THE COMBINED TREATMENT FOR CARCINOMA OF THE ESOPHAGUS WITH THE RADICAL RESSECTION AND THE PREOPERATIVE IRRADIATION

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The treatment for carcinoma of the esophagus has made a remarkable stride in recent years with a sharp decline in operative mortality. However, a low resectability rate with a poor five year survival rate still prevails and remains to be urgently solved.

Approximately one half of the patients were found to have unresectable tumors when the diagnosis was confirmed and were excluded from the candidates for the radical operation. Furthermore, it was found that the majority of the patients had been liable to succumb to recurrence of the carcinoma after the radical operation.

The autopsy findings in our clinic have revealed that the carcinoma tends to spread directly in the mediastinum rather than to the distant organs through the lymphatic stream. The carcinoma has been found to recur from the residual cancer cells in the resected end of the esophagus and periesophageal tissue.

In order to elevate the resectability rate and to minimize the local recurrence of the carcinoma after the resection, the combined treatment with the radical resection and the preoperative irradiation with the telecobalt or the linear accelerator has been performed since 1963 with favorable results.

THE REVIEW OF THE MATERIAL

The total cases of 350 patients with carcinoma of the esophagus and the cardia were hospitalized at Keio University Hospital between May, 1956 to

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May, 1964. Of these cases, 119 cases of adenocarcinoma arising in the cardiac end of the stomach were excluded from the present series because of the different sensitivity to the irradiation from squamous cell carcinoma. The present series concerns 231 cases of carcinoma of the esophagus.

All cases were diagnosed as squamous cell carcinoma by microscopic examination. Of these 231 cases, 189 patients underwent the operation without the preoperative irradiation, while 42 patients received the operation with the preoperative irradiation (Table 1).

<table>
<thead>
<tr>
<th>Site</th>
<th>Surgery alone</th>
<th>Surgery with preoperative irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total No. of Cases</td>
<td>Resect-ability</td>
</tr>
<tr>
<td>Cervical</td>
<td></td>
<td>No. %</td>
</tr>
<tr>
<td>Upper and middle thoracic</td>
<td>107</td>
<td>47</td>
</tr>
<tr>
<td>Lower thoracic</td>
<td>65</td>
<td>32</td>
</tr>
<tr>
<td>Total</td>
<td>189</td>
<td>84</td>
</tr>
</tbody>
</table>

THE METHOD OF THE PREOPERATIVE IRRADIATION

The 42 patients were irradiated with the telecobalt or the linear accelerator prior to the radical resection. Of these 42 patients, one half of the patients were treated with the telecobalt therapy and the other half of the patients were irradiated with the linear accelerator.

As the technique of the telecobalt irradiation, the rotating method was chosen for carcinoma of the upper and middle thoracic esophagus and two field cross fire method from front and back with the fixed unit was used for carcinoma of the cervical and lower thoracic esophagus with daily dose of 150 to 250 rads.

Recently the telecobalt therapy was replaced by the linear accelerator. In these cases irradiation with 180 degree pendular motion from front and back was used for carcinoma of the upper and middle thoracic esophagus and two field cross fire irradiation from front and back was used for carcinoma of the cervical and lower thoracic esophagus with the daily dose of 200 rads or with the dose of 400 rads every other day (Table 2).
TREATMENT FOR CARCINOMA OF THE ESOPHAGUS

Table 2

Methods of the preoperative irradiation for carcinoma of the esophagus

1. Irradiation technique

1) Telecobalt Gamma rays irradiation
   - Two field fire from ........... Cervical, lower part of thoracic esophagus and cardia
   - 360 rotation .................. Upper and middle part of thoracic esophagus

2) Linax X-rays irradiation
   - Two field cross fire from .... Cervical, lower part of thoracic esophagus and cardia
   - 180 pendulum from ........... Upper and middle part of thoracic esophagus

2. Tumor dose: R
   Daily 150 ~ 250 rads
   Weekly 750 ~ 1250 rads
   Total 5000 ~ 6000 rads
   [28 ~ 35 days]

4. Waiting period: 10 ~ 25 days
   (Duration between final irradiation and operation)

In order to set the beam of the irradiation in the location of the tumor exactly, a planning apparatus was used with the combination of cobaltograph or liniacograph, bringing the planning into complete accuracy. The total tumor dose ranged from 5,000 to 6,000 rads in 4 to 5 weeks.

The radical operation was performed between 10th and 25th day following the completion of the preoperative irradiation. Carcinoma of the esophagus was resected with the dissection of the adjacent lymph nodes; and intrathoracic esophagogastrostomy or the modified Wookey’s operation was performed.

THE EFFECT OF THE PREOPERATIVE IRRADIATION

The Changes in General Conditions—Dysphagia was relieved in almost all cases after the irradiation and the patients were enabled to take solid foods. The leucocytosis over 10,000 suggestive of mixed infection above the obstructed segment and mediastinitis was reversed to normal value as the result of the improvement in the condition of esophageal obstruction following the irradiation. The leukopenia below 3,000 which is of frequent occurrence after the irradiation was not observed. There were no changes in red cell count, hemoglobin content, plasma protein content, albumin globulin ratio, liver function test, pulmonary function test and electrocardiographic findings after the irradiation. None of the irradiated patients presented neurological abnormality referable to spinal cord necrosis (Fig. 1 and Fig. 2).
The Change on X-ray Film—In the majority of the cases, the length of the filling defect of the esophagus on X-ray film became shorter considerably after the irradiation, and in some cases the filling defect disappeared. No remarkable difference was observed in the effect of the irradiation between the telecobalt and the linear accelerator (Fig. 3, Fig. 4 and Fig. 5).

The Change on Azygography—the azygography suggests unresectable tumors with the findings of obstruction or stenosis which are due to the infiltration of carcinoma to the azygos vein beyond the muscular layer of the esophageal wall. The abnormal findings on azygography disappeared in one half of the total cases following the irradiation (Fig. 6).
Fig. 3 Changes of the filling defect on X ray film.

<table>
<thead>
<tr>
<th>Figures on Azygogram</th>
<th>Resected cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before irradiation</td>
<td>After irradiation</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
</tr>
</tbody>
</table>

- normal figure ———— resectable
- abnormal figure ———— unresectable

Fig. 6. Corelation between azygographic findings and respectability in the irradiated cases.
The Periesophageal Adhesion—As a routine procedure, the radical operation was performed in a month following the irradiation. No troublesome periesophageal adhesion was encountered at the operation.

Improvement in Resectability Rate—The resectability rate was remarkably improved in the irradiated patients. As table 1 indicates, the resectability rate in the non-irradiated patients showed 44 per cent, while that of the irradiated patients was 88 per cent (Table 1).

The Infiltration of Cancer Cells Outside of the Muscular Layer—The close correlation was observed between the size of tumor and the infiltration of cancer cells outside of the muscular layer which is the most frequent source of the recurrence from the periesophageal tissue. The infiltration of cancer cells outside of the muscular layer was found more frequently in the big tumors than in the small tumors. Since the tumor has an irregular form, the long axis was represented as the indicator of the size of the tumors and the correlation between the long axis of the tumor and the infiltration of cancer cells was analysed in the non-irradiated and the irradiated specimens. In the non-irradiated specimens, 5 out of 16 cases of which long axis showed less than 4 cm demonstrated the infiltration of cancer cells outside of the muscular layer, while 36 out of 50 cases having the long axis over 4 cm showed the infiltration of cancer cells beyond the muscular layer. In the majority of the irradiated specimens, the tumor decreased in size after the irradiation, indicating the long axis less than 4 cm. The decrease in the size of the tumor is naturally led to the decrease in the infiltration of cancer cells beyond the muscular layer. Seven out of 36 irradiated cases showed the infiltration of cancer cells outside of the muscular layer, while 41 out of 68 non-irradiated cases showed the infiltration of cancer cells beyond the muscular layer (Table 3).

Table 3
Invasion to the outer layer

<table>
<thead>
<tr>
<th>Site</th>
<th>Irradiated specimen</th>
<th>Non-irradiated Specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>positive</td>
<td>negative</td>
</tr>
<tr>
<td>Cervical</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Upper and middle thoracic</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Lower thoracic</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>60</td>
</tr>
</tbody>
</table>
Persistence of Cancer Cells in the Resected End of the Esophagus—The persistence of cancer cells in the resected end of the esophagus is another source of recurrence after the resection. Histological examination of the resected specimens in our clinic has revealed apparently the necessity of resecting the esophagus 5 cm beyond the macroscopic border of tumor in order to prevent the recurrence from the stump. However, in our experience it is not always easy to resect the esophagus long enough to obtain the intact stump in view of the technical difficulty involved in the esophageal reconstruction. In the non-irradiated specimens, 20 out of 61 cases revealed the presence of cancer cells in the resected end of the esophagus. The preoperative irradiation has successfully minimized the possibility of leaving cancer cells in the resected stump. Only 2 out of 36 cases showed residual cancer cells in the stump (Table 4).

Table 4
Persistence of cancer cells in the stump of the resected specimen

<table>
<thead>
<tr>
<th>Site</th>
<th>Irradiated specimen</th>
<th>Non-irradiated specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Cervical</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Upper and Middle Thoracic</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Lower Thoracic</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

Improvement in Radical Resectability Rate—The preoperative irradiation made a great contribution to minimize the persistence of cancer cells at the resected stump and the infiltration of cancer cells outside of the esophageal wall, leading the majority of the resection to the curative resection. The radical resectability rate has sprung from 50 per cent in the non-irradiated patient to 86 per cent in the irradiated patients (Table 5).

Table 5
Comparison of the radical resectability rate between the non-irradiated and the irradiated cases

<table>
<thead>
<tr>
<th>From hitopathological examination</th>
<th>Irradiated cases</th>
<th>Non-irradiated cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curative resection</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>Pailliative resection</td>
<td>5</td>
<td>35</td>
</tr>
</tbody>
</table>
Macroscopically the resected tumors are classified into 4 major types, namely a) ulcerative type, b) indurative type, c) ulceroindurative type and d) tumorous type.

The ulcerative specimen has an ulcer with desquamation of mucous membrane which marks the sharp boundary from the surrounding normal epithelium.

In the specimen of indurative type, a flat induration covered with normal epithelium was observed with gradual transition to the surrounding area.

The ulceroindurative specimen is characterized by the induration with an ulcer at the center.

The tumorous type shows the projection of a tumor on the mucous membrane.

Of these 4 types, the ulceroindurative specimen was of utmost frequency (Table 6, Fig. 7 and Fig. 8).

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Number of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcerative type</td>
<td>11</td>
<td>30%</td>
</tr>
<tr>
<td>Indurative type</td>
<td>12</td>
<td>32%</td>
</tr>
<tr>
<td>Ulceroindurative</td>
<td>13</td>
<td>35%</td>
</tr>
<tr>
<td>Tumorous type</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>37</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

The histological findings of the resected specimen are summarized as the following:

1) The destruction or disappearance of the cancer cells.
2) As regards the findings of cancer cells, the nuclei showed the findings of pyknosis and fragmentation with eventual dissolution. The protoplasm was vacuolized with occasional disappearance.
3) The infiltration of round cells, edema, fibrosis and cicatrization in the interstitial tissue.

The effect of the irradiation was evaluated on the ground of these histological findings (Fig. 9).

In order to check the persistence of viable cancer cells in the tumor, the examination was performed with serial section of the specimens with every
0.5 cm interval.

Five patterns were observed concerning the distribution of cancer cells in the resected specimens after the irradiation. In 14 out of 37 examined cases, cancer cells remained throughout the specimen, while in 6 cases no cancer cells were observed. In 10 cases cancer cells were localized at the central part of the specimen. Three cases have residual cancer cells at several parts of the specimen. In 4 cases, cancer cells remained at the proximal or distal half of the specimen. And no definite correlation was observed between the macroscopic appearance of the specimen and the distribution of the persistent cancer cells in the specimen (Fig. 10).

<table>
<thead>
<tr>
<th>Cancer Cells</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>diffusely remained</td>
<td>14</td>
</tr>
<tr>
<td>remained in a half part</td>
<td>4</td>
</tr>
<tr>
<td>remained in several regions</td>
<td>3</td>
</tr>
<tr>
<td>remained in the central part</td>
<td>10</td>
</tr>
<tr>
<td>no cancer cell remained</td>
<td>6</td>
</tr>
</tbody>
</table>

Fig. 10 Distribution of residual cancer cells in the resected specimens after irradiation.

THE SURVEY OF 2 YEAR SURVIVAL RATE

The survey of 2 year survival rate has disclosed the efficacy of the preoperative irradiation. The 2 year survival rate in the non-irradiated patients showed 25 per cent, while that of the irradiated patient was 46 per cent with the distinct difference of 21 per cent between the two groups (Fig. 11).
DISCUSSION

The preoperative irradiation has made a great contribution to minimize the extent of the tumor, enabling the majority of the irradiated patients to be subject to the radical resection without the persistent cancer cells at the resected stump and the periesophageal tissue.

There were no unfavorable effects on the irradiated patients reflected upon the routine examination. None of the irradiated patients presented any neurological abnormality referable to spinal cord necrosis which was warned against the irradiation in excess of 6,000 rads by Parker.6)

The resectability rate has increased from 44 per cent in the non-irradiated patients to 88 per cent in the irradiated patients. None of the previously reported series without the preoperative irradiation equaled this figure.7)

As stated before, the persistence of cancer cells at the resected end and periesophageal tissue is inevitable in the majority of the patients without the preoperative irradiation. Parker5) reported that only 11 out of 43 resected specimens had the intact stump with the radical resectability rate of 26 per cent. Katsura3) published that 41 out of 119 patients with carcinoma of the upper and middle thoracic esophagus underwent the curative resection, indicating the radical resectability rate of 34 per cent. The radical resectability rate in

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**Fig. 11** Survival rate of carcinoma of the esophagus.
the non-irradiated patient in our clinic was 50 per cent, which was improved to 86 per cent with the preoperative irradiation. This improvement in the radical resectability rate has brought about the remarkable increase in 2 year survival rate in the irradiated patients.

These results seem to indicate the feasibility of the preoperative irradiation in promoting the complete eradication of cancer cells in the treatment of carcinoma of the esophagus. However, many arguments have been raised concerning the feasibility of the preoperative irradiation. The objections may be summarized as the following remarks.2)

The first objection is directed against the occurrence of the adhesion following the irradiation which will make the operative procedure more difficult. However, in our experience, the radical operation in a month after the irradiation has completely eliminated this possibility. The slight adhesion was observed in some cases but offered no troublesome problem.

The second objection is raised against the potential vulnerability of the irradiated patients to the operative stress which will increase the operative mortality rate. The operative mortality rate of the irradiated patient in our series is 10 per cent, while that of the non-irradiated patients was 17 per cent. This difference in the operative mortality rate seems to consolidate the feasibility of the preoperative irradiation, since the radical operation was performed for the advanced patients who were unable to receive the radical operation without the preoperative irradiation.

The third objection is proposed against the possible dissemination of cancer cells throughout body for which the preoperative irradiation would be responsible. In this connection the data that substantiate this assumption are not available at the present time and this problem awaits further elucidation.

As regards the method of the preoperative irradiation, many theories have been advanced concerning the preference between the short-termed concentrated irradiation and the long-termed fractionated irradiation. The former consists in the irradiation of the total tumor dose of 2,000 to 3,000 rads in 1 to 2 weeks, while the latter represents the administration of the total tumor dose of 5,000 to 6,000 rads in 4 to 5 weeks. Some clinicians favor the short-termed concentrated irradiation, because this method can minimize the hospitalization with the considerable power of the destruction for cancer cells. However, serious complications such as bleeding or perforation of the esophagus due to necrosis of the carcinoma can happen following the irradiation in the event that the tumor cannot be removed by operation. The possible incidence of these complications prevents the universal
employment of this method.

The proponents of the long-termed fractionated irradiation maintain that it is the mild and safe method even for the debilitated patients and the patients with unresectable tumors can be treated with the additional irradiation with minimal complications. The effect of the irradiation for cancer cells is identical with the short-termed concentrated irradiation. It is claimed that these advantage of the long-termed fractionated irradiation can compensate for longer hospitalization. The merits of the long-termed fractionated irradiation led us to adopt this method for the preoperative irradiation.1)

However, the final preference should be determined on the ground of further elucidation of five year survival rate.

SUMMARY AND CONCLUSION

The preoperative irradiation has been undertaken in order to increase the resectability rate for the patients with carcinoma of the esophagus and to minimize the local recurrence after the resection.

The 42 patients were irradiated with the telecobalt or the linear accelerator prior to the radical resection. The total tumor dose of 5,000 to 6,000 rads was given in 4 to 5 weeks in divided dose with daily dose of 150 to 250 rads or 400 rads every other day.

The radical resection was performed in a month following the irradiation. Carcinoma of the esophagus was resected with the dissection of the adjacent lymph nodes; and intrathoracic esophagogastrostomy was performed for carcinoma of the thoracic esophagus and the modified Wookey's operation was done for carcinoma of the cervical esophagus.

The preoperative irradiation has minimized the extent of the tumor, enabling the majority of the irradiated patients to be subject to the radical resection without the persistent cancer cells at the resected stump and the periesophageal tissue.

The resectability rate has increased from 44 per cent in the non-irradiated cases to 88 per cent in the irradiated cases.

It is outstanding achievement that the radical resectability rate has sprung from 50 per cent in the non-irradiated patients to 86 per cent in the irradiated patients.

The preoperative irradiation did not pose any unfavorable effect for the irradiated patients.

The operative mortality rate has decreased from 17 per cent in the non-irradiated patients to 10 per cent in the irradiated patients despite of the application of the radical resection for the advanced cases.
It is our belief that this combined treatment program would increase five year survival rate and could obtain universal acceptance.

REFERENCES


Fig. 4 X ray film before irradiation.

Fig. 5 X ray film after irradiation.
Fig. 7 The non-irradiated specimen.

Fig. 8 The irradiated specimen.

Fig. 9 The histological findings of the irradiated specimen.