Randomized Clinical Trial on the Combination of Preoperative Irradiation and Surgery in the Treatment of Adenocarcinoma of Gastric Cardia (AGC) - Report on 370 Patients

Reviewers: John Han-Chih Chang, MD

Introduction
Gastric or stomach cancer is a rather uncommon malignancy in the United States, but has a high incidence in China, Japan and Chile. It is the second most common cause of cancer death in the world. The main risk factors include nitrosamines in preserved salted or smoked foods. Most cases are advanced at the time of diagnosis.

The mainstay of treatment is surgery. However, a study from the University of Minnesota in the early 1980's demonstrated a local recurrence rate of nearly 70%. Many other authors concur with the poor efficacy of surgery alone. Additional therapy seems to be needed to improve outcome. Still, numerous studies and retrospective reviews have been performed with equivocal results on survival with adjuvant therapy of any kind (i.e., chemotherapy or radiation therapy). This article details a prospective randomized trial of 370 patients with tumors of the gastric cardia (most cephalad aspect of the stomach—essentially just caudal to the gastro-esophageal junction) that ran from 1978 to 1989 in China.

Materials and Methods
The departments of radiation oncology and thoracic surgical oncology at the Cancer Institute (Hospital), Peking Union Medical College and Chinese Academy of Medical Sciences began this randomized prospective trial that enrolled 370 patients. All had adenocarcinomas of the gastric cardia (AGC) without evidence of distant metastasis.

The two arms consisted of surgery alone (S) versus preoperative radiation therapy (PrRT) followed by surgery. It was not specified whether a total or subtotal gastrectomy was performed in either case. One hundred and ninety-nine patients were randomized to surgery alone, while 171 were randomized to preoperative RT. RT fields included the 5-cm margins around the gross tumor along with distal esophagus, gastric fundus, cardia and lesser curvature including draining lymph nodes. Megavoltage or telecobalt irradiation delivered 40 Gy in 2 Gy fractions per day.

Median follow-up was over 10 years in both arms. Only 2-3% lost to follow-up, and 80% came back to the institution of treatment for follow-up. The rest were followed via correspondence with the local physician. Analysis was by intent-to-treat basis.

Results
The survival of the patients in the PrRT arm was far superior than the S arm. Analysis was by intent-to-treat basis. Figure 2 demonstrates this point. There is a divergence of the survival curve from the beginning to about 3 years and then continued separation to about 9 years. The 5 and 10-year survival rates were 30% and 20% for PrRT and 20% and 13% for S, respectively (p = 0.0094).

One hundred fifty-three (90%) of the PrRT patients and 158 (80%) of the S patients could be resected. For the PrRT patients, 80% were radically resected and 10% palliatively. The respective numbers for the S arm were 62% and 18%. Comparison of the 5 and 10-year survival rates is depicted in figure 3. Patients had a 22.5% and 16.6% rate, while PrRT patients had 33% and 25% (p = 0.15 - non statistically significant). The survival curve is similar for the first year but diverges from there.

For those that could only be explored and not resected (18 in PrRT and 41 in the S), survival was again much better with PrRT. Figure 4 depicts this in graphical form with the curves diverging from the beginning. The mean survival was 11 versus 5 months and median of 7 versus 4 months for the PrRT and S arms, respectively. The p-value for this survival difference was 0.008.
Regardless, they both do poorly without surgical resection (almost all patients die by 3 years).

The lymph node positivity was reduced with PrRT from 85% to 64%. The pathological stage was significantly reduced by PrRT as demonstrated in the following chart extracted from Table 1 in the article.

**Pathological stage after surgery**

<table>
<thead>
<tr>
<th></th>
<th>PrRt+S</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1 (0.6%)</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>48 (28%)</td>
<td>21 (11%)</td>
</tr>
<tr>
<td>III</td>
<td>103 (60%)</td>
<td>136 (68%)</td>
</tr>
<tr>
<td>IV</td>
<td>19 (11%)</td>
<td>42 (21%)</td>
</tr>
</tbody>
</table>

There appears to be an 18% downstaging from III and IV to I and II when comparing PrRT to S arms.

Sixty-six and 75% of those that failed had some component of locoregional recurrence in PrRT and S arms, respectively. Distant metastasis alone was seen in 16% of the PrRT arm and 12% of the S arm, though the overall distant metastasis rate (alone or with locoregional recurrence) was 24% in both arms.

Operative mortalities (mortality within 30 days of the operation) were not different in the PrRT (0.6%) arm versus the S arm (2.5%). Anastomotic leak was seen only in 2% of the PrRT patients, while it was 4% for the S arm.

**Discussion and Conclusion**

The mainstay of gastric cancer treatment remains surgery. But time and time again, we realize that it is not enough to just perform radical surgery. A retrospective review from Thomas Jefferson University demonstrated a survival advantage to patients who received adjuvant therapy (RT and/or chemotherapy).

However, randomized trial after randomized trial has failed to truly demonstrate a survival advantage. In the British Stomach Cancer Group three arm trial, there was no difference in overall or median survival in patients who received surgery alone versus surgery plus chemotherapy or surgery plus RT. A criticism was that over 30% of patients in the RT arm did not get full dose RT. The Gastrointestinal Tumor Study Group (GITSG) ran two prospective randomized trials on locally advanced gastric carcinoma (resected or unresected) patients attempting to define the role for RT. These demonstrated no advantage to adding RT to Chemotherapy.

The general opinion is that RT adds very little to the survival of gastric carcinoma patients though local control may be improved. This article is important in that it demonstrates an indication for RT for adenocarcinomas of the gastric cardia. Extrapolating this data for all carcinomas of the stomach may be premature, though. To lend more credence to this study, the authors should publish their stratification criteria, especially the distribution of radiographic and clinical stage prior to surgery. This would support that PrRT downstaging was a real phenomenon and not just secondary to less bulk of disease in the PrRT arm patients. Also, details of what constituted a radical resection should be explained.

Three hundred fourteen patients have died of the original 370 as testament to how far we still have to go with this disease. Perhaps the dose of RT was too low. We know adenocarcinomas of the esophagus get much higher biological doses in an attempt to obtain cure. The same may hold true for the stomach. Chemotherapy to be combined with RT may also improve the outcome. In many of the clinical trials underway, combined modality is utilized to reach synergy of cancer killing power. This article details a step in the right direction, but we must move forward into new avenues of improvement in this disease. As a Chinese proverb states, learning is like rowing upstream, to stop is to fall back.