extremely poor prognosis.<sup>3,4</sup>

The overall 5-year gastric cancer survival rate after surgery in Iran and several other developing countries are less than 5% which is very low and not acceptable.<sup>4</sup> How can we learn from our Japanese colleagues to improve survival among our gastric cancer patients? Patients enrolled in this study had “curable gastric cancer”. Most of our patients with gastric cancer are diagnosed in a “noncurable” stage. So the first step towards improving survival and moving towards conquering a deadly disease is early detection. Besides appropriate selection of patients, adequate surgical expertise could make a fatal disease like gastric cancer a treatable one with acceptable rates of survival. It is now well known that the stage at which gastric cancer

is diagnosed is the main determinant of efficacy of surgical therapy. In Japan during last three decades meticulous surgery has been the standard of care for gastric cancers at stage T2b (which invades the subserosa) and above.

While there are plans and actual attempts to prevent other cancers like those arising in colon, breast, and cervix in several countries around the globe, there has been no major plan in action for early detection of gastric cancer except for Japan in spite of high prevalence and a very high fatality rate. Following the recognition of the pivotal role of *H. pylori* as etiology of gastric cancer several studies have demonstrated that almost all patients with this cancer have evidence of *H. pylori* infection in the past. Infection with *H. pylori* alone could not explain the very high rate of gastric cancer observed in some ethnic groups such as native people of eastern Siberia with a male gastric cancer rate of over 100 per 100,000 population per year. In Iran the *H. pylori* infection rate is similar in Northern and southern provinces but the rate of gastric cancer is at least 5 times more in northern provinces<sup>6</sup> therefore the impacts of *H. pylori* infection on gastric cancer development differ among various ethnic groups. Several studies during the last two decades have shown that host factors, including age, gender, level of gastric acid secretion, and genetic polymorphisms in pro-inflammatory cytokines, in addition to bacterial virulent factors<sup>8</sup> and environmental risk factors like excess use of salt affect *H. pylori* related gastric cancer.<sup>3</sup>

Vaccination against *H. pylori* seems to be ideal for primary prevention of this fatal cancer. More than 10 years of studies to find an effective *H. pylori* vaccine for human was not successful because natural infection do not induce protective immunity and despite promise in preclinical models, the feasibility of vaccination against *H. pylori* in human remains unclear.

Populations that would benefit most from widespread eradication programs are those with high prevalence of *H. pylori* and high incidence of gastric cancer. Several studies have casted doubt on this strategy and population based *H. pylori* eradication is presently not recommended because of irreversible mucosal injury that has already occurred, possible beneficial effect of infection,<sup>9</sup> side effects and pathological consequences of eradication which outweigh currently projected beneficial roles.<sup>3</sup> Antibiotic resistance and compliance problems significantly reduce treatment efficacy. In developing countries, re-infection is common, and current treatment options are inadequate for infection control.<sup>7</sup>

As mentioned, the main factor in success of surgery is early detection. The excellent health infrastructure and tradition of endoscopic screening and early diagnosis of gastric cancer in Japan is the key to this high success rate of surgical teams in Japan. Other major reasons for the failure of non-Japanese surgical teams are the small volume of cases which limit the experience of the surgeons in performing a meticulous procedure like gastrectomy with D2 lymphadenectomy safely and effectively.<sup>3</sup> In Japan, with an aging population (20% more than 65 year old) and population size 40% more than Iran each year 100,000 new cases of gastric cancer occur; about 10 times the number of yearly gastric cancer cases in Iran.

Screening to detect early gastric cancer in high-risk regions of China (age standardized rate: 25) has been shown to be cost-effective<sup>10</sup> (\$28,836 per quality-adjusted life years saved) for men ages 50 to 70 while it has not been so in a low prevalence populations like American males with an ASR of less 10 (\$247,600 for each year of age adjusted quality of life gained).

Considering the available data, establishing active surveillance systems in areas harboring high risk of gastric cancer in Iran and other developing countries seems plausible. This needs specialized hospitals with appropriately trained therapeutic endoscopists and surgical teams capable of detecting and treating early gastric cancer effectively. To be cost effective, endoscopic screening needs to be limited to high risk groups. Low serum pepsinogen (PG) may prove to be a marker of high risk for gastric cancer. If this holds true, then serum PG screening (a relatively simple and inexpensive test) may be used to pick individuals at high risk for gastric cancer and then subject them to more sophisticated endoscopic screening methods. This may help in detecting a significant number of gastric cancer patients at a curable stage.<sup>11</sup> *H. pylori* eradication may be recommended in this high risk population as well. A prospective study in Japan has confirmed that *H. pylori* antibody and serum PG are good predictors for detection of at risk people for development of gastric cancer, This may make *H. pylori* eradication an option in patients having evidence of progression of gastric atrophy as manifested by low PG serum PG levels.<sup>12,13</sup>

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