A Prospective Study on Primary Gastric Stump Cancer following Partial Gastrectomy for Benign Gastroduodenal Diseases

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ABSTRACT

A prospective study was made on 3827 Japanese patients who had undergone partial gastrectomy for benign gastroduodenal diseases to examine whether they are at a high risk of mortality from primary gastric stump cancer (PGSC) and whether the risk is determined by the surgical procedure. The patients were followed up from the time of surgery (from 1948 to 1970) to June 30, 1981. Of 3,701 patients (96.7%), the vital status at the end of observation was determined, the total person-years at risk being 62,286.33. The observed deaths were compared with the expected deaths calculated from the mortality rates of Japan. An elapsed time of 10 years from operation to death was set not only to exclude possible recurrent, remaining, or multiple cancers but also to allow a certain latency period for the development of PGSC. The observed and expected deaths from PGSC were 11 and 52.85, respectively, the ratio being 0.21 (p < 0.01). The ratios were uniformly <1 for both sexes and across three operative groups: Billroth I, Billroth II with Braun’s anastomosis; or Billroth II without Braun’s anastomosis. No difference was observed between the death rates from PGSC by operation type. The possible role of the postoperative nonphysiological (pathological) environment or duodenogastric reflux in gastric stump carcinogenesis was not detected in the present study.

INTRODUCTION

Low acidity (achlorhydria), lack of vagal and gastrin stimulation, duodenogastric reflux, and changes of bacterial flora are seen in the gastric stump in patients partially gastrectomized for benign gastroduodenal diseases (6, 18, 22, 42). In addition, pathological features such as chronic atrophic gastritis, hyperplastic or polyoid changes, and intestinal metaplasia or dysplasia are observed in the stump (6, 8, 19, 22, 29, 31, 39, 40, 42). High concentrations of nitrite and carcinogenic N-nitroso compounds are detected in the gastric juice (33, 35, 38). Furthermore, animal experiments, the incidence of PGSC is higher in the group subjected to Billroth II procedures with obligatory duodenogastric reflux than in the group treated with BI procedures without reflux (6, 22).

RESULTS

The number of patients by sex and vital status as of June 30, 1981, is shown in Table 2. There were 3159 (82.5%) males
and 668 (17.5%) females. There were 2617 (68.4%) living patients as of the end of observation and 1084 (28.3%) patients had died. There were 126 (3.3%) cases of unknown status, and the follow-up rate was 96.7%. In Table 3, the number of patients and person-years at risk by sex and operation type are shown. The total person-years at risk was 62,286.33 at a mean observation period of 16.3 years. In this connection, the mean age at operation was 46.4 years. The number of patients by benign gastroduodenal disease is shown in Table 4. There were 2169 (56.7%) patients with gastric ulcer (including gastric and duodenal ulcers), 1040 (27.2%) patients with duodenal ulcer, 303 (7.9%) patients with benign tumor (mostly stomach poly), 239 (6.2%) patients with gastritis, and 76 (2.0%) patients with other diseases. Histological examinations of the resected stomach were done for 2412 (63.0%) patients.

The observed and expected deaths from stomach cancer with their ratios by operation type, irrespective of postoperative time interval, are shown in Table 5. All O/E ratios were <1, except in the female BI, B(+) group. The ratios for males and both sexes in BI; BII, B(-); and total operative groups were <1 (p < 0.01, 2-tailed). The numbers of cases with time intervals from operation to death <1 year, 1 to 4 years, 5 to 9 years, and 10 years or more were 6, 9, 8, and 11, respectively.

In selecting PGSC cases, the postoperative time interval was taken into account (Table 6). An elapsed time of 10 years, as proposed previously (4, 7, 9, 18, 41), was set not only to exclude recurrent, remaining, or multiple cancers which had been initially misdiagnosed or overlooked at operation but also to allow some latency period, which is indispensable under the assumption that a nonphysiological (pathological) environment in the stump plays some role in carcinogenesis. For comparison, the expected number was based on the population at risk who survived 10 years or more after the operation. Although the resected stomachs of 2 cases were not histologically verified as benign, as shown in Table 9, they were included in the figure because they had long elapsed times (19.6 and 14.0 years). The total observed and expected deaths from PGSC were 11 and 52.85, respectively. The O/E ratios were <1 in all sexes and operation types. The ratios for males and both sexes in BI; BII, B(-); and total operative groups were <1 (p < 0.01).

As shown in Table 6, PGSC mortality was not increased in the BI groups, regardless of Braun's anastomosis. In addition, direct (internal) comparison of mortality rates from PGSC by operation type and postoperative time interval was made for the patients who died 10 years or more after the operation (Table 7). No statistically significant difference was noted between the death rates from PGSC by operation type as well as by postoperative time interval (25).

In Table 8, PGSC mortality was compared among the groups by benign gastroduodenal disease. All O/E ratios were <1, except in females with stomach polyt. The ratios for males and both sexes in the groups with gastric ulcer as well as duodenal ulcer were <1 (p < 0.05 or 0.01). Therefore, no difference in PGSC mortalities was attributable to benign gastroduodenal diseases that had been treated surgically.

In Table 9, details of 11 PGSC cases (9 males, 2 females) were listed. Their original diseases were 5 gastric ulcers, 3 duodenal ulcers, and 3 stomach polyps. The number of cases operated on according to BI; BII, B(+); and BII, B(-) were 5, 2, and 4, respectively. The mean age at operation was 52.2 years. Underlying causes of death in 8 cases were described simply as stomach cancer on the death certificates, whereas those of the remaining 3 cases were described as PGSC, stomach cancer in the stump, and gastric cancer at the site of the gastrointestinal anastomosis, respectively. Autopsy was done for only one case.

DISCUSSION

In order to examine the incidence of (or mortality from) PGSC among patients partially gastrectomized for benign gastroduodenal diseases, 2 types of epidemiological studies (retrospective...
Table 5  
**Observed and expected number of deaths from stomach cancer with their ratios by operation type**

<table>
<thead>
<tr>
<th>Operation type</th>
<th>Male Observed no. of deaths</th>
<th>Male Expected no. of deaths</th>
<th>Male O/E ratio</th>
<th>Female Observed no. of deaths</th>
<th>Female Expected no. of deaths</th>
<th>Female O/E ratio</th>
<th>Total Observed no. of deaths</th>
<th>Total Expected no. of deaths</th>
<th>Total O/E ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>BI</td>
<td>11 36.79</td>
<td>0.30(a)</td>
<td></td>
<td>2 4.99</td>
<td>0.40</td>
<td></td>
<td>13 41.78</td>
<td>0.31(a)</td>
<td></td>
</tr>
<tr>
<td>BII, B(+)</td>
<td>5 6.05</td>
<td>0.83</td>
<td></td>
<td>1 0.73</td>
<td>1.37</td>
<td></td>
<td>6 6.78</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>BII, B(−)</td>
<td>11 46.75</td>
<td>0.24(a)</td>
<td></td>
<td>4 5.32</td>
<td>0.75</td>
<td></td>
<td>15 52.07</td>
<td>0.29(a)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>27 89.59</td>
<td>0.30(a)</td>
<td></td>
<td>7 11.04</td>
<td>0.63</td>
<td></td>
<td>34 100.63</td>
<td>0.34(a)</td>
<td></td>
</tr>
</tbody>
</table>

\* Significant at \( p < 0.01 \) (2-tailed).

Table 6  
**Observed and expected number of deaths from primary gastric stump cancer with their ratios by operation type for patients who died 10 years or more after partial gastrectomy**

<table>
<thead>
<tr>
<th>Operation type</th>
<th>Male Observed no. of deaths</th>
<th>Male Expected no. of deaths</th>
<th>Male O/E ratio</th>
<th>Female Observed no. of deaths</th>
<th>Female Expected no. of deaths</th>
<th>Female O/E ratio</th>
<th>Total Observed no. of deaths</th>
<th>Total Expected no. of deaths</th>
<th>Total O/E ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>BI</td>
<td>3 18.80</td>
<td>0.16(a)</td>
<td></td>
<td>2 2.15</td>
<td>0.93</td>
<td></td>
<td>5 20.95</td>
<td>0.24(a)</td>
<td></td>
</tr>
<tr>
<td>BII, B(+)</td>
<td>2 3.13</td>
<td>0.64</td>
<td></td>
<td>0 0.42</td>
<td>0</td>
<td></td>
<td>2 3.55</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>BII, B(−)</td>
<td>4 25.54</td>
<td>0.18(a)</td>
<td></td>
<td>0 2.81</td>
<td>0</td>
<td></td>
<td>4 28.35</td>
<td>0.14(a)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>9 47.47</td>
<td>0.19(a)</td>
<td></td>
<td>2 5.38</td>
<td>0.37</td>
<td></td>
<td>11 52.85</td>
<td>0.21(a)</td>
<td></td>
</tr>
</tbody>
</table>

\* Significant at \( p < 0.01 \) (2-tailed).

Table 7  
**Death rates from PGSC by operation type and postoperative time interval for patients who died 10 years or more after partial gastrectomy**

<table>
<thead>
<tr>
<th>Postoperative time interval (yr)</th>
<th>No. of deaths</th>
<th>Person-yr at risk</th>
<th>Death rate/10^a</th>
<th>No. of deaths</th>
<th>Person-yr at risk</th>
<th>Death rate/10^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>BI BII B(+) or BI BII B(−)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10−19</td>
<td>5 2,937.84</td>
<td>60.26</td>
<td>3 13,714.20</td>
<td>21.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20</td>
<td>0 1,138.50</td>
<td>0</td>
<td>3 3,424.01</td>
<td>87.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (≥10)</td>
<td>5 9,436.34</td>
<td>52.99</td>
<td>6 17,138.21</td>
<td>35.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

and prospective) (24) were carried out. In the retrospective (case-control) study, stomach cancer cases were compared with controls in terms of previous partial gastrectomy. Stalsberg and Taksdal (42) reported that the frequency of partial gastrectomy among autopsied gastric cancer patients was higher than that of controls and concluded that the statistically significant difference was not explained by biased study groups. On the other hand, Kivilaakso et al. (17) reported no difference in the past history of partial gastrectomy between autopsied cases and controls. Since selection bias (24, 36) is unavoidable in autopsy data, it is recommended that retrospective study using controls and unbiased incident stomach cancer cases should be done to examine the alleged association.

In the prospective study, patients partially gastrectomized for benign gastroduodenal diseases were followed up, and their incidence (or mortality) was examined. Some studies (7, 12, 20) have reported increased risk of PGSC among the patients; however, others (11, 13, 14, 23, 34, 44) observed lowered (or even) risk of PGSC. We reported that PGSC mortality was low among the partially gastrectomized (\( p < 0.01 \)). This means that not only relative risk but also attributable risk (24) (the proportion of PGSC in the whole stomach cancer) is low in the patients. No carcinogenic effect of nonphysiological (pathological) environment in the gastric stump on PGSC was detected in the present study. This evidence supports the idea that the risk of PGSC is naturally low because the distal two-thirds of the stomach, the most common location of the cancer, is resected. This also coincides with the fact that case reports of PGSC are limited in Japan (8, 41), although, as is well known, the incidence of stomach cancer in Japan is the highest in the world.

When the resected stomach is diagnosed as benign histologically, cancer in the remaining stomach is proposed to be PGSC, irrespective of time interval from operation to death (5). On the contrary, however, when the postoperative time interval is not long enough and whether the resected stomach is verified as free of cancer or not, cancer in the residual stomach does not seem to be PGSC but recurrent, remaining, or multiple (4, 7, 9, 18, 41). This is partly because the state of the residual stomach, as usual, is not thoroughly verified histologically at operation. In this respect, time interval (elapsed time, latency period) as well as histological confirmation always should be taken into account in the analysis of PGSC.

It was hard to evaluate the risk of PGSC among partially gastrectomized patients in some prospective studies (1−4, 10, 21, 30−32) since the observation period was not taken into account and the number of patients was used as denominator when calculating the risk of PGSC. By using person-years at risk as denominator, Dommelöf and Janunger (7), Helsingen and Hillestad (12), and Krause (20) from Scandinavian countries have reported significantly elevated incidence of (or mortality from) PGSC in partially gastrectomized patients. Hirohata (13) and Ihre et al. (14) reported that the O/E ratios were also >1; however, like other authors (11, 23, 34, 44), they concluded that the risk was not increased among patients. Some possible factors to explain the discrepancy between the reports from Scandinavian countries and ours, such as width of resection, length of observation, and dietary factors, should be investigated in the future.

Since the expected numbers in most prospective studies were based on mortality rates of the remnant stomach [cardiac region, upper part of the stomach, C region (15)] but on those...
of the total stomach, there was a pitfall in the comparison of the observed and expected numbers. Therefore, it is recommended that the expected number be calculated on the basis of the rates limited to the cardiac region. Because the proportion of mortality rates of the cardiac region in "the stomach cancer with specified parts" was 20%, which was close to the 25% reported by Saegesser and James (37), in Vital Statistics, 1975, Japan (28), dietary habits, smoking habits, and socioeconomic factors related to stomach cancer were not studied, and geographical variation of stomach cancer mortality was not adjusted in the present study. However, the results obtained were not considered to be explained by these factors alone.

Even if PGSC mortality is low in the partially gastrectomized as a whole, any difference in the mortality by operative procedure would be explained by the difference in duodenogastric reflux in the gastric stump. As mentioned before, there was neither increased PGSC mortality in the BiI group in which duodenogastric reflux is obligatory nor a difference in the mortality rates from PGSC between Bi and BiI operative groups. Accordingly, no carcinogenic effect of duodenogastric reflux was detected in the present epidemiological study, possibly because of the limited number of PGSC cases. In this regard, the least significant relative risk of 3.72 was calculated by using the population at risk and the mortality rate of the nonexposed (Bi) group and the type I and II error rates [e.g., α = 0.05 (2-tailed) and β = 0.20 (one-tailed)] (43). We might therefore need further observation in this issue.

Dietary habits, smoking habits, and socioeconomic factors related to stomach cancer were not studied, and geographical variation of stomach cancer mortality was not adjusted in the present study. However, the results obtained were not considered to be explained by these factors alone.

**ACKNOWLEDGMENTS**

The authors wish to thank Dr. M. Nishizumi, K. Funatsu, K. Hará, Y. Kaizuka, T. Tsuji, N. Machara, and Susan M. Arnold, Saga Medical School; K. Imamura and N. Kawasaki, Kyushu University; Dr. O. Sasaki, Fukuoka Dental College; N. Kawasaki, Tottori University; N. Narita and K. Morooka, National Fukuoka Central Hospital; Y. Ide and H. Ohmi, Saga Municipal Koseikan Hospital; the staff of the city (town, village) office and District Legal Affairs Bureau referred; and the staff of the Health and Welfare Statistics and Information Department, Minister’s Secretariat, Ministry of Health and Welfare, Japan, for their valuable advice and/or technical assistance.
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