Combined Modality Therapy for Oesophageal Squamous Cell Carcinoma

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COMBINED MODALITY THERAPY FOR OESOPHAGEAL SQUAMOUS CELL CARCINOMA

H. PEDERSEN, H. S. HANSEN, S. BERTELSEN and K. FISCHERMAN

Abstract

In a prospective study 110 patients with histologically confirmed oesophageal squamous cell carcinoma received radiation therapy combined with bleomycin or a retinoid. Surgery was initially intended in 34 patients and was later undertaken in 25 of them after irradiation; in 12 patients the operation was regarded as radical and in 4 of these no remaining tumour was found at operation. The survival rate was significantly higher in the operated than in the non-operated patients which entirely depended on the radically operated ones. Survivals up to more than 71 months were observed and the best results were apparently obtained in patients who became tumour-free after preoperative therapy. It is concluded, that the combined treatment was curative only in a few cases and that future studies should be focused on more intensive preoperative treatment and more critical selection of patients for surgery.

Key words: Oesophagus, neoplasms; squamous cell carcinoma, radiation therapy, surgery, bleomycin, retinoids.

The poor results of treatment of oesophageal carcinomas indicate that radiation therapy and surgery as single treatment modalities are insufficient in most cases. In a study of 1002 patients with oesophageal carcinomas, CEDERQUIST et coll. (2, 3) found a 5-year survival rate of 2.3 per cent and a median survival of 5.2 months. In 15 per cent of the patients surgery was attempted, and in 45 per cent of these a resection could be accomplished with a 5-year survival rate of 9.3 per cent. Very similar results are found elsewhere in the literature (4, 5).

Hypothetically the prognosis after surgery might be improved if the oesophageal tumour and the regional lymph node metastases could be eradicated or reduced by preoperative treatment. Radiation therapy offers a potential cure of regional disease and might therefore improve the prognosis when combined with surgery. The effect of chemotherapy is less well established but KOLARIC et coll. (8) found that bleomycin (BLM) given in combination with irradiation in squamous cell oesophageal carcinomas seemed to improve the results.

An effect of vitamin-A analogs, retinoids (RET), on squamous cell carcinomas has been demonstrated in animal studies (1).

In view of this, we have treated a number of patients with a combination of chemotherapy and radiation therapy, followed, if possible, by surgery.

Material and Methods

From October 1977 to December 1983, 110 patients with histologically confirmed oesophageal squamous cell carcinoma were included in this clinical investigation. There were 35 females and 75 males (sex ratio 1:2.1) aged 39 to 86 years (Table 1). All patients were considered to be without detectable regional or distant metastases. Before a patient was accepted for the study routine physical and laboratory examinations were performed including radiography of chest, oesophagus, and stomach, radionuclide liver scan, and electrocardiography.

Excluded from surgery were patients with tumour located above the aortic arch, oesophageal fistulae, senility, psychiatric disorder, congestive heart failure, chronic lung and kidney diseases, or insulin-demanding diabetes. Patients with other malignant disease within the past 5 years were also excluded from the study. Before treatment anaemia and fluid or electrolyte imbalance were corrected. Patients with more than 10 per cent loss of weight were supplied with parenteral nutrition (8). After

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subdivision into surgical and non-surgical groups the patients within the respective groups were randomised to receive BLM or the retinoid RO 10-9359 (RET) as an adjuvant to radiation therapy (Fig. 1).

Irradiation was given by an x-ray beam from a 6 MV linear accelerator; for the thoracic part with a three-field technique and for the upper part with two oblique fields. The fields extended 5 cm cranially and caudally from the tumor borders and with lateral margins of 2 to 3 cm on each side of the esophagus. A daily tumor dose of 2 Gy was given 5 days per week up to a total dose of 30 Gy. According to the randomisation, 5 mg BLM was given intramuscularly half an hour before irradiation or 100 mg RET was administered orally on each treatment day.

After radiation therapy the patients initially classified as operable were referred to surgery. Patients without known postoperative residual tumor who at the operation did not have tumor penetrating the esophageal wall or detected regional lymph node metastases were classified as radically operated. These patients did not receive any further treatment. Operated patients who did not fulfill the criteria mentioned for radicality were classified as palliatively operated. They were given postoperative chemotherapy with methotrexate 20 mg/m²/week intravenously for 6 weeks together with the same drug (BLM or RET) as was given during radiation therapy. Patients who had only exploratory surgery were postoperatively irradiated with an additional tumor dose of 30 Gy, given in the same way as the first course (maximal medullary dose less than half of tumor dose) and with the same adjuvant drug (BLM or RET).

Patients in the non-surgical group received after a 3-week interval a new course of radiation therapy of the same type as the first one and thus, totally received a tumor dose of 60 Gy. They also received during the second course the same type of adjuvant treatment (BLM or RET) as during the first course. After the treatment all patients were followed up clinically and with radiography of the chest and esophagus every third month during the first year and thereafter every sixth month.

Table 1
Comparison of operable and inoperable patients with respect to location of the tumour, TNM classification and length of the tumour as measured at radiography

<table>
<thead>
<tr>
<th>Location</th>
<th>Operable (n=34)</th>
<th>Inoperable (n=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>62.9 years</td>
<td>66.0 years</td>
</tr>
<tr>
<td>Range</td>
<td>39-76</td>
<td>42-86</td>
</tr>
<tr>
<td>Female/male</td>
<td>10/24</td>
<td>25/51</td>
</tr>
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Survival mentioned in the following was measured from the day of randomisation. Survivals between the groups were compared by the log-rank test (13).

Results

Among the 110 patients, 34 initially fulfilled the criteria for operability while 76 were not fit for operation. Table 1 shows the distribution of the patients within the 2 groups with respect to localisation and TNM classification (16).

In the 76 patients initially classified as inoperable there were a number of reasons why they were not suitable for surgery. The main reasons were: 1) location and/or extension of tumor making an operation technically impossible in 37 cases, 2) 3 patients had only small gastric rem-
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Fig. 2. Actuarial survival of the 34 patients primarily classified as operable and the 76 patients classified as inoperable.

Fig. 3. Actuarial survival of 12 radically operated patients and of the remaining patients in the operable group.

### Table 2

**Tumour location, TNM classification and tumour lengths in 25 patients submitted to different types of surgery. Numbers in parentheses denote patients apparently free of tumour after the preoperative therapy.**

<table>
<thead>
<tr>
<th>Location</th>
<th>Radical</th>
<th>Palliative</th>
<th>Exploratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td>10 (3)</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Distal</td>
<td>2 (1)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>TNM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>5 (3)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>T2</td>
<td>5 (1)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>T3</td>
<td>2 (0)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>&gt;8 cm</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&lt;4 cm</td>
<td>2 (2)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>4-8 cm</td>
<td>6 (0)</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>&gt;8 cm</td>
<td>2 (1)</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>=</td>
<td>2 (1)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

nients after a previous gastric resection, 3) 14 patients were excluded on other medical somatic grounds, 18 due to senility, and 2 because of psychiatric disorders; 2 patients refused surgery. Among the 34 potentially operable patients 2 died during the preoperative treatment, and 7 had to be excluded from surgery due to appearance of distant metastases or fistulae or due to clinical deterioration. These patients all died within 12 months.

In 25 patients (Table 2) surgical treatment was undertaken and in 12 of these the operation was regarded as radical according to the criteria mentioned. Four of these patients were free of tumour macroscopically and microscopically after the preoperative treatment. Of the radically operated patients 5 are still alive from 36 to 71 months after randomisation. Two patients have died without evidence of recurrence after 40 and 70 months, respectively (the reasons were pancreatitis and adenocarcinoma of the pancreas without post mortem evidence of recurrence of the oesophageal cancer).

Palliative resection was performed in 6 patients. This group of patients had lymph node metastases, infiltration of adjacent tissues or tumour in the resection line. With the exception of one patient who is still alive after 40 months (October 1986) all died within 4 months (3 in the postoperative period).

Exploratory operation was undertaken in 7 patients who were found inoperable either due to distant metastases detected during the operation or because removal of the tumour was technically impossible. All patients died within 4 months except for one who lived for 22 months.

Among the 76 patients initially classified as inoperable 16 died during the treatment period. One patient is still alive after 52 months and one died without recurrence after 50 months. The remaining patients survived a maximum of 19 months. Radiography of the oesophagus after the end of treatment demonstrated tumour regression in 40 patients (67%), no change in 11 and progressive disease in 4, while 5 were not examined.

There was no difference in the survival rates between the groups receiving adjuvant treatment with BLM or RET (p=0.26 log-rank). In each group 2 patients were free of tumour at the operation. Apart from a few cases with fever after BLM there were no side effects of the adjuvant therapy.

There was a highly significant difference (p=0.002 log-rank, Fig. 2) between the survival rates in the 34 patients classified as operable and the 76 patients classified as inoperable. This difference in survival rate depended on the radically operated cases when the radically operated cases were subtracted (p=0.78) (Fig. 3).

The operable patients had a median survival of 4 months and the inoperable ones 3.2 months. That the difference was so small could be explained by treatment mortality in the operable group.
Discussion

Only a minority of patients with oesophageal carcinoma are curable when the diagnosis is established (2–5). In this study we selected a group of patients in whom according to our evaluation the tumour had not spread outside the volume to be irradiated. In that group, 32 per cent of the patients were initially classified as fit for operation but, despite preoperative treatment, the surgery could be regarded as radical in only one-third of them. Also among the radically operated patients there was a number of recurrences but the 4 patients, who were free of tumour at the operation, remained without recurrence. This experience is consistent with that of others who have given multimodal treatment (6, 10).

Patients initially classified as operable but not radically operated upon and patients initially classified as inoperable had a similar median survival, i.e. 2.6 and 3.2 months, respectively. However, 67 per cent of the irradiated patients had an improved oesophageal passage after the radiation therapy and relief of symptoms. This suggests that more precise preoperative methods to disclose prognostically unfavourable factors, such as oesophageal wall penetration or lymph node metastases (15) are required. Preoperative computed tomography seems to be rather inaccurate concerning these parameters (9, 14). DNA analysis may give information of prognostic value. In biopsy specimens from oesophageal carcinomas chromosome aberrations have been found which makes it possible to subdivide the tumours into risk groups with different probability of penetration to surrounding tissues and of lymph node metastases (11).

In the present study no difference could be observed between irradiation plus BLM and irradiation plus RET. These drugs were given more with the aim to enhance the effect of irradiation than as proper chemotherapy. A more potent chemotherapy in combination with radiation therapy is probably needed in order to increase the prognostically favourable fraction of the patients. Kelsen et coll. (7) gave a combination of BLM, vindesine and cisplatinum and found objective regression in 53 per cent of the patients with the highest response rate in patients with regional disease. Preoperative therapy with this regimen combined with radiation therapy might improve the results but it will then be at the expense of a higher treatment morbidity.

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REFERENCES