Splenectomy combined with gastrectomy and immunotherapy for advanced gastric cancer.

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Abstract

We studied the effects of a splenectomy in combination with immunotherapy on the survival of patients who had undergone a total gastrectomy. It was found that a splenectomy was not effective against advanced gastric cancer at stage III, and that the spleen should be retained for immunotherapy. Splenectomy for gastric cancer at terminal stage IV, particularly in combination with immunotherapy, produced not only augmentation of cellular immunity, but also increased survival.

KEYWORDS: splenectomy, immunotherapy, levamisole, cellular immunity, survival rate

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Abstract. We studied the effects of a splenectomy in combination with immunotherapy on the survival of patients who had undergone a total gastrectomy. It was found that a splenectomy was not effective against advanced gastric cancer at stage III, and that the spleen should be retained for immunotherapy. Splenectomy for gastric cancer at terminal stage IV, particularly in combination with immunotherapy, produced not only augmentation of cellular immunity, but also increased survival.

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There have been numerous reports of splenectomies performed in combination with radical surgery to extirpate lymph nodes and to avoid serosal cancer infiltration in gastric cancer patients, and to increase the effectiveness of the operation in hopes of improving the prognosis (1). The spleen has come to be known as an organ which is greatly involved in the immune system (2), and it has been determined that a splenectomy can improve the prognosis if it is conducted when the spleen acts to inhibit immunity (3).

Now that immunotherapy has also been found to contribute the treatment of gastric cancer (4), such therapy is generally applied. However, it is assumed that immunotherapy is greatly influenced by the presence of the spleen. In the present study, we examined the effect of a splenectomy in or not in combination with immunotherapy on the tumor itself, on the survival of cancer patients, and on cellular immunity.

MATERIALS AND METHODS

During 1965 and 1981, the number of patients with gastric cancer whose stomach was resected in our Department of Surgery totalled 1,385, including 352 who underwent a total gastrectomy, of whom 168 underwent a splenectomy and 186 did not. In the latter half of the period, a greater proportion of the patients underwent a splenectomy than in the first half.

The subjects chosen for the present study, as shown in Table 1, included 90 cases at stage III (5) and 48 cases at stage IV, totaling 138 cases. Immunotherapy was conducted mainly after 1975 when the administration of the immunopotentiator, levamisole (LMS) (4), was started at a dosage of 150 mg/day, for 3 consecutive days every other week. For immunological
Table 1. Patients with cancer of the upper and middle gastric tract who underwent a total gastrectomy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Without splenectomy</th>
<th>With splenectomy</th>
<th>Total (cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immunotherapy - +</td>
<td>Immunotherapy - +</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>28 10 38</td>
<td>32 20 52</td>
<td>90</td>
</tr>
<tr>
<td>Stage IV</td>
<td>7   7  14</td>
<td>16 18 34</td>
<td>48</td>
</tr>
<tr>
<td>Total</td>
<td>35 17 52</td>
<td>48 38 86</td>
<td>138</td>
</tr>
</tbody>
</table>

*a: 1965 through 1981

examination, the PHA blast formation rate of peripheral blood lymphocytes (6), the peripheral blood lymphocyte count and skin reactions to PPD and PHA were examined. The cumulative survival rate was employed.

RESULTS

Splenectomy, lymph node metastasis and depth of cancer invasion in the gastric wall. Lymph node metastasis under the extent of $n_2(+)\text{ was observed in 92.3 \% of the patients who did not have a splenectomy, compared with 79.1 \% of those who did. There were lymph node metastases at the splenic hilus and at the perisplenic artery in 5.6 \% and 41.7 \%, respectively, of the patients not having a splenectomy, and 32.5 \% and 33.3 \%, respectively, in those who did, the latter group having a particularly high extent of lymph node metastasis at the splenic hilus. Cancer invasion of the gastric wall at the serosa exposed (se) level was observed in 90.3 \% of those not undergoing a splenectomy compared with 72.1 \% of those who did, which indicates that the cancer was more advanced in latter group.

Splenectomy and survival rate. The survival rates of stage III patients 1, 2, 3, 4 and 5 years after the gastrectomy were 81.6 \%, 52.6 \%, 36.0 \%, 29.8 \% and 26.3 \% respectively, when a splenectomy was performed, and a rather equal 68.4 \%, 48.9 \%, 48.9 \%, 34.9 \% and 30.8 \%, respectively, when no splenectomy was performed (Fig. 1). However, the survival rates were higher in stage IV patients who underwent a splenectomy than those who did not, the survival rates for the period of 1 to 5 years being 28.6 \%, 14.3 \%, 14.3 \%, 7.1 \% and 7.1 \% in the non-splenectomy group and 49.2 \%, 31.0 \%, 31.0 \%, 21.4 \% and 14.3 \% in the splenectomy group (Fig. 2). In the other words, a splenectomy did not increase survival of stage III patients, while it did of stage IV patients.

Splenectomy, immunotherapy and survival rate. The survival rates 1 to 5 years after the gastrectomy of stage III patients who did not undergo a splenectomy were 78.6 \%, 46.4 \%, 28.6 \%, 15.4 \% and 15.4 \% when immunotherapy was administered, and 90.0 \%, 70.0 \%, 59.2 \%, 59.2 \% and 42.3 \% when it was not. When a
Fig. 1. (left) Effect of splenectomy on survival rates of stage III gastric cancer patients with total gastrectomy. (●●●) With splenectomy, (○○○) Without splenectomy.

Fig. 2. (right) Effect of splenectomy on survival rates of stage IV gastric cancer patients with total gastrectomy. (●●●) With splenectomy, (○○○) Without splenectomy.

Fig. 3. Effect of splenectomy and immunotherapy on survival rates of stage III gastric cancer with total gastrectomy. (●●●) With immunotherapy, (○○○) Without immunotherapy.
spleenectomy was performed, the survival rates of those not having immunotherapy were 67.7 %, 43.4 %, 30.4 %, 26.3 % and 26.3 %, and of those having immunotherapy were 57.6 %, 57.6 %, 38.4 %, 38.4 % and 38.4 %, being slightly higher the latter rates (Fig. 3).

In the same manner, the survival rates of stage IV patients with neither spleenectomy nor immunotherapy were 42.9 %, 28.6 %, 28.6 %, 14.3 % and 14.3 %, and the rates of those with immunotherapy, but no spleenectomy, were 14.3 %, 0 %, 0 %, 0 % and 0 %. Thus, immunotherapy resulted in very low survival rates.

On the other hand, when a spleenectomy was performed on stage IV the survival rates without immunotherapy were 41.9 %, 25.1 %, 25.1 %, 12.6 % and 6.2 %, and those with immunotherapy were 62.5 %, 37.5 %, 37.5 %, 37.5 % and 37.5 %. Immunotherapy in combination with a spleenectomy resulted in higher survival ratio (Fig. 4).

*Splenectomy and cellular immunity.* There was no difference in cellular immunity in terms of PHA blast formation rate of peripheral lymphocytes and skin reactions to PPD and PHA between stage III patients having had a spleenectomy and those not having had one. The postoperative lymphocyte count in the peripheral blood decreased in patients not having a spleenectomy, while it increased in those having one. In stage IV patients, however, cellular immunity without PHA skin reaction, all increased after the spleenectomy, thus showing that cellular immunity was augmented by the performance of a spleenectomy (Fig. 5).

![Graph showing survival rates with and without spleenectomy and immunotherapy](http://escholarship.lib.okayama-u.ac.jp/amo/vol37/iss3/8)
Fig. 5. Difference in cellular immunity before and after operation in the cases of gastric cancer Stage IV with total gastrectomy. (●—●) With splenectomy, (○—○) Without splenectomy.

Postoperative complications. Among the 138 patients, postoperative complications occurred in 41 (29.7%). In 15 out of 51 patients not undergoing a splenectomy there were various complications including pulmonary complications (2), abdominal wound abscess (2), insufficiency of anastomosis (8) and ileus (3). Twenty-six of 87 patients undergoing a splenectomy had complications including 7 with pulmonary complications, 1 with mediastinitis, 4 with pancreatitis, 8 with
dumping syndrome and 1 with ileus. The frequency of complications was 29.4% in the former and 29.9% in the latter, between which there was no difference.

DISCUSSION

The spleen is known to be the organ in which T-cells and B-cells attain maturity and suppressor T-cells accumulate. The spleen is also concerned with producing killer cells and antibody dependent cellular immunity (7), but the particulars are not known. At a certain stage of cancer, the spleen is said to have immunosuppressive activity. A splenectomy performed soon after tumor transplantation augments cellular immunity and prolongs life (6). Yet the function of the spleen as it concerns cancer has not been elucidated.

We have conducted splenectomies on animals at different stages of cancer and found that a splenectomy performed during an early stage of cancer was effective in reducing the size of tumors and prolonging life. At 5 and 10 days after subcutaneous transplantation of $5 \times 10^6$ Ehrlich tumor cells into the back of DDS mice, a splenectomy was performed to study tumor proliferation and macrophage migration inhibition (MI) activity. Five days after tumor transplantation, during the early stage, inhibition of tumor proliferation including the disappearance of tumors, increased survival and an increase in MI activity were observed (6).

In another study using BDF$_1$ mice, $5 \times 10^7$ Lewis lung carcinoma cells were transplanted into the femur, and at 3, 7, 10 and 14 days after tumor transplantation, a splenectomy was conducted to see the effects on tumor proliferation, survival and the delayed hypersensitivity reaction. When a splenectomy was performed as early as 3 days after tumor transplantation, an anti-tumor effect and increased survival were observed. In addition, a decrease in pulmonary metastases larger than 3 mm and an increase of the delayed hypersensitivity reaction using picryl chloride were also observed (9). The spleen was shown to have an immunosuppressive effect in the early stage of cancer, but the effect of a splenectomy at the terminal stage could not be determined due to surgical intervention among other reasons.

In an attempt to eliminate the influence of surgical intervention, the effect of a splenectomy performed during an advanced stage of cancer was studied by Winn’s neutralization test. As a result, it was found that the spleen was immunosuppressive at that time. It is probable that the spleen has two opposite activities depending on the stage of cancer (3, 10). If immunotherapy is used in combination with other treatment, the activities of the spleen probably because more complicated.

There has been many clinical reports describing that in cases of cancer of the upper and middle stomach, a splenectomy should be done for complete
extirpation of the lymph nodes around the splenic hilus and trunca of the splenic artery (1), but there are some countervailing augments. In our present clinical study, for gastric cancer of upper and middle stomach a total gastrectomy combined with a splenectomy was conducted to dissect the lymph nodes around the splenic hilus and splenic artery and remove the cancer invasion around the gastric serosa. A splenectomy did not affect the survival rate when performed on the cases of gastric cancer stage III. However, when immunotherapy was applied, it was thought the spleen should be retained so that its immunoactivity against gastric cancer at stage III would be maintained. On the other hand, in stage IV gastric cancer patients, increased survival could be obtained when a splenectomy was combined with immunotherapy.

Although it has been reported that a splenectomy for advanced cancer could produce a negative effect, there are many reports that a splenectomy should be effective against advanced cancer from an immunological point, but more animal experiments and clinical studies will be necessary to decide which is the best therapy. Splenectomies are said to frequently give rise to postoperative complications (11), but in the present study no such problem was encountered.

REFERENCES

Fukuoka, Japan. 1982.