Diseases of the Esophagus (2002) 15, 61–66

DISEASES OF THE ESOPHAGUS

Original article

Histopathologic effects of neoadjuvant therapies for advanced squamous cell carcinoma of the esophagus: multivariate analysis of predictive factors and p53 overexpression

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SUMMARY. **In 97 patients (60, chemotherapy; 22, chemoradiotherapy; 15, radiotherapy), histopathologic effects were evaluated microscopically, and histologic response rates were compared among three neoadjuvant treatment modalities. Predictive factors for neoadjuvant therapies were analyzed by logistic regression, including the results of p53 immunohistochemical staining. In the chemoradiotherapy group, the pathologic response rate was 86.4%, and was significantly higher than that for chemotherapy ($P < 0.0001$) or for radiotherapy ($P = 0.0031$). In patients with normal p53 protein expression, the histopathologic response rate to chemotherapy was 20.0%, a higher rate than that for patients with abnormal p53 overexpression. In the chemoradiotherapy or radiotherapy group, however, the response rates were almost the same, irrespective of p53 oncoprotein status. From multivariate analysis, the neoadjuvant treatment modality itself was identified as the most powerful predictive factor for the effect. Chemoradiotherapy had the most powerful effect on advanced esophageal cancer, and p53 status did not influence the clinical outcome in this group.**

INTRODUCTION

Despite vigorous efforts to improve the outcome in advanced esophageal cancer, the overall 5-year survival in patients with this disease is still unsatisfactory. During the last decade, preoperative chemotherapy or radiotherapy have been advocated.[1,2] More recently, the efficacy of neoadjuvant chemoradiotherapy has also been recognized.[3] We cannot tell, however, which neoadjuvant modality for advanced esophageal cancer is the most effective among these three treatments (chemotherapy, radiotherapy, and chemoradiotherapy). Nor do we really know whether conventional CT scan evaluation, fiberoptic examination or endoscopic ultrasonographical assessment can tell the true therapeutic effect or not.[4,5] Here, we evaluated the anticancer effects of neoadjuvant therapies, not by tumor shrinkage, but by microscopic disappearance of cancer cells from surgically resected esophageal specimens, which is the gold standard.[6]

Tumor growth in esophageal cancer is very rapid compared with that of other gastrointestinal malignancies,[7] and the esophagus is anatomically located very close to major organs such as the trachea, bronchi, or descending aorta. When esophageal cancer is resistant to neoadjuvant therapies, it is almost impossible to surgically resect the esophagus because of the rapid invasion of these adjacent organs. It is accordingly quite important to predict the response before neoadjuvant therapies in advanced esophageal cancer.

From recent molecular biological studies *in vitro*, it is known that p53 tumor suppressor gene status may determine sensitivity to anticancer drugs or radiation via the apoptotic mechanism.[8,9] From clinical experience we do not actually know, however, whether p53 alteration plays an important role in the sensitivity to anticancer drugs or radiotherapy of esophageal cancer.[10–12] In this study, we assessed p53 alteration using immunohistochemical staining of cancer biopsy

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specimens obtained before neoadjuvant therapies, and compared the p53 oncoprotein status with histopathologic effects of neoadjuvant therapies, as judged from the resected specimens.

The aim of this study was to analyze predictive factors that had a significant influence on the true histopathologic effects of neoadjuvant treatment for advanced esophageal cancer, using multivariate logistic regression analysis, and to investigate the clinical value of p53 overexpression as a predictive factor for the efficacy of neoadjuvant therapies.

MATERIALS AND METHODS

Patients

Since 1990, we performed cisplatin and 5-fluorouracil-based preoperative chemotherapy, or radiotherapy, or concurrent chemoradiotherapy, followed by complete resection, in 97 patients with very advanced squamous cell carcinoma of the esophagus at Juntendo University School of Medicine and Toranomon Hospital, Tokyo. The characteristics of the patients are summarized in Table 1. All patients underwent investigations of barium study of the upper gastrointestinal tract, fiberoptic esophagoscopy, endoscopic ultrasonography (EUS), cervical, mediastinal and abdominal CT scan, and cervical and abdominal ultrasonography, to evaluate the depth of tumor invasion, distribution of lymph node metastases, and distant organ metastasis. When the tumor was resectable without distant metastasis, and there was no suspicion of a number of metastatic lymph nodes (less than five nodes), we elected to prefer surgical resection with extended (cervical, mediastinal, and abdominal) lymph node dissection, without neoadjuvant treatment.[13] The 97 patients enrolled into this study had very advanced diseases, with more than five lymph nodes with metastases or with distant organ metastasis, or suspected invasion to adjacent major unresectable organs, at preoperative examination. The 60 patients who were suspected to have more than five metastatic lymph nodes or distant organ metastases, received preoperative chemotherapy, anticipating systemic anticancer effects of the agents. When the depth of tumor invasion was into the neighboring organs, and the distribution of lymph node metastases was confined to a limited area, we chose preoperative radiotherapy alone in 15 patients before 1994, and concurrent chemoradiotherapy in 22 patients after 1995.

About 3–4 weeks after completing neoadjuvant treatment, 97 patients underwent esophageal resection with three-field (collo-thoraco-abdominal) lymph node dissection via right thoracotomy, median laparotomy, and cervical collar incision approaches.[13] In all patients, histopathologic effects of neoadjuvant therapies were evaluated microscopically from the resected esophageal specimen.

Table 1. Patients' characteristics according to the treatment group

	Chemotherapy (n = 60)	Chemoradiotherapy (n = 22)	Radiotherapy (n = 15)
Age (years)			
Median	58.0	60.0	59.0
Range	44–73	47–71	46–78
Sex (no. of points)			
Male	57	19	13
Female	3	3	2
Depth of tumor invasion (no. of points)			
T1	12	3	2
T2	9	2	1
T3	31	15	8
T4	8	2	4
Tumor size (cm)			
Mean	7.2	6.8	6.3
Range	2.2–18	2.0–12	2.0–10

Neoadjuvant protocols

Neoadjuvant treatment regimens were as follows: all chemotherapy group patients received CDDP 70 mg/m^2 for 2 days and high-dose 5-fluorouracil 700 mg/m^2 for 8 days during a 4-week period. To patients in the chemoradiotherapy group, we administered a combination of 5 mg of CDDP and 250 mg continuous infusion of 5-fluorouracil concurrently, and irradiated 2 Gy per day up to a total dose of 40 Gy. In the radiotherapy group, patients received 2 Gy radiation per day for 20 sessions.

Evaluation of histopathologic effects of neoadjuvant therapies and definition of histologic response rate

We operated on 97 patients through right thoracotomy and median laparotomy approaches, and resected the thoracic esophagus and upper stomach. From microscopic examination of esophageal cancers following neoadjuvant therapies, we can usually observe various histopathologic changes that occurred in the tumor. These include ballooning or vacuolation of cells, pyknosis of nuclei, degradation of glandular structures, necrosis or disappearance of cells, granuloma formation, and fibrosis.[14] From the resected specimen, we assessed histopathologic changes following neoadjuvant therapies at various points. The sites of examined sections were, for example, the plane across the maximal diameter of the tumor and the deepest point of the tumor invasion, etc. Approximately 20 points were examined for histopathologic assessment per patient. We quantitated these histopathologic changes caused by neoadjuvant therapies in the tumors. From the percentage of necrotic or disappeared tumor cells out of the estimated total number in the lesion, four categories of histopathologic therapeutic effects are derived

Table 2. Grading of histopathologic criteria according to the Japanese Guidelines for the Clinical and Pathologic studies on Carcinoma of the Esophagus

Grade	Degree of response
0 (ineffective)	No evidence of treatment effect
1 (slightly effective)	Treatment effect involving less than two-thirds of the gross tumor mass
2 (moderately effective)	Treatment effect in more than two-thirds of the gross tumor mass
3 (markedly effective)	No cancer cell is observed, pathologic complete response

according to the Japanese Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus.[15] Histopathologic effects of neoadjuvant therapies were classified into four categories, from grade 0 to 3. The definitions of each grade in pathologic efficacy are shown in Table 2. We then evaluated pathologic response as 'positive' when neoadjuvant therapy achieved grade 2 or 3, so 'positive pathologic response' means that the ratio of the amount of disappearance of cancer cells to the estimated total cancer volume is more than two-thirds. We evaluated 'negative pathologic response' in patients with grade 0 or 1. Finally, we compared the 'histopathologic response rate' of neoadjuvant therapies by c^2-test between the chemotherapy, radiotherapy, and chemoradiotherapy groups.

p53 Immunohistochemical staining

In every case, p53 overexpression was examined by immunohistochemical staining of biopsy specimens taken before neoadjuvant therapies via fiberoptic esophagoscopy. Paraffin-embedded tumor sections on silane-coated slides (Matsunami Glass, Osaka, Japan) were de-waxed in xylene and ethanol, and pretreated in a microwave oven to enhance p53 antigen accessibility to the antibody. Overexpression of p53 was judged positive when the number of immunohistochemically stained cells was more than 10% of all observed cells. Mouse monoclonal primary antibody DO7 (DAKO A/S, Glostrup, Denmark), which recognizes both wild-type and mutant-type p53 protein, was used in this study, and the staining was performed by the labeled streptavidin biotin (LSAB) method. Negative controls of immunohistochemical reactions were performed by omitting the primary antibody.

Statistical methods

Histopathologic response rates were compared using the χ^2-test among the three neoadjuvant treatment groups. Predictive factors that influenced the histopathologic effect of neoadjuvant therapies were analyzed by the logistic regression test using SPSSA software. In selecting clinical or pathologic variables, we entered 13 covariates: age, sex, location of the tumor (upper, middle, or lower thoracic), tumor size, depth of tumor invasion, histologic type, number of cancer lesions, venous invasion (present or absent), lymphatic invasion (present or absent), intramural cancer metastasis (present or absent), intraepithelial cancer spread (present or absent), type of neoadjuvant therapy (chemotherapy, chemoradiotherapy, or radiotherapy), and p53 protein status. Forward stepwise selection with a likelihood-ratio test was used for selecting variables for logistic regression analysis. The predictive power of covariates was expressed by calculation of an odds ratio with 95% confidence intervals. Differences with $P < 0.05$ were considered statistically significant.

RESULTS

The effects of neoadjuvant therapy, judged from histopathologic 'grade' and the method of neoadjuvant treatment with or without p53 overexpression, were cross-classified in Figs 1 and 2. In the chemo-

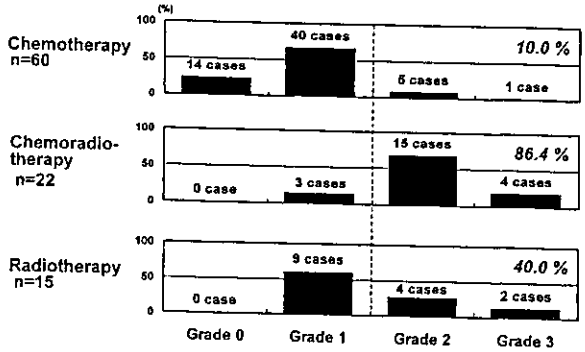

Fig. 1 The effects of neoadjuvant therapy judged from histopathologic 'grade' according to neoadjuvant treatment modality. The histopathologic response rate for chemoradiotherapy was 86.4%, and was significantly higher than that for chemotherapy alone ($P < 0.0001$) or radiotherapy alone ($P = 0.0031$).

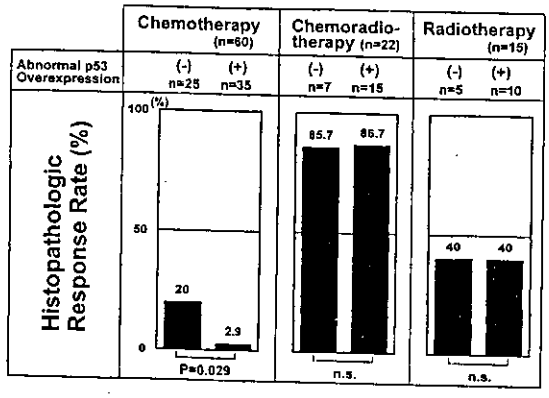

Fig. 2 The histopathologic response rate and p53 oncoprotein status, cross-classified according to neoadjuvant treatment modality. In the 'chemotherapy alone' group, patients with normal p53 expression achieved a higher histopathologic response rate. In the 'chemoradiotherapy or radiotherapy' group, however, no statistical difference was seen in the response rate, irrespective of p53 status.

therapy group, the pathologic response rate was only 10.0% (six out of 60 cases). However, in the chemoradiotherapy group, the pathologic response rate was 86.4% (19 out of 22 cases); and in the radiotherapy group, the response rate was 40.0% (six out of 15 patients). The histopathologic response rate for chemoradiotherapy was significantly higher than that for chemotherapy ($P < 0.0001$), or for radiotherapy ($P = 0.0031$) by the χ^2-test (Table 3). No histopathologic treatment effect ('grade 0') was observed in 14 patients (23.3%) in the chemotherapy group. There were also no 'grade 0' cases observed in the chemoradiotherapy or radiotherapy groups (Fig. 1). A histopathologic complete response ('grade 3') was achieved in 18.2% (four out of 22 cases) in the chemoradiotherapy group, and in 13.3% (two out of 15 cases) in the radiotherapy group. In the chemotherapy group, however, only 1.7% (one out of 60 cases) achieved 'grade 3'.

The histopathologic response rate and abnormal p53 overexpression are cross-classified in Fig. 2. The overall abnormal p53 overexpression rate was 61.9% (60 out of 97 cases). The positive p53 overexpression rate was 58.3% (35 of 60 cases) in the chemotherapy group, 68.2% (15 of 22 cases) in the chemoradiotherapy group, and 66.7% (10 of 15 cases) in the radiotherapy group. Differences in the positive p53 overexpression rates were not statistically significant between these three neoadjuvant treatment groups ($P = 0.658$). In chemotherapy patients with p53 abnormal oncoprotein overexpression, only one (2.9%) out of 35 cases achieved a pathologic response. In patients with normal p53 protein expression, however, the histopathologic response rate to chemotherapy was 20.0% (five responders out of 25), a significantly higher rate than that for patients with abnormal p53 overexpression ($P = 0.029$). In the chemoradiotherapy group, 13 (86.7%) of 15 cases with abnormal p53 overexpression were responders, whereas six (85.7%) out of seven cases with normal p53 expression also responded to chemoradiotherapy. The histopathologic response rates of these two groups were therefore almost the same irrespective of p53 oncoprotein status, and no statistical difference was seen in response rates according to p53 oncoprotein status ($P = 0.95$). In the radiotherapy group, the histopathologic response rate was also the same (40.0%) between normal and abnormal p53 expression groups (Fig. 2), and, of course, there was no statistical difference between the two groups.

Table 3. Histopathologic effect according to neoadjuvant treatment method

Treatment method	Histopathologic effect (−)	Histopathologic effect (+)	cases (%)
Chemotherapy ($n = 60$)	54 (90.0%)	6 (10.0%)	
Chemoradiotherapy ($n = 22$)	3 (13.6%)	19 (86.4%)	*
Radiotherapy ($n = 15$)	9 (60.0%)	6 (40.0%)	**

*$P < 0.0001$; **$P = 0.0031$.

Using multivariate logistic regression analysis, the neoadjuvant treatment modality (chemotherapy, chemoradiotherapy, or radiotherapy) was identified as the most powerful predictive factor for the histopathologic effect of neoadjuvant treatment ($P = 0.0002$). Other identified predictive factors for the successful neoadjuvant treatment were the absence of 'blood vessel invasion' ($P = 0.0166$) and 'intramural metastasis' ($P = 0.0417$). However, p53 oncoprotein status was not identified as a predictive factor for neoadjuvant treatment effect ($P = 0.154$). The odds ratio of chemoradiotherapy to chemotherapy was 63.8, and that of radiotherapy to chemotherapy was 6.4. Chemoradiotherapy therefore had the most significant therapeutic power compared with chemotherapy or radiotherapy. The second powerful neoadjuvant treatment modality was radiotherapy. When esophageal cancer is accompanied by blood vessel invasion or intramural metastasis, the predictive effect of neoadjuvant treatment decreased at a odds ratio of 0.41 ($P = 0.0166$) and 0.30 ($P = 0.0417$), respectively.

DISCUSSION

Although the 5-year survival rate for surgery alone for esophageal cancer has improved since the 1980s,[6] the growth of esophageal cancer is very rapid compared with that of other gastrointestinal malignancies[7] and we sometimes experience difficulty in achieving complete surgical resection. To improve the clinical outcome in advanced esophageal cancer, multimodal treatment has been strongly recommended in addition to surgery. At present, there is a lack of large-scale clinical trial data favoring the efficacy of adjuvant therapies following surgery of advanced esophageal cancer.[16] Recently, the efficacy of chemoradiotherapy for advanced esophageal cancer has been recognized, and trimodality therapy (combined chemotherapy and radiation with surgery) has been introduced into the general clinical field without significant scientific evidence.[6,17] Here, we compared the effect of three neoadjuvant treatment modalities (chemotherapy, chemoradiotherapy, and radiotherapy), and evaluated predictive factors for neoadjuvant effect, including p53 oncoprotein status.

For the evaluation of neoadjuvant therapy, measurement of tumor shrinkage by barium study, CT scan or EUS (endoscopic ultrasonography) examination has long been used. Following neoadjuvant therapy, however, these conventional measurements of therapeutic effect are sometimes incorrect and

difficult to evaluate precisely due to obscure tumor margins from neoadjuvant treatment effect.[4,5] Even if preoperative treatment is assumed to achieve a complete response by conventional evaluation methods, we sometimes find some viable cancer cells between fibrotic tissues in the surgically resected specimen. On the other hand, although we can detect some residual cancer using conventional preoperative examinations, sometimes we cannot find any cancer cells on histopathologic examination of the resected specimen. Histopathologic staging from a surgical specimen is therefore the gold standard.[6] Here, we evaluated the effects of preoperative therapies not with conventional barium, CT scan or EUS study, but with histopathologic evaluation of the resected esophagus, and assessed predictive factors which influenced the true histopathologic effect of neoadjuvant therapy by univariate and multivariate analyzes.

In the chemoradiotherapy group, the histopathologic response rate, which means the ratio of cases with 'grade 2' or 'grade 3' (disappearance of more than two-thirds of cancer cells) to the whole cases, was 86.4%, and was statistically higher than those for chemotherapy or radiotherapy alone (Table 3). The histopathologic response rate for the chemotherapy group was only 10.0%, and was significantly and unexpectedly low. The response rate for the radiotherapy group was 40.0%, and was a nearly halfway between those for chemotherapy and chemoradiotherapy. Strictly objective histopathologic assessment of resected esophagus indicated that chemoradiotherapy had by far the most powerful effect on advanced esophageal cancer, compared with chemotherapy alone or radiotherapy alone. Chemotherapy, when used alone, lacked adequate therapeutic effect as a neoadjuvant treatment for advanced squamous cell carcinoma of the esophagus.

From studies using cell lines *in vitro*, it is known that p53 alteration may determine resistance to chemotherapy or radiotherapy from an apoptotic point of view.[8,9] The clinical value of p53 alteration on sensitivity to neoadjuvant treatment in esophageal cancer is still, however, controversial. Here, we evaluated p53 alteration by immunohistochemical staining, and assessed the predictive value on neoadjuvant therapeutic outcome. In the 'chemotherapy alone' group, p53 overexpression, i.e. mutant-type p53 protein expression, was a significant factor for resistance to chemotherapy. In 'chemoradiotherapy and radiotherapy alone' groups, the histopathologic effect was almost the same for p53 positive and negative patients, and p53 status did not influence the clinical outcome.

Alteration of p53 may contribute in part to the sensitivity to neoadjuvant treatment, when the therapeutic power is modest or weak as for chemotherapy. In chemoradiotherapy, however, where the therapeutic power is strong enough, we can achieve adequate treatment effect irrespective of p53 oncoprotein status. We can therefore assume, in chemoradiation or radiation therapy, that the biologic mechanism of cancer cell death is not always related to 'p53-dependent apoptosis'. Although p53 status affects the sensitivity to chemotherapy or radiotherapy in bench studies, the proportion of p53 participation in the treatment effect may be small in the practical clinical field. From logistic regression analysis, p53 overexpression was not identified as a significant predictive factor for the effect of neoadjuvant treatment. Alteration of p53 from immunohistochemical examination cannot therefore predict sensitivity to neoadjuvant therapy before treatment.

From multivariate logistic regression analysis of neoadjuvant effect, the neoadjuvant treatment modality was identified the most significant ($P = 0.0002$) predictor of therapeutic effect with an odds ratio of 63.8 to chemotherapy alone, and 6.4 to radiotherapy alone (Table 4). These results mean that chemoradiotherapy has 63.8 times the therapeutic power of chemotherapy, and 6.4 times that of radiotherapy. From histopathologic evaluation, which is the gold standard for treatment evaluation, chemoradiotherapy was most powerful and effective as a neoadjuvant treatment for advanced squamous cell carcinoma of the esophagus.

Other significant predictive factors for neoadjuvant treatment effect were the presence of 'blood vessel invasion' and 'intramural metastasis' (Table 4). When esophageal cancer invades blood vessel structure or gives rise to intramural metastases, the anticipated therapeutic effect decreases by 0.41 times or 0.3 times, respectively. It is generally believed that the presence of 'blood vessel invasion' is a gateway to the intrusion into the systemic blood circulation of cancer cells, and the presence of 'intramural metastasis' is a result of lymphatic cancer spread in the submucosal layer. In patients with intramural metastasis, we often find many metastatic lymph nodes outside the esophagus. Clinically, both blood vessel invasion and intramural metastases are generally thought to be signs of biologically highly malignant esophageal cancer.[18–20] When a patient has blood

Table 4. Logistic regression analysis for predictive factors of neoadjuvant treatment ($n = 97$)

Histopathologic response of neoadjuvant treatment		
Variables	*P*	Odds ratio
Treatment method	0.0002	–
Chemotherapy	–	1.0
Chemoradiotherapy	–	63.8
Radiotherapy	–	6.4
Blood vessel invasion	0.0166	–
Absent	–	1.0
Present	–	0.41
Intramural metastasis	0.0417	–
Absent	–	1.0
Present	–	0.30

vessel invasion or intramural metastases, multimodal therapy is therefore strongly required. Our study shows, however, that there is little chance of adequate therapeutic effect, and it will be a serious problem in improving the survival of patients with highly advanced esophageal cancer presenting with blood vessel invasion or intramural metastases.

This study showed that chemoradiotherapy had by far the strongest anticancer effect on advanced esophageal cancer of the three treatment modalities using histopathologic confirmation, and was thought to be the most promising tool as a multimodal treatment in addition to surgery. But we do not know whether chemoradiotherapy really gives a survival benefit as a neoadjuvant or an adjuvant setting. It will now be necessary to plan a clinical trial comparing the effects of surgery alone vs. trimodality therapy (surgery plus chemoradiotherapy).

Acknowledgments

We thank K. Yokomizo, K. Okamoto, and K. Kodera for their excellent technical assistance for p53 immunohistochemical staining. This work was supported by a Grant-in-Aid for Scientific Research from the Japanese Ministry of Education, Science, Sports and Culture.

References

1. Kelsen D. Neoadjuvant therapy for upper gastrointestinal tract cancers. Curr Opin Oncol 1996; 8: 321–328.
2. Stahl M, Wilke H, Fink U *et al.* Combined preoperative chemotherapy and radiotherapy in patients with locally advanced esophageal cancer. Interim analysis of a phase II trial. J Clin Oncol 1996; 14: 829–837.
3. Coia L R, Sauter E R. Esophageal cancer. Curr Probl Cancer 1994; 18: 189–247.
4. Chak A. Pretreatment staging by endoscopic ultrasonography does not predict complete response to neoadjuvant chemoradiation in patients with esophageal carcinoma. Cancer 2000; 88: 1184–1186.
5. Mallery S, DeCamp M, Bueno R *et al.* Pretreatment staging by endoscopic ultrasonography does not predict complete response to neoadjuvant chemoradiation in patients with esophageal carcinoma. Cancer 1999; 86: 764–769.
6. Tepper J. Editorial: refluxtions on esophageal cancer: can we swallow the changes? J Clin Oncol 2000; 18: 453–454.
7. Rew D A, Wilson G D. Cell production rates in human tissues and tumours and their significance. Part II. clinical data. Eur J Surg Oncol 2000; 26: 405–417.
8. Lowe S W, Ruley H E, Jacks T, Housman DE. p53-dependent apoptosis modulates the cytotoxicity of anticancer agents. Cell 1993; 74: 957–967.
9. Lowe S W, Schmitt E M, Smith S W, Osborne B A, Jacks T. p53 is required for radiation-induced apoptosis in mouse thymocytes. Nature 1993; 362: 847–849.
10. Shimada Y, Watanabe G, Yamasaki S *et al.* Histological response of cisplatin predicts patients' survival in oesophageal cancer and p53 protein accumulation in pretreatment biopsy is associated with cisplatin sensitivity. Eur J Cancer 2000; 36: 987–993.
11. Kitamura K, Saeki H, Kawaguchi H *et al.* Immunohistochemical status of the p53 protein and Ki-67 antigen using biopsied specimens can predict a sensitivity to neoadjuvant therapy in patients with esophageal cancer. Hepatogastroenterology 2000; 47: 419–423.
12. Wang L S, Chow K C, Chi K H, Liu C C, Li W Y, Chiu J H, Huang M H. Prognosis of esophageal squamous cell carcinoma: analysis of clinicopathological and biological factors. Am J Gastroenterol 1999; 94: 1933–1940.
13. Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y. Radical lymph nodes dissection for cancer of the esophagus. Ann Surg 1994; 220: 364–373.
14. Japanese Research Society for Gastric Cancer. Response assessment of chemotherapy for gastric carcinoma. In: *Japanese Classification of Gastric Carcinoma*, (1st English edn). Tokyo, Japan: Kanehara Ltd, 1995; 101–104.
15. Japanese Society for Esophageal Diseases. Histopathologic criteria for the effects of radiation or anticancer chemotherapy. In: *Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus*, (9th edn). Tokyo, Japan: Kanehara Ltd, 1999; 55–58.
16. Kelsen D P, Ginsberg R, Pajak T F *et al.* Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. New Engl J Med 1998; 339: 1979–1984.
17. Adham M, Baulieux J, Mornex F, de La Roche de Bransat E, Ducerf C, Souquet J C, Gerard J P. Combined chemotherapy and radiotherapy followed by surgery in the treatment of patients with squamous cell carcinoma of the esophagus. Cancer 2000; 89: 946–954.
18. Watanabe M, Kuwano H, Araki K *et al.* Prognostic factors in patients with submucosal carcinoma of the oesophagus. Br J Cancer 2000; 83: 609–613.
19. Lam K Y, Ma L T, Wong J. Measurement of extent of spread of oesophageal squamous carcinoma by serial sectioning. J Clin Pathol 1996; 49: 124–129.
20. Kuwano H, Watanabe M, Sadanaga N *et al.* Univariate and multivariate analyses of the prognostic significance of discontinuous intramural metastasis in patients with esophageal cancer. J Surg Oncol 1994; 57: 17–21.

外科治療 Vol. 34 No. 3 (2001 : 3)

特集 癌の術後補助化学療法マニュアル

食道癌の術後補助療法

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特集 癌の術後補助化学療法マニュアル

食道癌の術後補助療法

Adjuvant therapy for squamous cell carcinoma of the esophagus

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食道癌は，ほかの消化器癌に比べて化学療法や放射線感受性が高く，また転移しやすく悪性度が高いことから術後補助療法が積極的に行われている．病理組織学的転移リンパ節個数が5個以上の場合にはCDDP/5-FUを主体とした化学療法を，頸部，上縦隔に限局した場合や局所の癌遺残が疑われる場合には化学放射線療法を行う．CDDPを大量投与する場合には厳重な副作用対策が必要である．

はじめに

癌の治癒切除後に，転移や再発を防止する目的で行う治療を「補助療法：Adjuvant Therapy」と言い，この際抗癌剤を用いると「補助化学療法：Adjuvant Chemotherapy」となる．消化器癌の術後補助療法の効果を統計学的な差をもって証明することはなかなか困難であり，世界的に見ても消化器癌において術後補助療法の有効性を証明できた大規模臨床試験は大腸癌でしか認められておらず，食道癌や胃癌では現在標準治療とよべる統一されたプロトコールはOncologicalには存在しない．しかし，再発例や切除不能癌に対して化学療法を行った場合には確かに腫瘍縮小例が存在することから，術後補助療法が全く無効であるとは結論できず，海外では有望と考えられる新たな化学療法剤が次々と臨床試験にかけられて，取捨選択されている．大規模臨床試験の結果からも，消化器癌に対する化学療法の奏効率は血液悪性疾患などに比べて低いことは事実ではあるが，食道癌は消化器癌の中でも化学療法や放射線療法に対する感受性が高いことが特徴的であり，またほかの消化器癌に比べて再発，転移率が高く生物学的に悪性度が高いことなどから，進行食道癌に対してはこれまでさまざまな術後補助療法が行われてきた．本稿では進行食道癌に対する術後補助療法として，化学療法だけでなく近年普及してきた化学放射線療法を含め広い意味でわれわれが現在行っている食道癌の術後補助療法の適応，実際の投与法，副作用対策を紹介したい．

I. 術後補助療法の適応

術後補助療法の適応はわが国と海外では異なっており，また，わが国でもそれぞれの施設によって異なっているのが現状である．術後補助療法の適応を決定したり，効果を評価するためには行わ

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Key words：CDDP/5FU／化学放射線療法／リンパ節転移個数／リンパ節転移部位／骨髄抑制

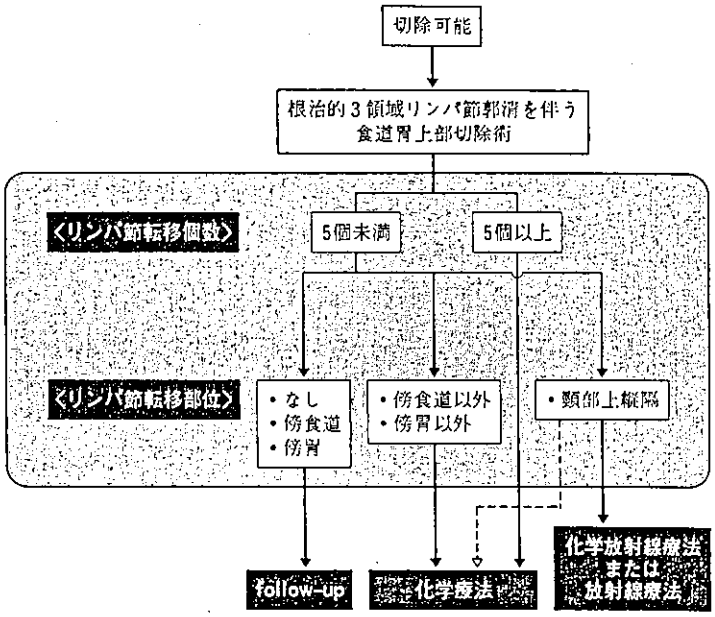


図1 術後補助療法適応決定のためのフローチャート

れた手術の質的内容を含めた総合的な判断が必要であり，臨床試験においては End Point が Survival であるため，術後補助療法の有効性を判定する際には手術内容，中でもリンパ節郭清精度の Quality Control が重要となる．また冷静に考えてみると術後補助療法が効果を発揮するためにはいくつかの逆説的条件が必要である．まず① microscopic な癌細胞の遺残が手術後にあることが必要である．癌細胞が手術で完全に取り除かれていると補助療法の効果は発揮しようがないからである．②逆に遺残癌細胞数があるレベルを超えると，もはや補助療法の治療限界を超えてコントロール不能になってしまうために，手術後に遺残している癌細胞数が一定数以下であることも必要である．術後補助療法の効果が期待できると予測される症例として，われわれは術後補助療法の適応を図1のように設定している．その適応の判断根拠となるのは，手術中の所見による局所の microscopic な癌細胞遺残の可能性の有無や郭清されたリンパ節中の病理組織学的転移リンパ節個数，およびその転移リンパ節の部位である．

1．術後化学療法，化学放射線療法の適応（リンパ節転移個数と転移部位から見た適応）

消化器癌において，リンパ節の郭清によって予後が確実に向上するか否かはわが国と海外では見解の相違が存在するところであるが，リンパ節の転移個数が患者さんの生命予後の予測因子であることは，わが国でも海外でも広く認められている．これまでの多数の食道癌手術の臨床経験から，転移個数が4～5個を超えると再発の危険性が急激に増加し，生命予後が不良となることにはほぼ世界的なコンセンサスが得られている．したがって，われわれは郭清リンパ節中の病理組織学的転移リンパ節個数が5個を一応の境界線と設定して術後化学療法の適応を決めている．すなわち，転移リンパ節個数が5個以上の場合は食道癌が Localized Disease から Systemic Disease にすでに進展している可能性が高いと判断して術後化学療法を行う．これに対して転移リンパ節個数が4個以下の場合には，その転移部位によって術後補助療法の適応を決定しており，個々の症例で図1に示したフローチャートにしたがって化学療法または化学放射線療法または放射線療法を選択し

ている．

1）(リンパ節転移個数)＝0の場合

通常われわれは，頸部・胸部・腹部の3領域リンパ節郭清によって150個前後のリンパ節を郭清するが，手術中所見で局所に癌の遺残がなく，郭清したリンパ節すべてに転移を認めなかった場合には一切の術後補助療法を行っていない．

2）(リンパ節転移個数)＝1～4の場合

(1)切除された食道および胃の近傍のみにリンパ節転移が認められた場合

傍食道リンパ節(#105，#108，#110)や噴門周囲リンパ節(#1，#2)，胃上部小彎のリンパ節(#3)などの食道や胃上部に近接したリンパ節は，手術によって確実に郭清されたと考えられるため，食道や胃の近傍だけにリンパ節転移を認め，リンパ節転移個数が4個以下の場合には術後の補助療法は追加していない．

(2)食道から離れた部位にリンパ節転移が認められた場合

食道から離れた部位のリンパ節転移とは，実際には頸部リンパ節転移や上縦隔，とくに反回神経周囲(#106 rec)リンパ節転移，腹部では(#7，#8，#9，#11)など胃からやや離れた部位のリンパ節転移を指す．このような場合は，リンパ節転移個数が4個以下であっても術後補助療法の適応としている．とくに腹部の腹腔動脈近傍のリンパ節に転移を認めた場合には，化学療法を第一選択としている．これに対して頸部や上縦隔に少数のリンパ節転移を認めた場合には1～2年前までは術後化学療法一辺倒であったが，近年では化学放射線療法の高奏効率に注目して術後化学放射線治療を行うことも多い．反回神経周囲のみに少数のリンパ節転移を認める場合は，現時点では化学療法と化学放射線療法のいずれを選択するかの明確な基準を設定していないが，最終的には主として次項で述べるように術中のリンパ節転移の程度，状況より判断している．

3）(リンパ節転移個数)≧5の場合

リンパ節転移個数が5個以上の場合は，食道癌がすでにsystemic diseaseとなり拡大している可能性が高いと判断し全身的な化学療法を選択する．

2．術後化学放射線療法，放射線療法の適応
(局所癌遺残の可能性から見た適応)

放射線療法や化学放射線療法など放射線が主体の治療法は，照射野を一定の範囲に限定せざるを得ず基本的には局所療法であることから，癌がすでに明らかに全身に拡大しSystemic Diseaseとなっている場合には適応ではなく，ある程度治療のFieldが限局された症例が適応となる．

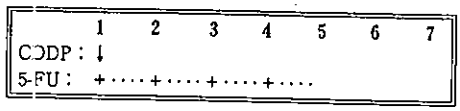
1）局所の癌遺残が否定できない場合

食道癌本体や転移リンパ節が予想以上に気管，気管支の膜様部や大動脈外膜などに浸潤しており，これらを損傷しないように癌ぎりぎりでメスなどで鋭的に剝離してようやく切除可能になった場合には，細胞レベルでは癌細胞は局所に遺残していると考えた方がよい．このような局所的な癌の遺残が疑われる場合は，放射線を主体とする治療法の良い適応となる．放射線療法を選択するか，化学放射線療法を選択するかの明瞭な選択基準は現時点では確立されていないが，われわれは患者さんが高齢者でなく，全身状態が許せば治療効果の優れていると考えられる化学放射線療法を選択している．局所に癌が遺残していることが疑われ，さらに郭清リンパ節中の病理組織学的転移リンパ節個数も多数で広範囲であった場合，食道癌はすでにsystemic diseaseとなっていることが予測されるため化学療法を選択する．

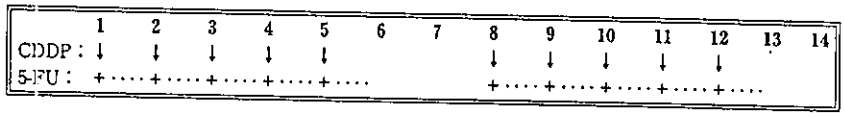
2）反回神経周囲リンパ節に病理組織学的転移を認めた場合

反回神経周囲は，食道癌リンパ節転移の好発部位であり十分に精度の高いリンパ節郭清が必要である[1]．また，残念ながらこの部位に再発を起こした場合，反回神経麻痺から誤嚥性肺炎を繰り返したり，総頸動脈に浸潤して致命的な大出血の原因となることもある．したがって，反回神経周囲領域は食道癌手術においてリンパ節郭清の最重要ポイントであり，理論的にはこの領域に肉眼的に転移が認められた場合，完全郭清するためには反

High Dose CDDP/5FU 投与法
CDDP 70 mg/m²×1, div/1 hr
5-FU 700 mg/m²×4, dir/24 hr で持続点滴



Low Dose CDDP/5FU 投与法
CDDP 10 mg/body×5, div/1 hr
5-FU 500 mg/body×5, dir/24 hr で持続点滴 これを 2 回繰り返す



化学放射線同時併用治療法：concurrent chemoradiotherapy
(CDDP 5 mg/body×5 5FU 250 mg/body×5)×2
放射線治療(月～金)に合わせて照射中に薬剤が同時に投与される.

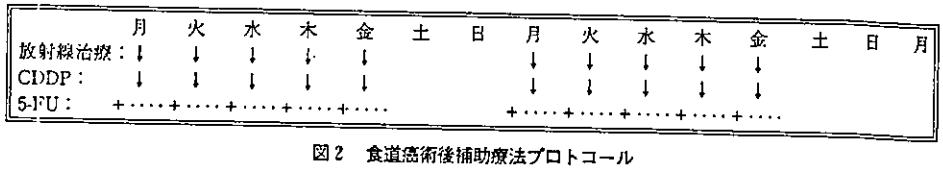


図2 食道癌術後補助療法プロトコール

回神経を合併切除して反回神経とともに郭清することが必要になる．しかし，実際には反回神経の合併切除は術後の QOL を大きく障害することになるため，術前すでに嗄声が認められている場合などを除いて極力反回神経は温存に努めている．反回神経周囲リンパ節に病理組織学的検査の結果転移が認められた場合，厳密な意味で microscopic な癌細胞の遺残があるか無いかは決定できないため，ほかの領域に多数のリンパ節転移が認められない場合には化学放射線治療を行っている．高齢者や poor risk 症例では放射線の単独照射を行うこともある．

II. 術後化学療法の実際
(High Dose CDDP/5-FU と Low Dose CDDP/5-FU)

現在わが国で食道癌に対して使用できる抗癌剤は，諸外国に比べ限定されており CDDP と 5-fluorouracil が主たる抗癌剤である．今日抗癌剤が単剤で使用されることはまれであり，食道癌では CDDP と 5-fluorouracil が併用して用いられることが一般的である．海外ではこのほかに Taxol など Taxane 系薬剤も広く使用されており，CDDP/5-fluorouracil 治療法に次ぐ治療法としての位置を占めている．現在わが国で行われている CDDP/5-fluorouracil 療法には High Dose の大量投与と Low Dose の少量投与の 2 種類の投与方法があり，われわれは従来 High Dose CDDP/5-FU投与（CDDP; 70 mg/m², 5-FU; 700 mg/m²)を行ってきたが，その後 Low Dose の CDDP/5-FU 投与法を行っている．われわれが実際に行っている High Dose CDDP/5-FU と Low Dose CDDP/5-FU 投与法のレジメンを図2に示す．

1．High Dose CDDP/5-FU 療法

High Dose CDDP/5-FU 療法と Low Dose CDDP/5-FU 療法の間には副作用の程度，副作用対策にかなり違いがあり，大量投与法では厳重な注意が必要である．High Dose CDDP/5-FU 療

法では嘔気，食欲低下が著しく，腎臓保護のために大量の水分負荷と利尿剤の投与が必要なため中心静脈栄養(IVH)ルートの確保が必要であり，また副作用の発現も重篤であるために厳重な監視が必要である．治療の実施に際してはいくつかの副作用対策が必要であるが，最も大切なことは薬剤投与後何日目頃にどのような副作用が発現する可能性があり，それに対してどのような副作用対策の準備を行っているかを治療開始前にあらかじめ医師自身が十分に理解し，さらに患者さんに良く説明しておくことである．これによって患者さんの不安は多少なりとも軽減され円滑な治療が可能となる．

1）High Dose CDDP/5-FU 療法のプロトコール

高容量の CDDP を投与するために，十分な水分負荷と利尿剤の投与により腎臓の保護を行うことが要点である．薬剤の投与は CDDP は Day 1 のみに 5-FU は Day 1 − 4 に行う 4 日投与であり，これを 2 回行い 1 クールとしている．実際には前日より IVH 通常投与量の +1000 ml 程度の輸液を行った後に，CDDP の投与を開始する．

Day 1

①朝から 3000 ml の輸液を 6 時間行う(500 ml/hr)．

②輸液開始 2 時間後にマンニトール 100 ml を全開で点滴静注すると同時に，上記①の点滴にマンニトール 200 ml を混注する．マンニトール 100 ml の点滴終了直後から CDDP；70 mg/m² の投与を 1 時間で行う．

③朝から行った 3000 ml の輸液が終了したら，IVH ルートからの通常の輸液に 5-FU；700 mg/m² を混注し，これを24時間で持続投与する．

Day 2〜4

5-FU；700 mg/m² を混注した IVH ルートからの通常の輸液を24時間で投与する．CDDP の投与は行わない．

2）副作用の種類と発現時期

High Dose CDDP/5-FU 治療後に発現する副作用とその時期には一定の傾向が認められ，これをあらかじめ理解しておくことは化学療法を安全に施行するうえで重要である．CDDP 大量投与当日は，通常何の副作用も起こらない．投与翌日に強い嘔気が現れ，1 週間から10日間ほど続く．このため CDDP 投与日から 5-HT_3 受容体拮抗制吐剤を予防投与して嘔気を抑制する．嘔気のピークは投与翌日でありことが多く，以後次第に軽減していく．化学療法施行後の嘔気には投与後早期に出現する acute emesis と，数日以降に出現する delayed emesis が存在するが，5-HT_3 受容体拮抗制吐剤は acute emesis には非常に有効であるが delayed emesis には無効であることが多い．嘔気は主として CDDP の副作用であるが，投与開始から数日経過すると，5-FU の副作用の一つである粘膜障害が現れ，口腔粘膜障害としての口内炎や腸管の粘膜障害としての下痢，腹痛が現れる．血便などが出現したら粘膜障害が高度である証拠であり，厳重な注意が必要である．腸管粘膜が広範囲に障害されると腸管内の細菌が粘膜の barrier を越えて "translocation" を起こし敗血症となる(=Bacterial Translocation)ため，ファンギゾンシロップやバンコマイシンの経口投与により早期の腸管内清掃を行い，Bacterial Translocation への対策が必要になる．また，腸管粘膜障害による腹痛は，食事の摂取により誘発されることが多いために食前にブスコパンなどを投与して予防することもある．さらに，どうしても腹痛が強い場合には鎮痛と腸管蠕動を抑える目的で少量のモルヒネを使用することも効果的である．CDDP／5-FU 投与後 2 週前後で好中球減少の nadir が訪れる．High Dose CDDP／5-FU 療法の好中球減少は高度で好中球数が 100/mm³ 以下に減少して febrile neutropenia となることもまれではい．G-CSF 製剤，抗生剤を投与し，空気清浄機を設置して逆隔離を行い，食事も電子レンジで殺菌してから供する．このような febrile neutropenia の状況では通常血小板減少も認められるが，臨床的に出血傾向が認められることはほとんどなく，血小板数が 1 万/mm³ 前後になるまでは血小板輸血は抗血小板抗体の出現を危惧して

行っていない．

実際の治療後，高度の好中球減少となった場合に医師，患者共に最も知りたい情報は骨髄抑制がどの程度継続し，いつ回復するかということである．近年，骨髄移植の際に骨髄機能を知る指標として網状赤血球およびその分画であるHFR，MFR，LFRが用いられているが，化学療法後の高度な好中球減少後の骨髄機能回復予測にもこれが利用できる[2]．HFR，MFR，LFRは各々High Fluorescence Ratio，Medium Fluorescence Ratio，Low Fluorescence Ratioを表しており，網状赤血球中のRNA含量をレーザーフローサイトメトリーで測定しこれを3等分してその分画に含まれる網状赤血球を%で表したものである．したがってHFR分画にはRNA含量が多く，細胞の活動性が今後高まると予測される網状赤血球が含まれており，化学療法後にHFRの低下が著しく0%になると高度の好中球球減少が予測され，一方nadir後にHFRが増加し始めた場合には好中球数が依然低値であっても骨髄機能が回復し始めたと判定することができる．このHFRの変動は好中球数の動きに数日先んじているために，臨床における高容量の化学療法後の骨髄機能低下や回復の予測に有用である．なおこの網状赤血球分画はほとんどの病院で採用されている自動血球測定装置で同時に測定可能であり，新たな設備投資は不要である．

2．Low Dose CDDP/5-FU 療法

近年，わが国の消化器癌化学療法で普及してきたのがLow Dose CDDP/5-FU療法である．High Dose CDDP/5-FU療法に比べCDDP投与前の大量の水負荷などが不要であり，治療施行上簡便であり，また副作用に関してもCDDP，5-FUいずれも総投与量がHigh Dose CDDP/5-FU療法に比べて少ないため嘔気，嘔吐，好中球減少などの副作用の発現が軽微であり，わが国では簡便性，低侵襲性から消化器癌補助化学療法のレジメンとして広く普及しつつある．

1）Low Dose CDDP/5-FU 療法のプロトコール

Low Dose CDDP/5-FU療法はHigh Dose CDDP/5-FUとは投与スケジュールが異なりCDDP，5-FUともに5日間連続投与後2日間休み，これを2週間行い1クールとしている．輸液は通常よりやや多めに行ったうえで薬剤の投与を行うが，High Dose CDDP/5-FU療法のような大量の輸液や利尿剤は不要である．CDDPは10 mg/body，5-FUは500 mg/bodyを投与しているが，高齢者や術後体力の回復の十分でない場合にはCDDP；5 mg/body，5-FU；250 mg/bodyのさらにLow Doseの投与量を選択することもある．

Day 1～5，Day 8～12

CDDP；10 mg/bodyを1時間で点滴静注した後に，5-FU；500 mg/bodyを24時間で持続点滴静注する．副作用対策はHigh Dose CDDP/5-FU療法に準じて行っているが，一般に高度の副作用を生じることはまれである．

Low Dose CDDP/5-FU治療法の最大の特徴は簡便性，低侵襲性であり，治療のコンプライアンスはHigh Dose CDDP/5-FUに比べ格段に優れている．しかし，海外では本治療法はほとんど行われておらず，以前アメリカのSWOG（South West Oncology Group）で行われた高度進行癌に対する臨床試験では明らかな有効性は認められなかった[3]．高度進行食道癌に対する術前化学療法のわれわれの経験を振り返っても，Low Dose CDDP/5-FU療法はHigh Dose CDDP/5-FU療法に比べてやや治療のパワーが弱いという印象は持っており，術後補助化学療法としてLow Dose CDDP/5-FU療法を行った場合，その治療効果（anti-cancer effect）は十分であるのか，経口抗癌剤と比べて差はあるのかなど治療の簡便性ばかりではなく治療効果の本質に関する考察が今後是非とも必要であろう．

III. 術後化学放射線療法の実際

近年，海外で化学放射線療法の高い奏効率が注目され，術前治療法としてわが国でも普及してきた．われわれの経験でも，術前治療を行った後に手術で切除し病理組織学的に治療効果を判定すると，術前化学療法では grade 2 以上の組織学的奏効率は11.8%であったのに対して，化学放射線療法では86.7%の高い組織学的奏効率をあげていた[4]．これらの臨床的事実から，ある程度限局した部位に集中的に治療効果を発揮させたい場合にわれわれは化学放射線療法を選択している．具体的には癌の隣接臓器への浸潤が激しく癌の遺残が危惧される場合や，頸部～上縦隔に限局してリンパ節転移が認められた場合などである．

1．化学放射線療法のプロトコール

Low Dose の CDDP/5-FU 投与を放射線治療と同時に行う concurrent chemoradiotherapy を行っている．放射線治療は月曜日から金曜日の5日間であるため，抗癌剤投与もこれに合わせて行い，CDDP は 5 mg/body を6時間かけて点滴静注し 5-FU は 250 mg/body を24時間かけて持続点滴投与している．図2に投与プロトコールを示す．放射線の照射は約 40 Gy 行い，照射野については放射線科医と定期的にディスカッションを行い正確を期している．

2．化学放射線療法の副作用

High Dose CDDP/5-FU 療法に比べると，Low Dose CDDP/5-FU を用いた化学放射線療法の副作用は軽度である．化学療法に起因する副作用よりも，放射線照射による副作用が主体となる．その主なものは皮膚・粘膜症状と骨髄抑制である．放射線照射が2週目に入り10回前後となる頃から皮膚や咽頭粘膜の障害が起こってくる．皮膚は照射部位に一致して日焼けのように赤くなり，さらに時間が経過すると黒ずんでくる．このころから咽頭の痛みを訴えることが多く，咽頭粘膜の障害によると考えられ，粘膜保護剤を服用してもらう．自覚はされないが重要な副作用は骨髄抑制である．放射線による骨髄抑制は化学療法後の骨髄抑制と程度や時間経過が異なるため注意が必要である．好中球減少の程度は化学放射線療法では High Dose CDDP/5-FU 療法後に比べて一般に軽度であり好中球数が 100/mm^3 以下となることはまれであり，重症化することもない．化学療法のみの場合，骨髄抑制の程度は高度であっても G-CSF 製剤の投与によって一旦好中球が増加に転じると数日以内に回復することがほとんどであるが，化学放射線療法後では一旦回復するかに見えた好中球数が再び減少するなど，骨髄機能は不安定であることが多く安心はできない．また，骨髄機能の抑制は長期間継続することがあり退院後も厳重な follow-up が必要である．

3．化学放射線療法の今後

化学放射線療法は食道癌の local control に優れていることは事実であるが，現実の臨床では化学放射線治療後に遠隔臓器転移が認められることがあるなど，systemic control には未だ難があると言わざるを得ない．最近，trimodality therapy という考え方が提唱され[5]，リンパ節郭清手術を十分に行ったうえで化学放射線療法を行うというものであるが，そのためには化学放射線療法の systemic control の効果を高める更なる工夫が必要であると考えられる．

むすび

食道癌の術後補助療法の有効性が統計学的に臨床試験で証明されていない現在，われわれの行っている術後補助療法のプロトコールが本特集の「癌の術後補助化学療法マニュアル」の名にふさわしい標準的治療法であるか否かは疑問である．しかし microscopic な癌の遺残があるために術後補助療法の恩恵を受ける患者さんが存在することもまた事実であり，食道癌術後補助療法は癌の遺残量がある範囲の限定された条件下では有効であると考えられる．今後は micrometastasis の

診断や遺伝子レベルでの悪性度診断などを向上させて術後補助療法の適応症例を科学的に明らかにしていかなければならないと考えられる．

文　献

1) 鶴丸昌彦，梶山美明，服部公昭　ほか：外科領域の争点，I. 胸部食道癌に対する郭清．外科　62：4-7，2000.
2) Kajiyama Y, Tsurumaru M, Udagawa H, et al: Predicting the onset and severity of granulocytopenia based on reticulocyte RNA content after chemotherapy for esophagea cancer. Proc Am Soc Clin Oncol 14: 1995 (abstr #989).
3) Williamson SK, Tangen CM, Maddox AM, et al: Phase II evaluation of low-dose continuous 5-fluorouracil and weekly cisplatin in advanced adenocarcinoma of the stomach. A Southwest Oncology Group study. Am J Clin Oncol Dec; 18 (6): 484-487,1995.
4) 梶山美明，鶴丸昌彦：特集　食道癌の治療－QOLの改善を目指して－浸潤食道癌の合併療法．外科治療　82：287-293，2000.
5) Tepper J: Refluxtions on esophageal cancer: can we swallow the changes? J Clin Oncol Feb; 18 (3): 453-4, 2000.

●お知らせ●

第38回 日本外科代謝栄養学会

会　期　2001年7月6日(金)，7日(土)
会　場　幕張プリンスホテル
　　(〒261-8525　千葉市美浜区ひび野2－3　Tel：043-296-1111)
会　長　平澤博之(千葉大学医学部救急医学)
テーマ：
　"Critical Care Metabolism and Nutrition"
　会長講演「Critical Careにおける全身状態評価法をめぐって」
　特別講演「Critical Care Nutrition」Gary P. Zaloga (Director of Research, IntensiMed)
　International Symposium「Cellular,Molecular and Genetic Aspects of Immunoinflammatory Response to Planned and Unplanned Injury」
一般演題：(公募)
　インターネットによる申込締切　2001年3月16日(金)
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http://www.ho.chiba-u.ac.jp/emccm/gekataisha.html)

Surgery Plus Chemotherapy Compared With Surgery Alone for Localized Squamous Cell Carcinoma of the Thoracic Esophagus: A Japan Clinical Oncology Group Study—JCOG9204

By Nobutoshi Ando, Toshifumi Iizuka, Hiroko Ide, Kaoru Ishida, Masayuki Shinoda, Tadashi Nishimaki, Wataru Takiyama, Hiroshi Watanabe, Kaichi Isono, Norio Aoyama, Hiroyasu Makuuchi, Otsuo Tanaka, Hideaki Yamana, Shunji Ikeuchi, Toshiyuki Kabuto, Kagami Nagai, Yutaka Shimada, Yoshihide Kinjo, and Haruhiko Fukuda

Purpose: **We performed a multicenter randomized controlled trial to determine whether postoperative adjuvant chemotherapy improves outcome in patients with esophageal squamous cell carcinoma undergoing radical surgery.**

Patients and Methods: **Patients undergoing transthoracic esophagectomy with lymphadenectomy between July 1992 and January 1997 at 17 institutions were randomly assigned to receive surgery alone or surgery plus chemotherapy including two courses of cisplatin (80 mg/m² of body-surface area × 1 day) and fluorouracil (800 mg/m² × 5 days) within 2 months after surgery. Adaptive stratification factors were institution and lymph node status (pN0 versus pN1). The primary end point was disease-free survival.**

Results: **Of the 242 patients, 122 were assigned to surgery alone, and 120 to surgery plus chemotherapy. In the surgery plus chemotherapy group, 91 patients (75%) received both full courses of chemotherapy; grade 3 or 4 hematologic or nonhematologic toxicities were limited. The 5-year disease-free survival rate was 45% with surgery alone, and 55% with surgery plus chemotherapy (one-sided log-rank, $P = .037$). The 5-year overall survival rate was 52% and 61%, respectively ($P = .13$). Risk reduction by postoperative chemotherapy was remarkable in the subgroup with lymph node metastasis.**

Conclusion: **Postoperative adjuvant chemotherapy with cisplatin and fluorouracil is better able to prevent relapse in patients with esophageal cancer than surgery alone.**

J Clin Oncol 21:4592-4596.

DURING THE past two decades, surgery has improved the survival of patients with advanced squamous cell carcinoma of the thoracic esophagus (pathologic stage IIA to IV). Nonetheless, the 5-year survival rate remains relatively modest at less than 40%.[1] The radical surgical treatment of esophageal carcinoma includes transthoracic esophagectomy with extensive lymphadenectomy,[2] which is the standard surgical treatment in Japan. As invasiveness of this procedure approaches the limit of tolerability for patients, more aggressive surgery is precluded. Therefore, to improve outcome for esophageal cancer patients, effective multimodality treatment must be developed.

When the Japan Esophageal Oncology Group (JEOG), a subgroup of the Japan Clinical Oncology Group (JCOG),[3] compared surgery alone with postoperative adjuvant chemotherapy using a combination of cisplatin and vindesine, no additive effect on survival of patients with esophageal squamous cell carcinoma (ESCC) was obtained beyond survival with surgery alone (JCOG8806).[4] However, poor results of a JEOG phase II study (JCOG8703)[5] of cisplatin and vindesine for patients with advanced esophageal cancer suggested that this particular combination of chemotherapy had only a modest effect. In contrast, a JEOG phase II study (JCOG8807)[6] of cisplatin and fluorouracil

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Submitted December 16, 2002; accepted September 12, 2003.

Supported by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labor, and Welfare of Japan (5S-1, 8S-1, 11S-3, 11S-4) and from the Second Term Comprehensive 10-Year Strategy for Cancer Control (H10-Gan-027, H12-Gan-012).

Presented in part at the 35th Annual Meeting of the American Society of Clinical Oncology, Atlanta, GA, May 15-18, 1999.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/03/2124-4592/$20.00

demonstrated a promising response rate of 36%. We therefore initiated a randomized controlled trial to determine whether postoperative adjuvant chemotherapy using a combination of cisplatin and fluorouracil has an effect on disease-free survival and overall survival that is additive with the survival benefit of transthoracic esophagectomy including lymphadenectomy.

PATIENTS AND METHODS

Patients were entered onto this study according to the following eligibility criteria: 1) histologically proven squamous cell carcinoma of the thoracic esophagus; 2) no microscopic residual tumor (R0); 3) pathologic stages IIA, IIB, III, or IV due to distant node involvement (M1 lym) only; 4) an Eastern Cooperative Oncology Group performance status [PS] of 0 to 2; 5) an age of 75 years or younger; 6) an essentially normal clinical laboratory profile (WBC $\geq$ 4,000/mm^3; hemoglobin $\geq$ 10g/dL; platelet count [Plt] $\geq$ 100,000/mm^3; total serum bilirubin $\leq$ 1.2 mg/dL; AST and ALT no higher than twice the normal level; creatinine [CRTN] $\leq$ 1.2 mg/dL; creatinine clearance [CCr] $\geq$ 60 mL/min; arterial oxygen tension $\geq$ 65 Torr; and 7) oral or written informed consent obtained before randomization in accordance with JCOG policy in 1992. Patients were ineligible if they had an additional synchronous or metachronous cancer.

After assessment of pathologic findings in the resected specimens, patients were randomly assigned to two arms within 2 months following surgery: no further treatment (surgery alone; arm A) and postoperative chemotherapy (surgery plus chemotherapy; arm B). A minimization method was used so institution and pathologic lymph node status (pN0 v pN1) would be balanced. Randomization was performed centrally at the JCOG Data Center (JCOG DC), with the order transmitted by telephone or fax.

Surgery

Patients enrolled onto this study had undergone right or left thoracotomy for curative resection by total or subtotal thoracic esophagectomy, as well as regional lymphadenectomy. No patient underwent transhiatal esophagectomy. Regional lymph nodes included not only mediastinal (paraesophageal, paratracheal, subcarinal, supradiaphragmatic, and posterior mediastinal lymph nodes) but also perigastric nodes, so regional lymphadenectomy represented at least a two-field lymphadenectomy. Dissection of distant lymph nodes such as cervical nodes (cervical paraesophageal, deep cervical, and supraclavicular lymph nodes), representing a three-field lymphadenectomy,[2] or celiac nodes, was considered acceptable for study inclusion. Esophageal reconstruction was performed using the stomach, colon, or jejunum.

Chemotherapy

In arm B, cisplatin at a dose of 80 mg/m^2 of body-surface area was given by slow drip infusion for 2 hours on day 1; fluorouracil was administered at a dose of 800 mg/m^2 of body surface area by continuous infusion on days 1 through 5. Two courses of chemotherapy were given, separated by a 3-week interval.

The second course of chemotherapy was suspended for WBC $<$ 2,000/mm^3, Plt $<$ 50,000/mm^3, CRTN $>$ 1.5 mg/dL, or CCr $<$ 40 mL/min. The dose of cisplatin was decreased by 50% in cases where 1.2 mg/dL was less than CRTN $\leq$ 1.5 mg/dL or 40 mL/min $\leq$ CCr less than 60 mL/min. The dose of fluorouracil was decreased by 50% in cases where 2,000/mm^3 $\leq$ WBC less than 4,000/mm^3 or 50,000/mm^3 $\leq$ Plt less than 100,000/mm^3. Adverse events were classified according to WHO toxicity criteria.[7]

Study Design and Statistical Analysis

This trial was designed as a multicenter prospective randomized phase III study, and the study protocol was approved by the Clinical Trial Review Committee of the JCOG and the institutional review board of each participating institution that had already established an institutional review board by 1992.

The primary end point was disease-free survival. The secondary end points were overall survival and toxicities. This study was designed to include 290 randomly assigned patients over 5-year accrual with 5 years of additional follow-up to detect a 13% improvement in 5-year disease-free survival (40% in arm A v 53% in arm B), with a one-sided alpha of 0.05 and 0.80.

Clinicopathologic parameters are expressed according to the tumor-node-metastasis system Classification of the International Union Against Cancer.[8]

Overall survival was measured from the date of surgery to the date of death or last follow-up, and censored at the last contact date in surviving patients. Disease-free survival was measured from the date of randomization to the date of first evidence of relapse or death as a result of any cause, whichever was observed first. For patients who had not relapsed or died, disease-free survival was censored at the last date that the absence of relapse was confirmed. Recurrences were documented by means of clinical examination, chest radiography, computed tomography of the chest and abdomen, or ultrasonography of the neck and abdomen. Overall and disease-free survival curves were calculated by the Kaplan-Meier method and compared by the unstratified log-rank test. Confidence intervals of survival distribution were based on Greenwood's formula. A proportional hazards regression model was used for the adjustment of confounding baseline variables and the estimation of relative risks by means of hazard rate ratio.[9] Comparison between the arms had been monitored semi-annually by the Data and Safety Monitoring Committee of the JCOG until 1996. After that date, no comparison was performed before the end of accrual in compliance with the amended JCOG policy. This study was designed and conducted on the basis of one-sided testing, and the results are presented with one-sided P values. All calculations were performed with SAS software (SAS/STAT User's Guide, Version 6, Cary, NC, SAS Institute, 1990) by the JCOG DC.

RESULTS

Study Course

Since the accrual period had exceeded 4 years and the accrual rate was low, the study chair (N.A.) decided to terminate accrual in March 1997. The primary analyses were performed in October 1998. According to the favorable disease-free survival in chemotherapy arm (one sided P = .051, unadjusted log-rank test) even with no difference in overall survival, JEOG decided to adopt adjuvant chemotherapy with fluorouracil and cisplatin as a control arm in the next phase III trial. Updates of follow-up data and re-analyses were performed in December 2001 for this publication.

Patient Characteristics

During the period from July 1992 to January 1997, 242 patients were entered onto the study at 17 institutions, including 122 patients in arm A (surgery alone) and 120 patients in arm B (surgery plus postoperative chemotherapy). These patients comprised 10.1% of all patients (242 of 2,403) with resection of esophageal cancer at participating institutions during the study period, and 47.4% of all patients (242 of 511) who met eligibility criteria apart from the informed consent. No remarkable differences were observed in the male/female ratio or the age distribution between the study population and all patients undergoing resection.

There was one ineligible patient with positive resected margin in arm A, and two ineligible patients in arm B (one was entered at 8 months after surgery, the other was 76 years old). However, these three cases were included in all analyses.

In arm B, 29 patients were not able to fully complete planned courses of postoperative chemotherapy. Twenty-one of these

Table 1. Characteristics of the Eligible Patients

Characteristic	Surgery Alone (arm A; n = 122)	Surgery + Chemotherapy (arm B; n = 120)
Sex		
Male	111	107
Female	11	13
Age, years		
Range	40-75	40-76
Mean	59	59
Location of tumor		
Upper	5	13
Middle	75	65
Lower	42	42
pT		
T1	25	31
T2	18	18
T3	77	69
T4	2	2
pN		
N0	21	23
N1	101	97
pM		
M0	102	97
M1 LYM	20	23
p stage		
stage IIA	21	22
stage IIB	34	37
stage III	47	38
stage IV	20	23

Abbreviations: pT, pathologic T-stage; pN, pathologic N-stage; pM, pathologic M-stage; LYM, lymphoma; p, pathologic.

patients underwent only one course of chemotherapy because of either toxicity or patient refusal. Eight underwent no chemotherapy, six because of refusal. Baseline prognostic variables, such as tumor location, pT, pN, pM, and pathologic stage were well balanced between arms (Table 1). Here, pathologic stage IV indicates patients with positive cervical and/or celiac nodes (pM1 lym).

Characteristics of Surgery

Esophagectomy via right thoracotomy was performed in 120 patients in both arms. Left thoracotomy was performed in two patients in arm A only. No patients underwent transhiatal esophagectomy without thoracotomy, in compliance with exclusion criteria of this study. Two-field lymphadenectomy (regional mediastinum and abdomen) was performed in 61 patients in arm A and in 46 patients in arm B. Three-field lymphadenectomy (regional mediastinum and abdomen plus neck) was performed in 61 patients in arm A and in 74 patients in arm B.

Toxicity

Toxicity profiles are shown in Table 2. Grade 3 toxicities in arm B were observed for hemoglobin, WBC, nausea or vomiting, and diarrhea; grade 4 toxicities involved granulocytopenia, infection, fever, and arrhythmia. One patient in arm B died of causes related to treatment, including severe diarrhea, hypotension, and anuria associated with grade 3 leucocytopenia and thrombocytopenia, and grade 4 arrhythmia at the end of the first course of chemotherapy. The immediate cause of death was identified as lactic acidosis related to thiamine deficiency by the Data and Safety Monitoring Committee review of the adverse event reports.

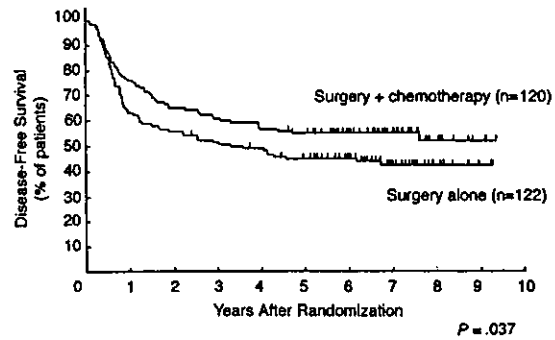
Table 2. Number of Patients With Toxicity During Postoperative Chemotherapy

Toxicity	Grade 0	1	2	3	4
Hemoglobin	44	59	14	2	0
Leucocytes	36	48	30	5	0
Granulocytes	29	24	30	19	3
Platelets	98	15	3	3	0
Nausea/vomiting	28	50	29	10	0
Diarrhea	60	39	15	3	0
Stomatitis	95	17	5	0	0
Creatinine	114	5	1	0	0
Arrhythmia	112	1	3	0	1
Infection	111	4	1	0	1
Fever	96	18	2	0	1

Disease-Free and Overall Survival

As of the updated analyses, the median follow-up time from randomization in all randomly assigned patients was 62.8 months. Disease-free survival curves are shown in Figure 1. The 5-year disease-free survival was 45% (95% CI, 36% to 54%) in arm A and 55% (95% CI, 46% to 64%) in arm B ($P = .037$). The unadjusted relative risk estimate (hazard rate ratio) of arm B against arm A was 0.73 (95% CI, 0.51 to 1.03). Relative risk estimates of arm B versus arm A for disease-free survival adjusted for baseline prognostic variables by a multivariate proportional hazard model was 0.75 (95% CI, 0.52 to 1.07), which did not differ from the unadjusted estimates. Baseline prognostic variables included age, sex, performance status, tumor location, pathologic T-stage, intramural metastasis, pathologic N-stage, pathologic M-stage, and extent of lymphadenectomy.

Disease-free survival curves according to lymph node metastasis and adaptive stratification factor are shown in Figure 2. Risk reduction in arm B was remarkable in the subgroup with lymph node metastasis. To identify the other subgroups in which more patient benefit might be expected, we assessed interactions



No. at Risk

Surgery + chemotherapy	120	91	78	73	68	64	48	30	10
Surgery alone	122	77	68	62	58	51	39	22	8

Fig 1. Disease-free survival curves of all registered patients. The 5-year disease-free survival was 45% in patients with surgery alone and 55% in patients with surgery plus chemotherapy ($P = .037$).

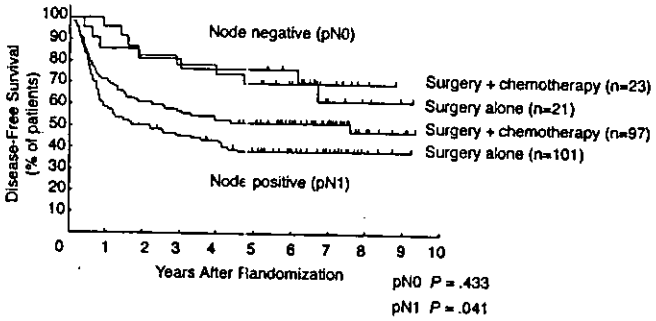


Fig 2. In the pN0 subgroup, the 5-year disease-free survival was 76% in surgery-alone group and 70% in surgery plus chemotherapy group (P = .433). In the pN1 subgroup, it was 38% in surgery-alone and 52% in surgery plus chemotherapy (P = .041).

in terms of disease-free survival among treatment effects and baseline variables as well as lymph node status. Disease-free survival difference by arms tended to be larger in higher T stage (T3 to T4) and better PS (PS = 0; data not shown).

Overall survival curves are shown in Figure 3. The 5-year overall survival was 52% (95% CI, 43% to 61%) in arm A and 61% (95% CI, 52% to 70%) in arm B (P = .13). Subgroup analyses for overall survival showed no remarkable differences.

Site of Recurrence and Subsequent Therapy After Recurrence

Cancer recurrences developed in 63 patients in arm A and in 45 patients in arm B. The frequency of local recurrences in lymph nodes, particularly in the cervical and mediastinal nodes, was slightly higher in arm A than in arm B. Of 63 patients in arm A with cancer recurrence, 54 (86%) underwent local or systemic treatments for recurrence; 36 (80%) of 45 patients did so in arm B. The frequency of chemoradiotherapy was higher in arm A than in arm B (Table 3).

DISCUSSION

The issue of whether to add chemotherapy to esophageal cancer surgery remains under investigation. Neither preoperative chemotherapy[10-14] nor postoperative chemotherapy[15] with a combination of cisplatin and fluorouracil improved survival of the patients with ESCC and/or adenocarcinoma. Recently, the

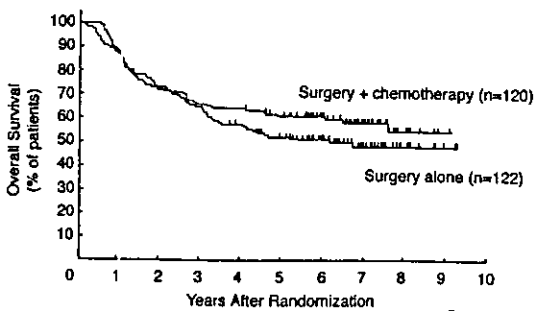


Fig 3. Overall survival curves of all registered patients. The 5-year overall survival was 52% in patients with surgery alone and 61% in patients with surgery plus chemotherapy (P = .13).

Table 3. Site of Recurrence and Treatment for Recurrence

	Surgery Alone (arm A; n = 54)	Surgery + Chemotherapy (arm B; n = 36)
Site of recurrence		
Cervical lymph node	17	8
Mediastinal lymph node	30	12
Abdominal lymph node	9	6
Lung	5	7
Liver	11	12
Bone	1	8
Other	13	8
Treatment for recurrence		
CT	11	7
RT	16	14
Chemoradiotherapy	19	9
Surgery and CT, RT	8	6

Abbreviations: CT, chemotherapy; RT, radiotherapy.

Medical Research Council Esophageal Cancer Working Party[16] found in a study of 802 patients that preoperative chemotherapy with the same combination improved survival relative to outcome with surgery alone. However, 30% of patients treated with surgery alone underwent incomplete resection, and survival in the group with surgery alone was unusually poor (median, 13 months). In the Western countries, preoperative (neoadjuvant) chemotherapy or chemoradiotherapy[17,18] predominates. We preferred to wait until after surgery to avoid increasing operative morbidity, considering the invasiveness of the standard procedure used in Japan (transthoracic esophagectomy with extensive lymphadenectomy).

In this study, we chose disease-free survival as the primary end point, because after recurrence patients could be treated with any therapy considered useful. We found that disease-free survival in the surgery-plus-chemotherapy arm was superior to that with surgery alone with marginal statistical significance, even though no difference was shown for overall survival. We can offer two hypotheses to explain the divergence between disease-free survival and overall survival. One would be the effect of imbalance in extent of lymphadenectomy between the arms. Three-field lymphadenectomy comprised 62% (74 of 120 patients) of the surgery-plus-chemotherapy arm, but 50% (61 of 122 patients) of the surgery arm. Recurrence in cervical and mediastinal lymph nodes was more frequent in the surgery arm than in the surgery-plus-chemotherapy arm. Therefore, the difference in disease-free survival between the arms might be caused by a difference in extent of lymphadenectomy rather than by chemotherapy. However, the 5-year disease-free survival with two-field lymphadenectomy was 42% in arm A and 50% in arm B (P = .25), while with three-field lymphadenectomy, it was 47% in arm A and 58% in arm B (P = .23). Adjustment with the Cox proportional hazard model showed no remarkable interaction between lymphadenectomy extent and arm concerning disease-free survival. Thus, imbalance in lymphadenectomy extent was not considered to be the cause of the difference in disease-free survival between the arms.

Another explanation involves distortion of overall survival data. We believe that the difference in disease-free survival

between the two study arms probably resulted from eradication of intranodal and perinodal micrometastatic disease by chemotherapy. The benefit of chemotherapy for overall survival was diluted by subsequent therapy given after recurrence. The frequency of local recurrence in lymph nodes was slightly higher in arm A than in arm B. Consequently, as treatment for recurrence, subsequent chemoradiotherapy was given more frequently in arm A (35%) than in arm B (25%). Lack of a difference in overall survival between the study arms might reflect subsequent chemoradiotherapy given to patients in arm A on discovery of local recurrences. We favor this second hypothesis and consider disease-free survival prolongation by adjuvant chemotherapy to reflect the true patient benefit.

Although an overall survival benefit was not observed, toxicity during chemotherapy was tolerable. A fatal adverse reaction occurred only in one patient. The observed difference of approximately 10% increase in 5-year disease-free survival and a hazard ratio of 0.73 would be considered clinically meaningful even with marginally statistical significance. Bosset et al[17] also reported prolonged disease-free survival without improved overall survival in a comparison of chemoradiotherapy followed by surgery with surgery alone in 282 patients with squamous cell carcinoma of the esophagus. They also concluded that improved disease-free survival reflected mainly a local effect, as suggested by a longer interval free of local disease in the combined-treatment arm.

As for generalizability of the results, observed differences in disease-free survival between the arms are remarkable in the subsets defined by node metastasis, higher pT, and better PS. These would suggest that the benefit from adjuvant chemotherapy would be expected mainly in patients with good performance status but advanced tumor extension.

The weakness of this study can be summarized as follows: early termination of accrual limited the sample size and the primary analyses and the updated analyses were not in the prospectively designed manner; however, we performed only twice comparisons of efficacy end points after termination of accrual, therefore, possible bias due to multiple comparison should not affect our conclusion; only 76% of patients could complete both courses of chemotherapy; there were several patients lost to follow-up, four patients in arm A and three patients in arm B; however, all randomly assigned patients were included in the analyses in compliance with the intent-to-treat principle.

On the basis of these data, we concluded that postoperative adjuvant chemotherapy with cisplatin and fluorouracil has a detectable preventive effect on relapse in patients with ESCC compared with surgery alone. Accordingly, a randomized controlled trial comparing postoperative adjuvant chemotherapy with neoadjuvant chemotherapy using cisplatin and fluorouracil is ongoing (JCOG9907).

ACKNOWLEDGMENT

We thank the JCOG Data Center staff, Ms Yukiko Fujikura, and Dr Miyuki Niimi for data management, and Dr Naoki Ishizuka for the updated analyses.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

REFERENCES

1. Ando N, Ozawa S, Kitagawa Y, et al: Improvement in the results of treatment of advanced squamous esophageal carcinoma over fifteen consecutive years. Ann Surg 232:225-232, 2000

2. Akiyama H, Tsurumaru M, Udagawa H, et al: Radical lymph node dissection for cancer of the thoracic esophagus. Ann Surg 220:364-373, 1994

3. Shimoyama M, Fukuda H, Saijo N, et al: Japan Clinical Oncology Group (JCOG) Jpn J Clin Oncol 28:158-162, 1998

4. Ando N, Iizuka T, Kakegawa T, et al: A randomized trial of surgery with and without chemotherapy for localized squamous carcinoma of the thoracic esophagus: The Japan Clinical Oncology Group study. J Thorac Cardiovasc Surg 114:205-209, 1997

5. Iizuka T, Kakegawa T, Ide H, et al: Phase II evaluation of cisplatin and vindesine in advanced squamous cell carcinoma of the esophagus: Japan Esophageal Oncology Group Trial. Jpn J Clin Oncol 21:176-179, 1991

6. Iizuka T, Kakegawa T, Ide H, et al: Phase II evaluation of cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the esophagus: Japan Esophageal Oncology Group Trial. Jpn J Clin Oncol 22:172-176, 1992

7. World Health Organziation: WHO Handbook for reporting results of cancer treatment. Geneva, 1979

8. International Union Against Cancer. TNM classification of malignant tumors. Fifth fully revised edition. New York, Springer-Verlag, 1997

9. Armitage P, Berry G: Survival analysis in statistical methods in medical research. Third ed. Oxford, Blackwell Scientific Publications, 1994

10. Ajani JA, Roth JA, Ryan B, et al: Evaluation of pre- and postoperative chemotherapy for resectable adenocarcinoma of the esophagus or gastroesophageal junction. J Clin Oncol 8:1231-1238, 1990.

11. Law S, Fok M, Chow S, et al: Preoperative chemotherapy versus surgical therapy alone for squamous cell carcinoma of the esophagus : A prospective randomized trial. J Thorac Cardiovasc Surg 114:210-217, 1997

12. Kelsen D, Ginsberg R, Pajak T, et al: Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 339:1979-1984, 1998

13. Ancona E, Ruol A, Santi S, et al: Only pathologic complete response to neoadjuvant chemotherapy improves significantly the long term survival of patients with resectable esophageal squamous cell carcinoma. Cancer 91:2165-2174, 2001

14. Urschel JD, Vasan H, Blewett CJ: A meta-analysis of randomized controlled trials that compared neoadjuvant chemotherapy and surgery to surgery alone for resectable esophageal cancer. Am J Surg 183:274-279, 2002

15. Pouliquen X, Levard H, Hay JM, et al: 5-fluorouracil and cisplatin therapy after palliative surgical resection of squamous cell carcinoma of the esophagus. A multicenter randomized trial. French Associations for Surgical Research. Ann Surg 223:127-133, 1996

16. Medical Research Council Oesophageal Cancer Working Party: Surgical resection with or without pre-operative chemotherapy in oesophageal cancer: a randomized controlled trial. Lancet 359:1727-1733, 2002

17. Bosset JF, Gignoux M, Triboulet JP, et al: Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 337:161-167, 1997

18. Urba SG, Orringer MB, Turrisi A, et al: Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 19:305-313, 2001