Preoperative Concurrent Chemotherapy and Radiation Therapy Followed by Surgery for Esophageal Cancer

Masahiko Yano, MD,1 Masatoshi Inoue, MD,2 and Hitoshi Shiozaki, MD3

Currently, the most promising strategy to improve the prognosis of advanced esophageal cancer is preoperative chemoradiation (CRT) followed by surgery. The superiority of CRT over radiation therapy alone has been demonstrated by several randomized studies. Many phase II studies of CRT followed by surgery have shown that the pathologic complete response (CR) rate ranges from 17 to 40%, and the median survival time (MST) is 12 to 31.3 months. Five randomized trials have compared preoperative CRT followed by surgery with surgery alone for resectable esophageal cancer, and four of them did not find any significant survival benefit for the combined treatment group. There are several issues in interpreting these findings, such as the quality of the surgery, the accuracy of the preoperative staging, the statistical power and design of the trials. Until comprehensive evaluation can be done, the standard therapy for resectable esophageal cancer should be considered to be surgery alone. The histological response in the resected specimen correlates well with the prognosis. Patients with pathologic CR display significantly better survival than those with microscopic residual cancer cells in the resected specimens. These findings suggest that more potent regimens leading to higher pathologic CR rates should improve the prognosis. Chemotherapy or radiation therapy sensitivity testing needs to be established. If accurate prediction of the response is possible prior to therapy, non-responders can be excluded. Cell cycle-related genes, apoptosis-related genes, and drug metabolizing genes have been investigated in many pilot studies and need to be evaluated by large-scale clinical studies. At present, pathologic CR can not be accurately diagnosed before surgery. Endoscopic biopsy is also unreliable for the diagnosis. In the future, new diagnostic tools such as positron emission tomography scanning, a sensitivity test or molecular markers may enable accurate diagnosis of pathologic CR to guide the choice of treatment strategies for individual patients. (Ann Thorac Cardiovasc Surg 2002; 8: 123–30)

Key words: locally advanced esophageal cancer, squamous cell carcinoma, chemoradiation, neoadjuvant therapy, multimodal therapy

Introduction

Among the many gastrointestinal cancers, esophageal cancer has one of the poorest prognoses because it easily metastasizes to lymph nodes as well as to distant organs.1,2 Every submucosal tumors, lymph node metastasis is observed in about 40% of the cases, which is much more frequent than for gastric or colorectal cancers (about 10%).3 Furthermore, esophageal cancer often infiltrates neighboring organs such as the aorta, trachea and bronchus, since the esophagus lacks serosa and is located in a very narrow mediastinal space. Once such organs are infiltrated, complete surgical resection of the tumors is very difficult, and even if it were possible, the prognosis of such patients is extremely poor.4,6 One way of improving the prognosis of patients with locally advanced esophageal cancer is multimodal therapy. Radiation therapy...
alone may improve locoregional control but does not improve overall survival, whether given preoperatively or postoperatively. Increased incidence of clinically apparent distant organ metastasis during follow-up after radiation therapy suggests that systemic micrometastasis may have been present at the time of diagnosis, and thus systemic therapy is also required.\textsuperscript{7-12) Adjuvant chemotherapy alone has not been reported to improve survival to date.\textsuperscript{13,14) Recently, neoadjuvant chemoradiation therapy given prior to surgical resection has been anticipated to control both local recurrence and distant metastasis of esophageal cancer.}

### Concurrent Chemoradiation for Esophageal Cancer

The rationale behind preoperative chemoradiation therapy is as follows: 1) preoperative therapy permits higher resectability in the subsequent surgery; 2) chemoradiation therapy is more tolerable before surgery than after it; 3) simultaneous treatment with chemotherapy and radiation may control not only local but also occult distant disease; 4) 5-fluorouracil and cisplatin, most frequently used in chemoradiation regimens, both act as radiation sensitizers.\textsuperscript{15) On the other hand, the disadvantages of this strategy is that a substantial percentage of patients who do not respond to it may lose the chance of surgery and that the toxicity of the preoperative treatment may increase operative morbidity and mortality.

The superiority of concurrent chemoradiation therapy over radiation therapy alone has been demonstrated by several randomized studies as shown in Table 1. Araujo et al. compared treatment using 5-fluorouracil (5-FU)/mitomycin C (MMC)/bleomycin (BLM) plus 50 Gy of radiation therapy with treatment using radiation therapy (50 Gy) alone for 59 patients. They reported that although survival was not improved by the combined therapy, local (46.5\% vs. 74\%) and distant (9\% vs. 22\%) failure rates decreased in the chemoradiation therapy group.\textsuperscript{16) Sischy et al. in 1990 for the Eastern Cooperative Oncology Group (ECOG) reported the results of their randomized trial comparing 5-FU/MMC plus 60 Gy of radiation therapy with radiation therapy (60 Gy) alone in 119 patients with squamous cell carcinoma. The median survival time (MST) for chemoradiation therapy was 14.8 months, which was significantly longer than the 9.1 months for radiation therapy alone (p=0.03).\textsuperscript{17) Herskovic et al. in 1992, with an update in 1997 for the GI Intergroup, randomized 121 patients with localized disease of 15 cases of adenocarcinoma and 106 cases of squamous cell carcinoma to treatment using either 5-FU plus cisplatin (CDDP) with 50 Gy of radiation therapy or treatment using radiation therapy (64 Gy) alone. The MST was 9.3 months for the radiation therapy alone group, compared with the 14.1 months for the chemoradiation therapy group. The 2- and 5-year survival rates in the former group were 10\% and 0\%, respectively, whereas those for the combined therapy group were 38\% and 27\% (p<0.0001). Both the local (44\% vs. 65\%) and distant (12\% vs. 26\%) recurrences were significantly fewer in the chemoradiation therapy group.\textsuperscript{18,19) At present, it is generally accepted that concurrent chemoradiation therapy has a significant advantage over radiation therapy alone. Therefore, recent studies recommend chemoradiation therapy as an adjuvant or definitive treatment.

### Concurrent Chemoradiation without Surgery

Many phase II trials of concurrent chemotherapy and radiation therapy as definitive therapy without surgery have

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Regimen</th>
<th>RT</th>
<th>No. of patients</th>
<th>MST (mo)</th>
<th>2 years Survival</th>
<th>3 years Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Araujo\textsuperscript{16)</td>
<td>5-FU/MMC/BLM</td>
<td>50 Gy</td>
<td>28</td>
<td>NS</td>
<td>38%</td>
<td>16%</td>
</tr>
<tr>
<td>Sischy\textsuperscript{17)</td>
<td>5-FU/MMC</td>
<td>60 Gy</td>
<td>119\textsuperscript{*}</td>
<td>14.8*</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Herskovic\textsuperscript{18,19)</td>
<td>5-FU/CDDP</td>
<td>64 Gy</td>
<td>60</td>
<td>9.3</td>
<td>10%</td>
<td>0%</td>
</tr>
</tbody>
</table>

RT: radiation therapy, MST: median survival time, 5-FU: 5-fluorouracil, MMC: mitomycin C, BLM: bleomycin, CDDP: cisplatin, NS: not stated
\textsuperscript{*}: total number of patients receiving chemoradiation and radiation alone
\textsuperscript{*}: p=0.03, **: p<0.0001 vs. radiation therapy alone
been conducted, with selected studies outlined in Table 2. Leichman et al. conducted a pilot nonoperative study on 20 patients with squamous cell carcinoma. Surgery was not planned after chemoradiation therapy based on their early studies showing high operative mortality after chemoradiation therapy and an uncertain contribution of surgery to survival benefit. The regimen consisted of two cycles of 5-FU and CDDP given concurrently with 30 Gy of radiation followed by an additional two cycles of chemotherapy with MMC and BLM. An additional boost of radiation therapy (20 Gy) was given after completion of chemotherapy. The MST in this series was 22 months. Leichman et al. conducted a pilot nonoperative study on 20 patients with squamous cell carcinoma. Surgery was not planned after chemoradiation therapy based on their early studies showing high operative mortality after chemoradiation therapy and an uncertain contribution of surgery to survival benefit. The regimen consisted of two cycles of 5-FU and CDDP given concurrently with 30 Gy of radiation followed by an additional two cycles of chemotherapy with MMC and BLM. An additional boost of radiation therapy (20 Gy) was given after completion of chemotherapy. The MST in this series was 22 months.

Castro et al. reported the results of 57 patients with squamous cell and adenocarcinoma treated with chemoradiation therapy alone. Patients were treated with 5-FU and MMC given concurrently with 60 Gy of radiation therapy. The MST was 18 months with 3-year and 5-year survival rates of 29% and 18%, respectively. Local control was achieved in 70% of the patients. Of the 29 patients with recurrences, local and distant failures occurred in 48% and 72%, respectively. John et al. reported the results of 30 patients treated with 5-FU and MMC given concurrently with 60 Gy of radiation therapy. The MST was 18 months with 3-year and 5-year survival rates of 29% and 18%, respectively. Local control was achieved in 70% of the patients. Of the 29 patients with recurrences, local and distant failures occurred in 48% and 72%, respectively.

Whether surgery after chemoradiation therapy actually does contribute to survival remains unknown and needs to be proven by randomized study. However, in theory, concurrent chemoradiation followed by surgery seems to offer the highest curability for patients. Local control should be better than that from a non-surgical approach because residual cancer cells in the esophagus and regional lymph nodes can be removed by surgery. Thus, until further evidence is obtained, chemoradiation therapy without surgery should not be used for the treatment of patients with localized, surgically curable disease. Chemoradiation therapy alone should only be used when the tumors are unresectable.

### Concurrent Chemoradiation Followed by Surgery

Phase II studies of concurrent chemotheraphy and radiation therapy followed by surgery are summarized in Table 3. The first report of preoperative chemoradiation therapy for esophageal cancer came from Franklin et al. They had obtained successful results for anal cancer and applied it to the treatment for esophageal cancer. Their regimen consisted of 30 Gy of radiation with 5-FU and MMC followed by surgery. Of the 30 patients enrolled in their study, resection was done for 23. Six of these 23 patients (26%) had no evidence of cancer cells in the resected specimens. The MST was 18 months. All the patients with residual tumor in the resected esophagus showed recurrence during the follow-up, whereas four of the six pathologic complete response (CR) patients were alive at 95 to 190 weeks. Many subsequent studies modified this protocol and used CDDP in place of MMC because CDDP was reported to be effective in combination with 5-FU for advanced esophageal cancer. As shown in Table 3, the pathologic CR rate of these phase II studies ranged from 17 to 40%, and the MST was 12 to 31.3 months. These encouraging results have made neoadjuvant chemotherapy followed by surgery one of the most promising strategies for locally advanced esophageal cancer.

Whether surgery after chemoradiation therapy actually does contribute to survival remains unknown and needs to be proven by randomized study. However, in theory, concurrent chemoradiation followed by surgery seems to offer the highest curability for patients. Local control should be better than that from a non-surgical approach because residual cancer cells in the esophagus and regional lymph nodes can be removed by surgery. Thus, until further evidence is obtained, chemoradiation therapy without surgery should not be used for the treatment of patients with localized, surgically curable disease. Chemoradiation therapy alone should only be used when the tumors are unresectable.

### Table 2. Phase II studies of concurrent chemoradiation without surgery

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Regimen</th>
<th>RT</th>
<th>No. of patients</th>
<th>Major response</th>
<th>MST (mo)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leichman</td>
<td>5-FU/CDDP+MMC/BLM</td>
<td>30+20 Gy</td>
<td>20</td>
<td>NS</td>
<td>22</td>
<td>NS</td>
</tr>
<tr>
<td>Coia</td>
<td>5-FU/MMC</td>
<td>60 Gy</td>
<td>57 (Stage I, II)</td>
<td>NS</td>
<td>18</td>
<td>29% (3 yrs), 18% (5 yrs)</td>
</tr>
<tr>
<td>John</td>
<td>5-FU/CDDP/MMC+MTX/5-FU/LV</td>
<td>41.5-50.4 Gy</td>
<td>30</td>
<td>77%</td>
<td>15</td>
<td>29% (2 yrs)</td>
</tr>
<tr>
<td>Le Prise</td>
<td>5-FU/CDDP</td>
<td>60 Gy</td>
<td>50</td>
<td>NS</td>
<td>13</td>
<td>63% (1 y), 36% (2 yrs)</td>
</tr>
<tr>
<td>Minsky</td>
<td>5-FU/CDDP (NAC)+5-FU/CDDP (CRT)</td>
<td>64.8 Gy</td>
<td>37</td>
<td>NS</td>
<td>20</td>
<td>NS</td>
</tr>
</tbody>
</table>


*: The trial was terminated because of toxicity.
Table 3. Phase II studies of concurrent chemoradiation followed by surgery

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Regimen</th>
<th>RT</th>
<th>No. of patients</th>
<th>Resectability</th>
<th>Operative mortality</th>
<th>Path CR</th>
<th>MST (mo)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Franklin (35)</td>
<td>5-FU/MMC</td>
<td>30 Gy</td>
<td>30</td>
<td>76%</td>
<td>13%</td>
<td>20%</td>
<td>18°</td>
<td>30% (3 yrs)*</td>
</tr>
<tr>
<td>Leichman (36)</td>
<td>5-FU/CDDP</td>
<td>30 Gy</td>
<td>21</td>
<td>71%</td>
<td>27%</td>
<td>24%</td>
<td>18</td>
<td>NS</td>
</tr>
<tr>
<td>Poplin (37)</td>
<td>5-FU/CDDP</td>
<td>30 Gy</td>
<td>106</td>
<td>49%</td>
<td>11%</td>
<td>17%</td>
<td>12</td>
<td>16% (3 yrs)</td>
</tr>
<tr>
<td>Seydel (38)</td>
<td>5-FU/CDDP</td>
<td>30 Gy</td>
<td>41</td>
<td>66%</td>
<td>4%</td>
<td>20%</td>
<td>13</td>
<td>8% (3 yrs)</td>
</tr>
<tr>
<td>Forastiere (39)</td>
<td>5-FU/VBL/CDDP</td>
<td>37.5-45 Gy</td>
<td>43</td>
<td>91%</td>
<td>2%</td>
<td>24%</td>
<td>29</td>
<td>34% (5 yrs)</td>
</tr>
<tr>
<td>Wolfe (40)</td>
<td>CDDP/VCR (Sq)</td>
<td>45 Gy</td>
<td>104</td>
<td>53%</td>
<td>5%b</td>
<td>40%</td>
<td>25.5*</td>
<td>25% (5 yrs)*</td>
</tr>
<tr>
<td>Forastiere (41)</td>
<td>5-FU/CDDP (Adeno)</td>
<td>45 Gy</td>
<td>45</td>
<td>67%</td>
<td></td>
<td>20%</td>
<td>29.1*</td>
<td>20% (5 yrs)*</td>
</tr>
<tr>
<td>Forastiere (41)</td>
<td>5-FU/CDDP</td>
<td>44 Gy</td>
<td>50</td>
<td>90%</td>
<td>0%</td>
<td>40%</td>
<td>31.3</td>
<td>58% (2 yrs)</td>
</tr>
</tbody>
</table>


*: data for resected cases, b: operative mortality for both Sq and Adeno

Table 4. Randomized trials comparing concurrent chemoradiation followed by surgery with surgery alone

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Regimen</th>
<th>RT</th>
<th>No. of patients</th>
<th>Resectability</th>
<th>Operative mortality</th>
<th>Path CR</th>
<th>MST (mo)</th>
<th>3 y-survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nygaard (42)</td>
<td>CDDP/BLM</td>
<td>35 Gy</td>
<td>53</td>
<td>88.7%</td>
<td>23.5%</td>
<td>NS</td>
<td>9</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Surgery alone</td>
<td></td>
<td>50</td>
<td>82.0%</td>
<td>13.2%</td>
<td></td>
<td>8.4</td>
<td>9%</td>
</tr>
<tr>
<td>Le Prise (43)</td>
<td>5-FU/CDDP</td>
<td>20 Gy</td>
<td>41</td>
<td>85.0%</td>
<td>8.5%</td>
<td>10%</td>
<td>NS</td>
<td>19.2%</td>
</tr>
<tr>
<td></td>
<td>Surgery alone</td>
<td></td>
<td>45</td>
<td>93.0%</td>
<td>7.0%</td>
<td>NS</td>
<td>13.8%</td>
<td></td>
</tr>
<tr>
<td>Walsh (44)</td>
<td>5-FU/CDDP</td>
<td>40 Gy</td>
<td>58</td>
<td>100%</td>
<td>6.9%</td>
<td>25%</td>
<td>16*</td>
<td>32%*</td>
</tr>
<tr>
<td></td>
<td>Surgery alone</td>
<td></td>
<td>55</td>
<td>100%</td>
<td>3.6%</td>
<td>11</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Bosset (45)</td>
<td>CDDP</td>
<td>37 Gy</td>
<td>143</td>
<td>96.5%</td>
<td>12.3%</td>
<td>26%</td>
<td>18.6</td>
<td>37%</td>
</tr>
<tr>
<td></td>
<td>Surgery alone</td>
<td></td>
<td>139</td>
<td>98.6%</td>
<td>3.6%</td>
<td>18.6</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>Urba (46)</td>
<td>5-FU/VBL/CDDP</td>
<td>45 Gy</td>
<td>50</td>
<td>94.0%</td>
<td>2.0%</td>
<td>28%</td>
<td>16.9</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Surgery alone</td>
<td></td>
<td>50</td>
<td>100%</td>
<td>4.0%</td>
<td>17.6</td>
<td>16%</td>
<td></td>
</tr>
</tbody>
</table>


*: p=0.01 vs. surgery alone

domized trials which compared preoperative chemoradiation followed by surgery with surgery alone have been conducted for resectable esophageal cancers. (32-36) (Table 4) Only one study reported by Walsh et al. demonstrated a significantly better median survival time and 3-year survival for the chemoradiation group. (34) However, criticism of their paper work pointed out that their control group showed very poor survival (3-year survival of 6% and MST of 11 months), which might have led to a significant difference in their results. The other four studies failed to show any significant survival benefit for the combined treatment group.

From these findings, the question arises of whether preoperative chemoradiation is necessary. When interpreting these literature findings, attention must be paid to several points. First, the quality of the surgery is a critical factor. High operative mortality (2.0-23.5%) and the choice of surgical procedure (transhiatal esophagectomy or esophagectomy with lymphadenectomy through right thoracic and abdominal routes) may affect the outcome. Second, the accuracy of the preoperative staging of the disease is important. Since nodal involvement is an important prognostic factor for esophageal cancers, the number and extent of lymph node metastases must be accurately diagnosed for even randomization. Therefore, well-designed trials of high quality which overcome these problems are needed to prove the significant survival benefit of preoperative chemoradiation. Until this is done, standard therapy for resectable esophageal cancer should be considered to be surgery alone.
Future Directions

Most studies have shown that patients with pathologic CR displayed significantly better survival than those with a pathologic partial response (PR). Forastiere et al. reported that pathologic CR patients had a median survival duration of 70 months and 60% were alive at 5 years, while those with residual tumors in the resected specimen had a median survival duration of 26 months and 32% were alive at 5 years. Previously, we reported the results of neoadjuvant chemoradiation therapy followed by surgery for 43 patients with primary inoperable T4 esophageal cancer. Pathologic CR was found in 8 (28.6%) of 28 surgical specimens. As shown in Fig. 1, the histological response in the resected specimen correlated well with the prognosis. Most of the long-term survivors (more than 5 years) were in the pathologic CR group, whereas there were few 5-year survivors among those with microscopic residual cancer cells in the resected specimen. Mandard et al. demonstrated that pathologic CR was the only significant predictor of disease-free survival for patients with esophageal cancer by multivariate analysis. These findings suggest that more potent regimens having higher pathologic CR rates should improve the prognosis of patients and make preoperative chemoradiation followed by surgery a standard therapy for esophageal cancer in the future.

Paclitaxel is a candidate drug which leads to a higher pathologic CR rate in combination with radiation therapy since it is a potent radiosensitizer and has an antitumor effect against esophageal cancer. Preliminary results suggest that preoperative concurrent paclitaxel-based combination chemotherapy with radiation therapy is very effective for esophageal cancer. In addition, a new radiosensitizer which enhances the radiation effect or an agent which reduces cytotoxicity should also be developed. Cytoprotective drugs such as amifostine are under investigation for clinical use. Hyperfractionated radiation is another approach to increasing the pathologic CR rate. Kim et al. conducted a phase II study of preoperative hyperfractionated radiation (48 Gy/40 fr/4 weeks) with concurrent chemotherapy (5-FU/cisplatin) followed by surgery for 94 resectable esophageal cancer patients. The pathologic CR rate was 49% for 53 resected patients, which was better than the historical control.

Chemotherapy or radiation therapy sensitivity testing is another important issue. If accurate prediction of response becomes possible pretherapeutically, non-responders who would receive no benefit from the treatment can be excluded. Cell cycle-related genes, apoptosis-related genes, and drug metabolizing genes have been investigated in many pilot studies. Miyata et al. reported that p53 mutation seems to be correlated with resistance to the treatment and that CDC25B, one of the cell cycle regulators involved in G2/M arrest, is also a candidate for a predictor. Imdahl et al. demonstrated that a higher proliferation index (>39%) as determined by MIB-1 positivity indicates a responder to the treatment. Yamamoto et al. reported that metallothionein expression in tumor tissue correlated well with the pathologic response. Metallothionein is an intracellular metal-binding protein and is involved in detoxification of heavy metals including cadmium, copper and mercury. Immunohistochemical analysis of pretherapeutic biopsy specimens revealed that 13 out of 14 patients with metallothionein-negative tumor cells were responders, whereas 10 out of 16 pa-

Fig. 1. Relationship between survival rates and histologic effect of the main tumors. Histologic effect is defined as follows: grade 3, complete disappearance of cancer cells; grade 2, more than 2/3 disappearance; grade 1, less than 2/3 disappearance.
tients with metallothionein-positive tumor cells were non-responders. Large-scale clinical study is necessary for evaluation of these factors.

The next question that arises is whether surgery can be omitted if pathologic CR is accurately diagnosed after chemoradiation therapy. The answer is probably “yes”. Non-surgical, definitive chemoradiation trials summarized in Table 2 show substantial percentages of long-time survivors, which seems to correspond to the pathologic CR rates reported in phase II trials of preoperative chemoradiation followed by surgery as shown in Table 3. Patients who truly need surgery after chemoradiation and can benefit from it may be only those with microscopic residual tumors. However, conventional methods such as CT scan and endoscopic ultrasound can not correctly evaluate pathologic CR. As shown in Fig. 2, endoscopic biopsy is also unreliable because most residual tumor cells after the treatment are located not in the mucosal layer but in the muscular and deeper layers of the esophageal walls. Positron emission tomography (PET) scan was reported to be more sensitive than CT in the detection of nodal involvement of esophageal cancer. Brucher et al. reported that the pathologic tumor response after preoperative chemoradiation therapy can be evaluated by tumor uptake of FDG. The diagnostic power of PET for microscopic residual tumors remains unknown, but PET alone or in combination with other tools such as a sensitivity test may enable accurate diagnosis of pathologic CR in the future.

Advances in molecular biology are contributing to elucidating the mechanism of esophageal tumorigenesis, metastasis, and response to treatment. Findings from such work should guide the choice of future treatment strategies.

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