Table 3 Toxicity Associated with This Chemotherapy

Toxicity	Grade				
	0	1	2	3	4
Hematological toxicity					
Leucopenia	2	0	1	2	5
Neutropenia	2	0	1	2	5
Anemia	10	0	0	0	0
Non-hematological toxicity					
Nausea/Vomitting	7	1	1	1	0
Alopecia	6	1	3		
Stomatitis	9	1	0	0	0
Rash	9	1	0	0	0

コース終了後，Grade 4の白血球減少を生じたため，doseを3割減量し，白血球数の回復を待ち，2コース目を施行した。しかし，1コース終了時にはSDであった転移巣が2コース終了後にPDとなった。その他のGrade 3以上の有害事象は悪心，嘔吐が1名のみで，Grade 2以下では，悪心，嘔吐（2例），脱毛（4例），口内炎（1例），皮疹（1例）をそれぞれ認めた。

IV．考　察

本検討例では，全例FP療法，FAP療法あるいは5 FU・CDGPといった化学療法を前治療に行った中での無効もしくは再発症例であったにもかかわらず，PR 2例，SD 6例であった。また，術後の補助化学療法も含めた前化学療法開始日からの50%生存期間は392日，TXT・CDGP開始日から170日であった。本対象例におけるsecond-line化学療法の多くは1コースのみであり，HayashiらのJCOG 9407でのFP療法における50%生存期間は201.5日[2]であり，今後TXT，CDGPの薬剤自体が生存期間に影響する可能性についても検討する必要がある。

TXTはヨーロッパいちいの針葉樹抽出物より半合成し得られた抗がん剤で，その作用機序は微小管の重合促進および脱重合抑制であり，既存の微小管に作用する抗がん剤とは異なっておりtaxane系の薬剤に分類される[13]。また，taxane系の薬剤の抗腫瘍作用発現はp 53非依存性でp 53に関連するといわれているCDDPや5 FUとの交差耐性がないとの報告もある[14,15]。

本邦における報告は進行・再発頭頸部癌に対する第Ⅱ相試験が最初で，今回の用量設定の基本となったが，TXT 60 mg/m^{2}の用量で奏効率22.2%を示した[7]。食道癌に対するTXT 70 mg/m^{2}を用いた第Ⅱ相試験では，20.4%の奏効率を示し，原発巣以上にリンパ節転移，肺，肝といった臓器転移に縮小効果が得られた[5,6]。また，CDDP，CDGP，先行投与例に対しても15.8%の奏効率を示した[5,6]。併用療法では，本邦では田中らの術後＋FP療法後の再発食道癌におけるsecond-lineでの10例の検討があり[16]，5 FU 500 mg/body 5日間，CDDP 10 mg/body 5日間，TXT 60 mg/m^2 1日投与の3剤併用療法で，PR 4例，SD 2例，PD 4例と報告されている。

一方，CDGPは，CDDPの有効性を落とすことなく腎毒性を軽減する目的で開発された第2世代の白金化合物で，薬効はCDDPと同様であるが，血漿中でほとんどが蛋白非結合型白金化合物として存在し，DNAの複製を阻害し抗腫瘍効果を示す。本邦では田口らのCDGP 100 mg/m^{2}を単剤で用いた第Ⅱ相臨床試験で，奏効率51.7%と単剤投与としてはきわめて優れた成績がえられ[4]，CDDPによる先行治療後の無効例に対しても50%の奏効率が得られた[4]。また，併用療法では術後再発または切除不能食道癌に対する5 FUとCDGPを併用した第Ⅱ相臨床試験でYoshiokaらはCDGP 80または100 mg/m^2 1日投与，5 FU 350または500 mg/m^2 5日間投与で53.8%の奏効率を認め[17]，室らはCDGP 90 mg/m^2 1日，5 FU 800 mg/m^2 5日間投与で39.5%の奏効率を示し[18]，FP療法より高い奏効率が得られている[2]。以上に加えて腎毒性などCDDPより軽いことも考慮するsecond-lineの薬剤として有望と考えられる。

有害事象は，TXTにおける第Ⅱ相試験で，Grade 3以上の有害事象として血液毒性が顕著で，白血球減少（73.5%），好中球減少（87.8%），貧血（12.2%），発熱性好中球減少（18.4%）と報告されている[5,6]。今回われわれはTXT 60 mg/m^{2}の用量設定で本検討を開始したが，同様に白血球減少，好中球減少がGrade 3以上で70%と高率に認められ，その中の2名に敗血症の発症をみた。いずれの症例も救命しえたが，前治療に手術，化学療法，放射線治療を行っており，患者自身の予備力が少なかったことが影響したと考えられた。また，症例8は

血液毒性により2コース目で減量がなされ，効果もSDからPDとなっており，投与量が関係した可能性がある。

欧米での第Ⅱ相試験では75～100 mg/m²の用量設定で[9,19,20]，日本でも室らは70 mg/m²と設定している[5,6]。second-lineの化学療法ということを考慮すると患者の予備力もなく，Grade 4の有害事象は避けたいが，最大限の効果を得ることも必須である。症例8から，現在のdose設定を検討するよりは，分割投与など，投与方法の検討をした方が良いと考えられた。しかし，TXTに関して，一括あるいは低用量分割投与の比較試験は行われておらず，今後の検討課題といえる。

本検討のように過去の報告例でもTXTの有害事象に骨髄抑制，特に白血球減少，それに伴う感染症を併発した症例は報告されている[5,6,9,19,20]。しかし，進行胃食道癌に対するSchullらの報告ではTXT 50 mg/m²，CDDP 50 mg/m²を1，15日分割投与で奏効率も46%を示しているにもかかわらず，Grade 3以上の白血球減少は24%と低値を示している[9]。彼らは総白血球数1000～2000 /μlにてGCSFを5 μg/kg/dayを5日間投与する方法をとっており，GCSF投与も化学療法の1つと位置付けている。人種や投与方法の違いもあり，有害事象の出現の差異に関しての比較は難しいところである。しかし，われわれの検討でもGCSFはGrade 3以上で全例使用しており，結果としてnadirは投与後8日前後で迎え，適切なGCSFの投与により3日前後で改善することなども考慮すると，本化学療法においては，血液毒性である白血球減少は不可避な有害事象のひとつと位置付け，積極的な血液検査やGCSFの投与，予防的抗生剤の投与など，管理上での改善を検討する必要があると思われる。

V．まとめ

進行・再発食道癌のsecond-lineの化学療法としてTXT・CDGP併用療法を行い，PR 2例，SD 6例，PD 2例と比較的良好な成績を示した。しかし，いくつかの問題点も提起された。特に，有害事象において，血液毒性である白血球減少を起こす頻度が高率であり，抗生剤の予防投与など検討が必要であることが示唆された。

文　献

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

2）Hayashi, K., Ando, N., Watanabe, H., et al.: Phase II evaluation of protracted infusion of cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the esophagus: a Japanese Esophageal Oncology Group (JEOG) Trial (JCOG 9407). Jpn. J. Clin. Oncol., 31: 419–423, 2001.

3）安田卓司，甲　利幸，石黒信吾・他：局所進行食道癌に対するFAP療法の試み．癌と化療，22：1538–1541，1995.

4）田口鐵男，涌井　昭，鍋谷欣市・他：254-S (Cis-diammine glycolato platinum)の消化器癌に対する第Ⅱ相臨床試験．癌と化療，19：483–488，1992.

5）陳　勁松，室　　圭，兵頭一之介・他：進行・再発食道癌に対するRP 56976 (Taxotere) の臨床第Ⅱ相試験．日癌治，37：300，2002.

6）Muro, K., Hamaguchi, T., Ohtsu, N., et al.: A phase II study of single-agent docetaxel in patients with metastatic esophageal cancer. Ann. Oncol., 15: 955–959, 2004.

7）犬山征夫，形浦昭克，戸川　清・他：進行・再発頭頸部癌に対するRP 56976 (Docetaxel) の後期第Ⅱ相臨床試験　多施設共同研究．癌と化療，26：107–116，1999.

8）室　　圭，白尾國昭，島田安博・他：進行または切除後再発食道癌に対するネダプラチン (254-S) +5FU併用療法の第Ⅰ–Ⅱ相臨床試験．日癌治，33：213，1998.

9）Schull, B., Kornek, G.V., Schmid, K., et al.: Effective combination chemotherapy with bimonthly docetaxel and cisplatin with or without hematopoietic growth factor support in patients with advanced gastroesophageal cancer. Oncology, 65: 211–217, 2003.

10）Therasse, P., Arbuck, S.G., Eisenhauer, E.A., et al.: New guidelines to evaluate the response to treatment in solid tumors. J. Natl. Cancer Inst., 92: 205–216, 2000.

11）JCOG運営委員会：National Cancer Institute-Common Toxicity Criteria (NCI-CTC Version 2.0, Jan. 30, 1998)～日本語訳JCOG版～．癌と

Journal of Surgical Oncology 2005;89:244–250

Correlation Between Histological Effects on the Main Tumors and Nodal Status After Chemoradiotherapy for Squamous Cell Carcinoma of the Esophagus

MASAHIKO YANO, MD,* TAKUSHI YASUDA, MD, HIROSHI MIYATA, MD, YOSHIYUKI FUJIWARA, MD, SHUJI TAKIGUCHI, MD, AND MORITO MONDEN, MD

Department of Surgery and Clinical Oncology, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan

Background and Objectives: Although the histological effectiveness of preoperative chemoradiotherapy against the main tumor is reported to be the strongest prognostic factor for patients with esophageal cancer, it remains unknown whether such chemoradiotherapy is equally effective against metastatic lymph nodes.

Methods: We studied 103 consecutive patients with esophageal cancer, who were given preoperative chemoradiotherapy followed by surgery. The histological effectiveness against the main tumor of the chemoradiotherapy was correlated with lymph mode metastasis and other clinico-pathological factors.

Results: The histological effectiveness against the main tumor was grade 3 in 26 patients, grade 2 in 49 and grade 1 in 28. The number of pathological node-negative patients was 21 (80.8%), 19 (38.8%), and 7 (25.0%) in those having grade 3, 2, and 1 responses of their main tumors, respectively. The average number of pathological metastatic lymph nodes was 0.19, 1.4, and 4.4 in patients with grade 3, 2, and 1 responses, respectively. Endoscopic biopsy after the chemoradiotherapy could not accurately diagnose the pathological complete response (CR) of the main tumors, with a high false negative rate (60.9%).

Conclusions: The effects of chemoradiotherapy against main tumors significantly correlated with nodal status. Most patients with main tumors of pathological CR are node-negative. Patients with a grade 2 response have at most a few positive nodes. Surgery would be most beneficial for such patients.

J. Surg. Oncol. 2005;89:244–250. © 2005 Wiley-Liss, Inc.

KEY WORDS: **esophageal neoplasms; concurrent chemotherapy and radiation therapy; histological effect; lymphatic metastasis**

INTRODUCTION

The prognosis of patients with esophageal cancer is poor. Because the tumor easily metastasizes to lymph nodes and infiltrates the neighboring organs such as the trachea and aorta, treatment by surgery alone has limited ability to completely cure the disease [1–3]. Even after curative resection by esophagectomy with extended three-field lymph node dissection, about 50% of these patients show recurrence [4–6]. Therefore, multimodality therapy is necessary to improve the prognosis. At present, the most promising strategy is preoperative chemoradiotherapy followed by surgery [7]. Recently, many studies have shown that preoperative chemoradiotherapy leads to downstaging of the disease and increases the curative resection rate [8–11]. Although randomized controlled trials comparing surgery alone with preoperative chemoradiotherapy followed by surgery have not yet

*Correspondence to: Masahiko Yano, MD, Department of Surgery and Clinical Oncology, Graduate School of Medicine, Osaka University, 2-2-E2 Yamadaoka, Suita, Osaka 565-0871, Japan. Fax: 81-6-6879-3259.
E-mail: myano@surg2.med.osaka-u.ac.jp

Accepted 3 January 2005

DOI 10.1002/jso.20209

Published online in Wiley InterScience (www.interscience.wiley.com).

yielded definitive conclusions on the usefulness of chemoradiotherapy [12–16], many investigators have reported that responders to chemoradiotherapy show better prognosis than non-responders. In particular, the prognosis of patients having tumors with pathological complete response (CR) is much better than that of other patients [9,17]. According to Mandard et al. [18] multivariate analysis revealed that pathological effectiveness against the tumors of chemoradiotherapy is the strongest prognostic factor for patients who underwent preoperative chemoradiotherapy followed by surgery. Theoretically, if the metastatic lymph nodes are as sensitive as the main tumors to chemoradiotherapy, patients having main tumors with pathological CR should not need to undergo esophagectomy with lymphadenectomy. This hypothesis is indirectly supported by recent studies showing the results of definitive chemoradiotherapy without surgery. The 2 or 3 years survival rates of patients treated with definitive chemoradiotherapy is 29%–36% [19–21], which is comparable to what has been reported for the pathological CR rate in patients treated with preoperative chemoradiotherapy followed by surgery. Many phase II and phase III studies on preoperative chemoradiotherapy followed by surgery showed that the pathological CR rate ranges from 20% to 40% [8–11,14–16].

Thus far, there have been many reports regarding chemoradiotherapy for esophageal cancers. However, few studies have examined the correlation between the histological effects on the main tumors and those on the metastatic lymph nodes, and the histological effects according to tumor location, tumor depth and other clinico-pathological factors.

This retrospective study evaluated the correlation between pathological CR and preoperative clinicopathological factors by analyzing the data for 103 esophageal cancer patients who underwent preoperative chemoradiotherapy followed by surgery.

MATERIALS AND METHODS

Patient Eligibility

Between August 1989 and December 2002, a total of 103 patients with esophageal cancer, who underwent preoperative chemoradiotherapy followed by surgery at our hospital, were enrolled in this study. The patients were newly diagnosed and had no prior treatment. The eligibility for this study was as follows: the patients were 80 years old or younger and showed performance status (Eastern Cooperative Oncology Group [ECOG]) of 3 or less. Patients with any T (T1–T4) and nodal involvement including regional lymph nodes (N1) and distant lymph nodes (M1LYM) within the radiation field were enrolled in this study, but not those with distant organ metastasis or distant lymph nodes outside the radiation field. The stage was assigned according to the criteria of the American Joint Committee on Cancer [22]. The T and N statuses of the disease were routinely diagnosed by computed tomography (CT), esophagography and/or bronchoscopy. MRI was employed in some cases to improve the accuracy of the T4 diagnosis. Bronchoscopy was carried out when tracheal invasion was suspected by the CT scan. For enrollment, all patients had to have adequate bone marrow function (white blood cell count of $>3{,}500$ cells/μl, platelet count of $>100{,}000$ cells/μl), normal renal function (serum creatinine level of <1.2 mg/dl or creatinine clearance of >50 ml/dl), and normal liver function (serum transaminases <2 times the upper limit of normal level). Written informed consent was obtained from all patients.

Treatment Regimen

The treatment regimen consisted of radiation and concurrent administration of cisplatin and 5-fluorouracil. Of the 103 patients, the 20 enrolled from August 1989 to March 1994 were treated with Protocol A, in which 5-FU was administered intravenously at 750 mg/m^2/day on days 1–5 and 22–26 and cisplatin was administered on days 1 and 22 at a dose of 70 mg/m^2/day by drip infusion for 2 hr with sufficient pre- and post-hydration to prevent renal toxicity. The remaining 83 patients, enrolled from April 1994 to December 2002, were treated with Protocol B, in which the administration schedules of 5-FU and cisplatin were completely synchronized with that of the irradiation. 5-FU at a dose of 400 mg/m^2/day and cisplatin at 10 mg/m^2/day were administered by continuous intravenous infusion for 5 days per week for 4 weeks. In the case of thoracic esophageal cancer, the width of the radiation field for the mediastinum was 7–8 cm. The lower margin of the radiation field was at least 5 cm from the anal edge of the tumor. Bilateral supraclavicular nodes and the upper mediastinum were also included in the T-shaped field. In the case of cervical esophageal cancer, the bilateral supraclavicular nodes, and the upper mediastinum were covered by the radiation field. The radiation technique consisted of parallel-opposed fields using an anterior and posterior portal arrangement. In both protocols, radiation was delivered via a 10 mV X-ray linear accelerator daily for 5 days per week for 4 weeks at a rate of 2 Gy/day for a total dose of 40 Gy.

Two weeks after completing the chemoradiotherapy, the patients were re-evaluated for therapeutic responses of the main tumor and metastatic lymph nodes by barium study, tissue biopsy obtained by endoscopy, and chest and abdominal CT scans. The treatment response was categorized using general criteria [23]. A CR was defined as 100% regression of the disease. A partial response (PR) was defined as regression of more than 50% in

the tumor and metastatic lymph nodes, as confirmed by esophagography and CT scans. Progressive disease (PD) was defined as an increase in the tumor mass and/or metastatic nodes or the appearance of new lesion(s). The patients were scheduled for surgery approximately 4 weeks after the last day of the chemoradiotherapy. Histological effectiveness was defined as follows: grade 3, complete disappearance of cancer cells; grade 2, more than 2/3 disappearance; grade 1, less than 2/3 disappearance.

Statistical Methods

For ordered categorical data of histological effectiveness in the main tumors, the Kruskal–Wallis test was used for comparisons among subgroups of patients with each clinico-pathological factor. For comparison of the number of metastatic nodes, one-factor factorial ANOVA was used. The survival time was calculated by the Kaplan–Meier method and statistically compared among patient subgroups by the log-rank test. A two-sided $P < 0.05$ was considered significant.

RESULTS

Patient and Tumor Characteristics

The clinico-pathological characteristics of the 103 patients are summarized in Table I. Tumor location was cervical in 25, upper thoracic in 18, middle thoracic in 46, and lower thoracic in 14. The disease stages were Stage IIA in 16, Stage IIB in 6, Stage III in 55, Stage IVA in 10, and Stage IVB in 16.

TABLE I. Clinico-Pathological Characteristics of the 103 Patients

Number of patients	103
Male/female	92/11
Age	59.9 + 7.9 (38–80)
Location of tumor	
Cervical	25
Upper thoracic	18
Middle thoracic	46
Lower thoracic	14
Histology	
Well differentiated SCC	12
Moderately differentiated SCC	35
Poorly differentiated SCC	27
SCC	4
Unknown	25
Disease stage	
Stage IIA	16
Stage IIB	6
Stage III	55
Stage IVA	10
Stage IVB	16

Clinical and Histological Responses to Chemoradiotherapy

All the 103 patients in this study underwent surgery after chemoradiotherapy. The total planned chemotherapeutic dosage and radiation was administered to 99/103 (96.1%). The radiation dosage given was 40 Gy for 79 patients, 41–59 Gy for 5, and 60 Gy for 15. Four patients were given radiation of less than 40 Gy depending on the cytotoxicity level. Table II shows the summary of the clinical and histological effects of the chemoradiotherapy. More than 80% of the patients (6 CR + 80 PR) showed a major clinical response. The histological effects were also fairly good, with 26 (25.2%) grade 3 responses for the main tumors. Compared with the clinical stages before the chemoradiotherapy, the histological disease stages were down-staged.

Next, to examine whether the histological effect is affected by the pretreatment clinico-pathological factors, its correlation with tumor location, depth of tumor infiltration, and clinical N status was examined (Table III). With regard to tumor location, we found that tumors at the lower thoracic esophagus were significantly more resistant than those at other sites. The histological effects were not significantly associated with tumor depth or clinical N status.

We tried to compare the histological effects on the main tumors with those on the metastatic lymph nodes. Because accurate diagnosis of lymph node metastasis before chemoradiotherapy was not possible, assessment of the histological effects on the individual metastatic lymph nodes is difficult. We therefore counted the number of histological metastatic nodes in the resected

TABLE II. Clinical and Histological Effects of Chemoradiotherapy

Clinical response	
CR	6 (5.8%)
PR	80 (77.7%)
NC	16 (15.5%)
PD	1 (1.0%)
Histological effects in the main tumor	
Grade 3	26 (25.2%)
Grade 2	49 (47.6%)
Grade 1	28 (27.2%)
Histological lymph node metastasis	
pN0	47 (45.6%)
pN1	37 (35.9%)
pM1lym	19 (18.4%)
Histological disease stage	
pathological CR	21 (20.4%)
pStage I	6 (5.8%)
pStage IIA	14 (13.6%)
pStage IIB	16 (15.5%)
pStage III	27 (26.2%)
pStage IVA	4 (3.9%)
pStage IVB	15 (14.6%)

TABLE III. Histological Effects of the Main Tumors According to Clinico-Pathological Factors

Clinico-pathological factor	Grade 3	Grade 2	Grade 1	Total
Tumor location				$P = 0.77$
Cervical (n = 25)	8 (32.0%)	11 (44.0%)	6 (24.0%)	
Upper thoracic (n = 18)	6 (33.3%)	7 (38.9%)	5 (27.8%)	
Middle thoracic (n = 46)	11 (23.9%)	20 (43.5%)	15 (32.6%)	
Lower thoracic (n = 14)	1 (7.1%)	11 (78.6%)	2 (14.3%)	
Depth of tumor infiltration				$P = 0.42$
T1b (n = 3)	2 (66.7%)	0 (0%)	1 (33.3%)	
T2 (n = 12)	4 (33.3%)	7 (58.3%)	1 (8.3%)	
T3 (n = 32)	8 (25.0%)	13 (40.6%)	11 (34.4%)	
T4 (n = 56)	12 (21.4%)	29 (51.8%)	15 (26.8%)	
Clinical N status				$P = 0.46$
N0 (n = 29)	7 (24.1%)	14 (48.3%)	8 (27.6%)	
N1 (n = 48)	13 (27.1%)	25 (52.1%)	10 (20.8%)	
M1lym (n = 26)	6 (23.1%)	10 (38.5%)	10 (38.5%)	

specimens and checked their correlation with the histological effects in the main tumors. The average number of metastatic lymph nodes was 0.2, 1.4, and 4.4 in patients with grade 3, 2, and 1 histological effects on their main tumors, respectively. Patients having main tumors with higher histological responses are likely to have fewer histologically metastatic lymph nodes. This tendency was the same irrespective of the pretreatment clinical N status (Table IV). Of the 26 patients having grade 3 responses in their main tumors, 21 (80.8%) were histologically node-negative. The remaining five patients had only one positive node per patient. In contrast, the number of node-negative patients with grade 2 and 1 tumors was 19 (38.8%) and 7 (25.0%), respectively (data not shown).

Comparison of Patient Prognosis by Pretreatment Clinical N Status

Figure 1 shows the prognosis of patients with grade 3 response of the main tumors depending on the clinical N status. The survival curves of N positive- and N negative-patients with a grade 3 response did not significantly differ. On the other hand, in patients with grade 1 and 2 responses, the survival curve was significantly better for N negative-patients than for N-positive patients (Fig. 2).

Assessment of Pathological CR in the Main Tumors by Endoscopic Biopsy

In 79 of 103 patients, endoscopic biopsy of the main tumor was performed before surgery. The results of Table V show that 46 patients were biopsy-negative, while 33 were positive. Among the biopsy-negative patients, only 18 (39.1%) were found to display pathological CR in the surgically resected specimens, and 28 patients (60.9%) had residual cancer cells in the main tumors. Analysis of the histological effects by the preoperative tumor depth revealed that the deeper the tumor was, the lower was the incidence of pathological CR. For tumors with a depth of T2 or more, accurate diagnosis of pathological CR was difficult by endoscopic biopsy alone.

TABLE IV. Number of Metastatic Lymph Nodes Per Patient

Clinical N status	Histological effects in the primary tumors			P-value by one-factor ANOVA
	Grade 3	Grade 2	Grade 1	
N0	0.3 ± 0.5	0.7 ± 0.7	1.6 ± 1.7	0.05
N(+)	0.2 ± 0.4	1.7 ± 2.1	5.5 ± 8.1	0.0008
Overall	0.2 ± 0.4	1.4 ± 1.8	4.4 ± 7.1	0.0003

DISCUSSION

This retrospective analysis of 103 patients who underwent preoperative chemoradiotherapy followed by surgery revealed that the pathological CR rate in the main tumors was 26/103 (25.2%), which is comparable with the results published by other investigators [8–11,14–

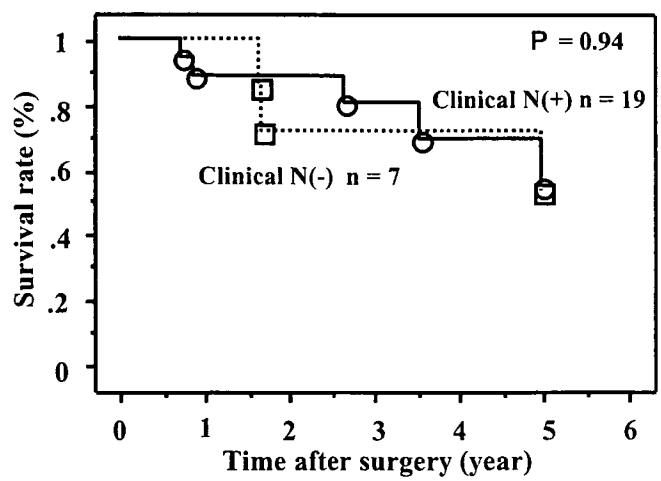

Fig. 1. Survival curves of patients with grade 3 response in their main tumors were compared by pretreatment clinical N status. The thick line indicates pretreatment clinical N(+) patients and the dotted line N(−) patients. Statistical analysis was done by log-rank test.

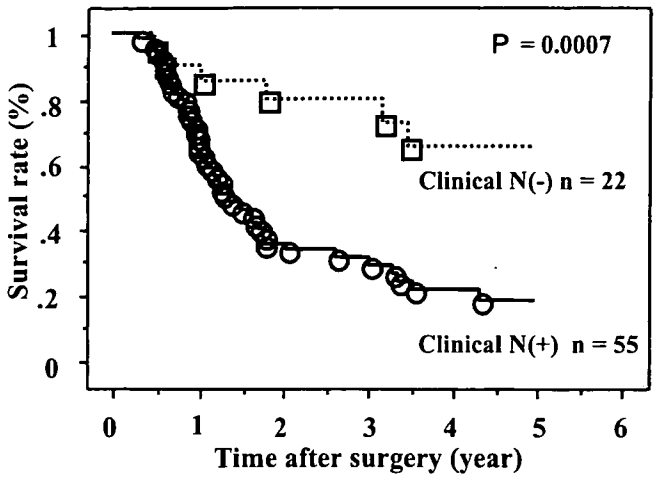

Fig. 2. Survival curves of patients with grade 1 or 2 response in their main tumors were compared by pretreatment clinical N status. The thick line indicates pretreatment clinical N(+) patients and the dotted line N(−) patients. Statistical analysis was done by log-rank test.

16]. Although there have been many studies reporting the pathological CR rate for the main tumors, few have reported the pathological effects on metastatic lymph nodes. The reason for this lies in the fact that the sensitivity for preoperative diagnosis of lymph node metastasis is very low by conventional imaging such as CT, endoscopic ultrasonography, or positron emission tomography [24,25]. Therefore, assessment of the pathological effects on individual metastatic nodes is difficult. To overcome this issue, we counted the number of metastatic nodes by pathological examination and correlated them with the histological effects on the main tumors. A highly significant correlation was found between the effects on the main tumors and the number of metastatic nodes. The average number of metastatic nodes in patients with a grade 3 response in their main tumors was only 0.2, and more than 80% of those were node-negative. In contrast, patients having main tumors with a grade 1 or 2 response had a substantial number of node metastases. These results suggest that the sensitivity to chemoradiotherapy does not differ between the main tumors and metastatic nodes. If the main tumors are sensitive, then the metastatic nodes should also be sensitive.

The possibility of patients with a grade 3 response of the main tumors being node-negative from the beginning is doubtful. Therefore, highly sensitive tumors can be considered to be unlikely to metastasize to lymph nodes. If this is the case, clinical N negative patients should have had a higher pathological CR rate for the main tumors than clinical N positive patients. However, in this study, the pathological CR rate for the main tumors was not affected by the pretreatment N status. In addition, the histological node-negative rate in patients showing a grade 3 response for their main tumors did not differ with the clinical N status (84.2% and 71.4% for clinical N(+) and clinical N(−) patients, respectively). Furthermore, survival curves for patients with a grade 3 response in the main tumors were also unaffected by the preoperative N status. These results exclude the possibility of patients with a grade 3 response at the primary site as being node-negative from the beginning. Instead, the results strongly suggest that the indication for surgery after chemoradiotherapy can be determined according to the histological effects in the primary tumors. Because patients with a grade 2 or higher response at the primary site have at most a few positive nodes, surgery can be expected to eradicate the metastatic nodes and lead to a good prognosis. On the other hand, for patients with a grade 1 response, surgery may not be able to control the disease, because many metastatic nodes may exist. If the histological effect in the main tumor can be preoperatively assessed with accuracy, patients may be efficiently directed towards either surgery or treatment by other modalities.

Endoscopic biopsy does not seem to be reliable for accurate assessment of histological effects. In this study, only 39.1% of the biopsy negative patients were found to show a grade 3 response. This discrepancy between the negative biopsy and a grade 3 response in the resected esophagus increased as the tumor depth increased. As we previously reported, after chemoradiotherapy, residual cancer cells are more often seen in the muscular or deeper layers than the epithelial layer, which may cause misdiagnosis of a grade 3 response by endoscopic biopsy [26].

Positron emission tomography (PET) scan is noninvasive and has a higher accuracy for diagnosis of histological effects. In the future, PET may play an important role in the decision-making for multimodal treatment of

TABLE V. Relationship Between the Results of Preoperative Endoscopic Biopsy and the Histological Effects on the Main Tumors of Surgical Specimens

Preoperative endoscopic biopsy	Histological effects in the surgical specimen			
	Grade 3	Grade 2	Grade 1	Total
Negative				
Total	18 (39.1%)	15 (32.6%)	13 (28.3%)	46 (100%)
T1	2 (100%)	0 (0%)	0 (0%)	2 (100%)
T2	3 (60.0%)	2 (40.0%)	0 (0%)	5 (100%)
T3	5 (41.7%)	5 (41.7%)	2 (16.7%)	12 (100%)
T4	8 (29.6%)	8 (29.6%)	11 (40.7%)	27 (100%)
Positive				
Total	3 (9.1%)	21 (63.6%)	9 (27.3%)	33 (100%)
T1	0 (0%)	0 (0%)	1 (100%)	1 (100%)
T2	0 (0%)	4 (80.0%)	1 (20.0%)	5 (100%)
T3	3 (21.4%)	6 (42.9%)	5 (35.7%)	14 (100%)
T4	0 (0%)	11 (84.6%)	2 (15.4%)	13 (100%)

esophageal cancer. At present, there are no diagnostic tools for knowing whether tumors have reached pathological CR or not before surgery. When advances in molecular biology and diagnostic devices have made possible prediction or accurate diagnosis for truly pathological CR, such patients can be followed up without surgery.

Surgery and chemoradiotherapy are both local treatment modalities, which aim to completely eradicate cancer cells within a field of surgical resection or a radiation field, respectively. However, the characteristics of these two modalities seem to be different. With regard to the effect on the main tumors, chemoradiotherapy has a local pathological CR rate of 66.7% in T1, 33.3% in T2, 25.0% in T3, and 21.4% in T4. On the other hand, the effects of surgery on the main tumors depends on tumor depth, that is, surgery is considered to have a 100% local control rate for T1 to T2 tumors, but 0% for unresectable T4 tumors. With regard to lymph node metastasis, because chemoradiotherapy is considered to have comparable histological effects on the main tumors and metastatic nodes, complete eradication of metastatic nodes can be expected in 20%–30% of node-positive patients. On the other hand, for patients who have undergone surgery, as the number of metastatic lymph nodes increases, the prognosis worsens. As the number of positive nodes increases, the chance increases of cancer cells existing in the lymphatic vessels and extranodular regions. Therefore, complete eradication of cancer cells might be difficult in patients having many metastatic nodes.

CONCLUSIONS

The nodal status after preoperative chemoradiotherapy significantly correlates with the histological effects on the main tumors. Most patients with main tumors of pathological CR are node-negative. Patients with a grade 2 response have at most a few positive nodes. Surgery would be most beneficial for such patients. Theoretically, pathological CR patients do not require surgery. However, at present, surgery is necessary because the pathological CR cannot be accurately diagnosed prior to surgery.

REFERENCES

1. Sugimachi K, Inokuchi K, Kuwano H, et al.: Patterns of recurrence after curative resection for carcinoma of the thoracic part of the esophagus. Surg Gynecol Obstet 1983;157:537–540.
2. Goseki N, Koike M, Yoshida M: Histopathologic characteristics of early stage esophageal carcinoma. Cancer 1992;69:1088–1093.
3. Iizuka T: Surgical treatment for A3 esophageal carcinoma (in Japanese). Kyobu Geka. 1980;80:822–827.
4. Isono K, Sato H, Nakayama K: Results of a nationwide study on the three-field lymph node dissection of esophageal cancer. Oncol 1991;48:411–420.
5. Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y: Radical lymph node dissection for cancer of the thoracic esophagus. Ann Surg 1994;220:364–373.
6. Kato H, Watanabe H, Tachimori Y: Evaluation of neck lymph node dissection for thoracic esophageal carcinoma. Ann Thorac Surg 1991;51:931–935.
7. Ilson DH, Kelsen DP: Combined modality therapy in the treatment of esophageal cancer. Semin Oncol 1994;21:493–507.
8. Seydel HG, Leichman L, Byhardt R, et al.: Preoperative radiation and chemotherapy for localized squamous cell carcinoma of the esophagus: A RTOG Study. Int J Radiat Oncol Biol Phys 1988; 14:33–35.
9. Forastiere AA, Orringer MB, Perez-Tamayo C, et al.: Preoperative chemoradiation followed by transhiatal esophagectomy for carcinoma of the esophagus: Final report. J Clin Oncol 1993;11: 1118–1123.
10. Wolfe WG, Vaughn AL, Seigler HF, et al.: Survival of patients with carcinoma of the esophagus treated with combined-modality therapy. J Thorac Cardiovasc Surg 1993;105:749–756.
11. Forastiere AA, Heitmiller RF, Lee DJ, et al.: Intensive chemoradiation followed by esophagectomy for squamous cell and adenocarcinoma of the esophagus. Cancer J Sci Am 1997;3:144–152.
12. Nygaard K, Hagen S, Hansen HS, et al.: Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: A randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. World J Surg 1992;16:1104–1110.
13. Le Prise E, Etienne PL, Meunier B, et al.: A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. Cancer 1994;73:1779–1784.
14. Walsh TN, Noonan N, Hollywood D, et al.: A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 1996;335:462–467.
15. 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 1997;337:161–167.
16. 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 2001;19:305–313.
17. Yano M, Tsujinaka T, Shiozaki H, et al.: Concurrent chemotherapy (5-fluorouracil and cisplatin) and radiation therapy followed by surgery for T4 squamous cell carcinoma of the esophagus. J Surg Oncol 1999;70:25–32.
18. Mandard AM, Dalibard F, Mandard JC, et al.: Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma: Clinicopathologic correlations. Cancer 1994;73:2680–2686.
19. Coia LR, Engstrom PF, Paul AR, et al.: Long-term results of infusional 5-FU, mitomycin-C, and radiation as primary management of esophageal carcinoma. J Radiat Oncol Biol Phys 1991;20: 29–36.
20. John MJ, Flam MS, Mowry PA, et al.: Radiotherapy alone and chemoradiation for nonmetastatic esophageal carcinoma. A critical review of chemoradiation. Cancer 1989;63:2397–2403.
21. Le Prise EA, Meunier BC, Etienne PA, et al.: Sequential chemotherapy and radiotherapy for patients with squamous cell carcinoma of the esophagus. Cancer 1995;75:430–434.
22. American Joint Committee on Cancer: Esophagus. In: Beahrs OH, Henson DE, Hutter RV, Kennedy BJ, editors. Manual of Staging of Cancer, 4th edn. Philadelphia: JB Lippincott; 1993. pp 75–79.
23. Kelsen DP, Heelan R, Coonley C, et al.: Clinical and pathological evaluation of response to chemotherapy in patients with esophageal cancer. Am J Clin Oncol 1983;6:539–546.

24. Kim K, Park SJ, Kim BT, et al.: Evaluation of lymph node metastases in squamous cell carcinoma of the esophagus with positron emission tomography. Ann Thorac Surg 2001;71:290–294.
25. Rasanen JV, Sihvo EI, Knuuti MJ, et al.: Prospective analysis of accuracy of positron emission tomography, computed tomography, and endoscopic ultrasonography in staging of adenocarcinoma of the esophagus and the esophagogastric junction. Ann Surg Oncol 2003;10:954–960.
26. Yamamoto M, Doki Y, Shiozaki H, et al.: Evaluation of the histologic effect of chemoradiation therapy for squamous cell carcinomas of the esophagus by assessing morphologic features of surgical specimens. Dis Esoph 2000;13:293–300.

COMMENTARY

In the accompanying article by members of the surgical and oncology departments at Osaka University, 103 consecutive patients with esophageal cancer were given neoadjuvant chemotherapy and radiation therapy followed by surgical excision. Most of these patients had squamous cell carcinoma, although 25 patients (or 24%) had undefined histology. Two separate neoadjuvant protocols were used, but the difference was in timing rather than in quantity or quality of chemotherapeutic agents or radiation.The effectiveness of the preoperative therapy was correlated with the presence of nodal metastases in the resection specimen, histological grade, and preoperative post-therapy endoscopic evaluation. All patients were able to undergo surgical resection.

The findings can be summarized as such: (1) most (>80%) of patients showed a major clinical response to neoadjuvant therapy and histological disease stages were correspondingly downstaged, (2) distal thoracic lesions were refractory to the protocol, (3) patients with better histological responses had fewer metastatic lymph nodes at time of resection, and (4) higher stage tumors preoperatively are less amenable to accurate post therapy pre-surgical re-staging. As with most good prospective clinical trails, this article asks as many questions as it answers. The authors did not address the morbidity of their neoadjuvant protocols, whereas many trials have shown significant morbidity and mortality from aggressive protocols as utilized in this study.

The prevailing clinical question in any neoadjuvant therapy trial has been if it really improves survival, both qualitatively and quantitatively. Some groups, including ours, have shown that survival is only improved in pathologically complete responders. The benefits of neoadjuvant therapy also include the achievability of surgical resection or the allowance of smaller resections in certain organs (e.g., breast). Smaller and safer esophageal procedures are not standards of care at present. Neoadjuvant therapy may be of benefit, albeit negatively, by allowing patients with more aggressive or refractory disease to progress whilst on therapy, essentially obviating the need for future surgery.

Yano et al. have shown that the subset of patients with fewer positive lymph nodes and grade 1 and 2 (but not 3) histologic responses has improved overall survival. The adjuvant data presented here, the real crux of any neoadjuvant study, is severely limited by the inability to quantify accurately and preoperatively the presence of lymph node metastases. Therefore, how can we select out these patients before treatment and avoid potentially unnecessary, expensive, and toxic therapies in patients who statistically do not need them? That is the rub, and only improved preoperative imaging, whether by PET or combination PET/MR imaging, endoscopic ultrasound guided fine needle aspirations, or subtle tumor markers as yet undiscovered will allow us this crucial differentiating ability. Until then, we only have the scientific curiosity and efforts of investigators like Yano et al. to guide us.

David W. McFadden, MD, FACS*
Department of Surgery
Robert C. Byrd Health Science Center
West Virginia University
Morgantown, West Virginia

*Correspondence to: David W. McFadden, MD, FACS, Chairman of Surgery, Surgeon-in-Chief, Department of Surgery, Robert C. Byrd Health Science Center, West Virginia University, Morgantown, WV, 26506. Fax: 304-293-4824. E-mail: dmcfadden@hsc.wvu.edu

DOI 10.1002/jso.20210
Published online in Wiley InterScience (www.interscience.wiley.com).

Jpn J Clin Oncol 2005;35(6)316–323
doi:10.1093/jjco/hyi095

Clinical Impact of Criteria for Complete Response (CR) of Primary Site to Treatment of Esophageal Cancer

Makoto Tahara[1], Atsushi Ohtsu[1], Shuichi Hironaka[1], Narikazu Boku[1], Satoshi Ishikura[2], Yoshinori Miyata[3], Takashi Ogino[2] and Shigeaki Yoshida[1]

[1]Division of Digestive Endoscopy and Gastrointestinal Oncology, [2]Division of Radiation Oncology, National Cancer Center Hospital East, Kashiwa, Chiba and [3]Department of Internal Medicine, Saku Central Hospital, Saku, Nagano, Japan

Received January 25, 2005; accepted May 4, 2005; published online June 16, 2005

Background: With the development of chemoradiotherapy for esophageal cancer, the complete response (CR) rate would become an important surrogate end-point. However, the Response Evaluation Criteria in Solid Tumors (RECIST) do not provide criteria for a response at the primary site of esophageal cancer. The objective of this study was to assess the validity of the endoscopic CR criteria for the primary site of esophageal cancer treated with chemoradiotherapy.
Methods: We reviewed 139 patients with T1–T4, N0–1, M0–1a esophageal cancer treated with definitive chemoradiotherapy from August 1992 to April 1999. CR was tentatively defined upon endoscopic observation of the entire esophagus as: (i) disappearance of the tumor lesion; (ii) disappearance of ulceration (slough); and (iii) absence of cancer cells in biopsy specimens.
Results: CR at the primary site (primary-CR) was achieved in 80 patients (58%). Of these, 71 (89%) were evaluated as having primary-CR within 6 months from the start of therapy. With a median follow-up of 53 months, a remarkable difference in the 5-year survival rate was observed between patients evaluated as having primary-CR and having non-CR (46 and 6%, $P < 0.0001$). Local failure was observed in 15 patients and the local control rate in patients with primary-CR was 78% at 5 years.
Conclusions: These criteria appear to represent an appropriate surrogate end-point because they are convenient to apply, require only a short time before a primary-CR can be declared and their fulfillment can predict long-term survival. It is recommended that RECIST include precise endoscopic findings for primary lesions in esophageal cancer in the CR criteria.

Key words: Response Evaluation Criteria in Solid Tumors (RECIST) – esophageal cancer – chemoradiotherapy – complete response (CR) – endoscopy

INTRODUCTION

Definitive chemoradiotherapy for patients with locally advanced esophageal cancer has resulted in high complete response (CR) rates and has greatly impacted on survival (1–4). Recent results obtained with chemoradiotherapy in clinical trials have supported a new standard of care in non-surgical treatment of potentially curable esophageal cancer. With the development of chemoradiotherapy, the CR rate would become an important surrogate end-point in the treatment of esophageal cancer. However, we are not aware of any published clinical studies on chemoradiotherapy for locally advanced esophageal cancer that have precisely outlined CR criteria for the primary site. Slabber et al. (5) used standard Eastern Cooperative Oncology Group (ECOG) response criteria, which considered gastrointestinal malignancies as 'non-measurable, non-evaluable' lesions and defined CR as: (i) complete disappearance of all clinically detectable malignant disease for at least 4 weeks; and (ii) pathological proof of a clinically CR after rebiopsying areas of known malignant disease. The Radiation Therapy Oncology Group (RTOG) phase III intergroup trial (RTOG 85-01) described evaluation after treatment as including esophagoscopy and barium esophagography, with biopsy if the patient was symptomatic (2). However, these methods of evaluation have not been fully validated.

New guidelines, 'Response Evaluation Criteria in Solid Tumors (RECIST)', were published in 1999 (6) and have become the most commonly used criteria worldwide. RECIST

For reprints and all correspondence: Makoto Tahara, Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan. E-mail: matahara@east.ncc.go.jp

Presented at the 37th Annual Meeting of the American Society of Clinical Oncology (ASCO).

gives specific size requirements for measurable lesions at baseline to distinguish target from non-target lesions. It is difficult to measure accurately the primary site of esophageal cancer as distinct from the normal esophageal wall in one dimension, because a computed tomography (CT) scan detects a primary lesion of esophageal cancer according to wall thickness of the esophagus. Therefore, the primary site of esophageal cancer is often identified as a 'non-target lesion'.

Although non-target lesions are taken into account in the evaluation of the best overall response, CR for non-target lesions is defined as the disappearance of all non-target lesions and normalization of tumor marker levels. However, it is impossible to confirm the disappearance of primary site lesions in esophageal cancer by CT scan. Furthermore, development of cicatrical stenosis of the esophagus after chemoradiotherapy often prevents accurate evaluation of tumor response by esophagography, which is usually performed to provide useful information on the degree of luminal narrowing and the location and length of the lesion in the diagnosis of esophageal cancer.

RECIST does not refer to CR criteria for primary lesions by endoscopy in detail, and endoscopic methods of evaluation have not yet been fully validated. Additionally, RECIST has recommended that utilization of endoscopy for an objective tumor response should be restricted to purposes related to validation in specialized centers.

In the treatment of esophageal cancer, we have utilized endoscopy to evaluate tumor response accurately, and propose new endoscopic CR criteria for the primary site of esophageal cancer. Therefore, the objective of this study is to assess the validity of endoscopic criteria for CR of the primary site of esophageal cancer treated with chemoradiotherapy.

PATIENTS AND METHODS

PATIENTS

A total of 217 esophageal cancer patients were treated with definitive chemoradiotherapy between April 1992 and April 1999 at the National Cancer Center Hospital East (NCCHE). For this study, we selected 139 patients from the database who fulfilled the following criteria: (i) esophageal cancer patients treated with definitive chemoradiotherapy at the NCCHE between April 1992 and April 1999; (ii) histologically proven squamous cell carcinoma; (iii) clinical stage T1–T4, N0/1, M0/M1a by the International Union Against Cancer tumor node metastasis (TNM) classification; (iv) age $\leq$75 years with an ECOG performance status of $\leq$2; (v) adequate bone marrow, renal and hepatic function; (vi) no prior chemotherapy; (vii) no severe medical complications; and (viii) no other active malignancies (except early cancer). Patients with non-cervical primary tumors with positive supraclavicular lymph nodes were defined as M1a.

Details of the treatment including the schedule and radiation field were described previously (4,7). Briefly, chemoradiotherapy consisted of two cycles of protracted infusion of 5-fluorouracil (5-FU) 400 mg/m^2/day on days 1–5 and 8–12, and cisplatin (CDDP) 40 mg/m^2 on days 1 and 8, every 5 weeks with concurrent radiotherapy consisting of 60 Gy in 30 fractions over 8 weeks. For patients who showed an objective response to treatment, additional chemotherapy was administered and consisted of protracted infusion of 5-FU 800 mg/m^2/day on days 1–5 combined with CDDP 80 mg/m^2 on day 1.

PROPOSED ENDOSCOPIC CR CRITERIA

Response at the primary site was evaluated as CR (primary-CR) by endoscopic examination when all of the following criteria were satisfied under observation of the entire esophagus: (i) disappearance of the tumor lesion; (ii) disappearance of ulceration (slough); and (iii) absence of cancer cells in biopsy specimens. When these criteria were not satisfied, a non-CR was designated. Existence of an erosion, a granular protruded lesion, ulcer scar and lugol voiding lesion did not prevent a CR evaluation. The first evaluation was performed $\sim$1 month after the completion of chemoradiotherapy to determine whether or not disease progression was observed. Although repeat assessments were not essential to confirm primary-CR after the criteria for response were first met, endoscopic examinations were performed every 2 or 3 months. All 139 patients were reviewed according to the above criteria. Responses of metastatic lymph nodes were assessed according to the World Health Organization (WHO) criteria for measurable disease.

STATISTICAL ANALYSIS

Overall survival time was determined from the date of the first administration of chemoradiotherapy to the date of death or the last confirmation of survival. Time to locoregional failure was calculated from the date of the first administration of chemoradiotherapy to the date of documented locoregional disease, which was designated as the first failure. Time to determination of a primary-CR was considered to be the period between the date of the first administration of chemoradiotherapy and the date of the first confirmation of primary-CR. Survival analysis was performed using the Kaplan–Meier method (8).

RESULTS

PATIENT CHARACTERISTICS

Out of 217 patients who received definitive or palliative chemoradiotherapy during the period studied, 78 patients were excluded from analysis. The reasons for exclusion have been described in a previous report of this study population (7). For the present study, 139 patients were selected as subjects. Patient characteristics are shown in Table 1. The median age was 62 years (range 38–75). Most of the patients had good performance status. All had histologically proven squamous cell carcinoma. Fifteen patients had T1, 11 had T2, 60 had T3, 53 had T4 and 38 had M1a disease. Clinically involved sites in the 53 cases of T4 disease were as follows: tracheobronchial

Table 1. Patient characteristics

Characteristic	No. of patients (n = 139)
Age, years	
Median	62
Range	38–75
Sex	
Male	121
Female	18
Performance status	
0	96
1	42
2	1
Histology	
Squamous W/D	5
Squamous M/D	88
Squamous P/D	45
Adenosquamous	2
Tumor length, cm	
Median	5
Range	1–20
Site	
Ut	23
Mt	81
Lt	35
T stage	
T1	15
T2	11
T3	60
T4	53
N stage	
N0	55
N1	84
M stage	
M0	101
M1a	38
Stage	
I	13
IIA	22
IIB	8
III	58
IVA	38
Involved sites of T4	
Bronchial tree only	21
Aorta only	22
Bronchial tree and aorta	8
Other	2

W/D, well differentiated; M/D, moderately differentiated; P/D, poorly differentiated; Ut, upper thoracic portion; Mt, mid-thoracic portion; Lt, lower thoracic portion.

tree (n = 21), thoracic aorta (n = 22), both sites (n = 8) and other (n = 2). One hundred and thirty-three patients (96%) completed at least the chemoradiotherapy segment that included a total radiation dose of 60 Gy. Sixty-six patients (47%) received two or more additional cycles of chemotherapy.

Response and Survival

Primary-CR was achieved in 80 of the 139 patients [58%; 95% confidence interval (CI), 45–70]. Primary-CR rates in patients with T1, T2, T3 and T4 were 93% (14 out of 15), 82% (nine out of 11), 62% (38 out of 61) and 37% (19 out of 52), respectively. Persistence of local disease was observed in 59 patients (42%; 95% CI 31–53). Among the 87 patients with T1–T3, persistence of local disease was observed in 24 patients (28%; 95% CI 16–39). Among the 80 patients with primary-CR, persistence of regional lymph nodes was observed in seven (5%) patients. With a median follow-up of 53 months, the overall survival rate at 3 and 5 years among all patients was 37% (95% CI 31–43) and 29% (95% CI 24–34), respectively. The overall survival at 3 and 5 years was 55% (95% CI 43–67) and 46% (95% CI 36–56), respectively, among the primary-CR group, while overall survival was 11% (95% CI 8–13) and 6% (95% CI 4–8), respectively, among the primary-non-CR group ($P < 0.0001$, Fig. 1).

Time to Determination of a Primary-CR

Time until determination of a primary-CR is provided in Table 2. Of the 80 patients, 71 (89%) were evaluated as having a primary-CR within 6 months from the start of therapy. However, in nine patients (11%), primary-CR was only determined after 6 months from the start of therapy because before that time biopsy specimens from the primary site were not obtained in two patients, disappearance of ulceration (slough) was not observed in three patients due to radiation esophagitis, and cicatrical stenosis of the esophagus was observed in four patients.

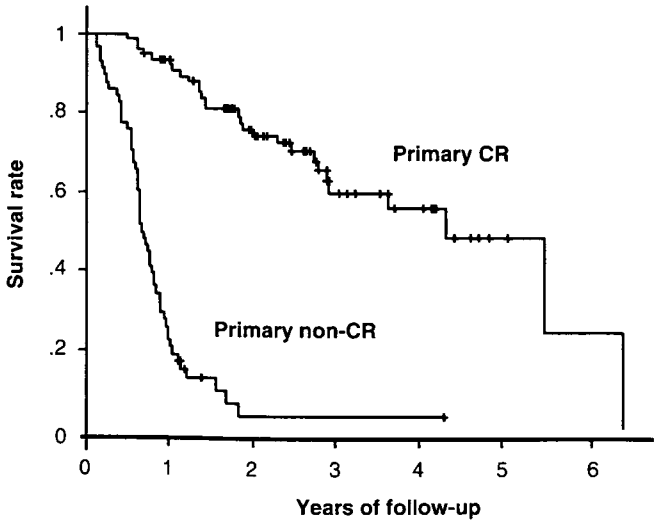

Figure 1. Overall survival in patients according to proposed endoscopic CR criteria.

Table 2. Time from the initial date of treatment to determine a CR at the primary site

	No. of patients (n = 80)	%
<3 months	25	31
3–6 months	46	58
>6 months	9	11

Table 3. First relapse site in patients with primary-CR

	No. of patients (n = 80)	%
Local failure	13	16
Regional failure	1	1
Local and distant failure	2	3
Distant failure	13	16
Treatment failure	29	36

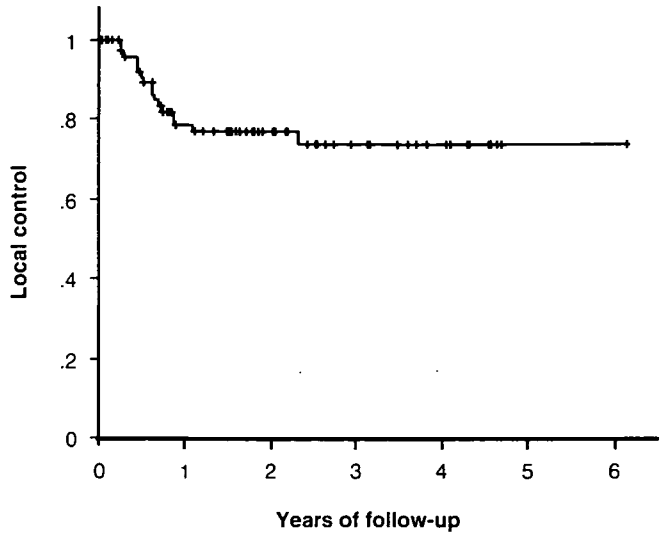

Figure 2. Local control in patients with primary CR. The local control rate is 74% at 3 years, and the curve seems to plateau after 2.2 years.

First Relapse Site

The first relapse sites in patients with primary-CR are shown in Table 3. Among the 80 patients with primary-CR, local failure occurred in 15 (19%) patients, including two with both local and distant failure. Local failure was detected within 1 year from the start of therapy in 10 of these 15 patients (67%). Regional failure alone was observed in one patient (1%). Distant failure alone as the first failure occurred in 13 (16%) patients. Twenty-nine patients (36%) experienced treatment failure. Local control in patients with primary-CR is shown in Fig. 2. The local control rate among patients with primary-CR was 78% at 5 years; this curve appeared to plateau after 2.2 years.

Death from Causes Other Than Treatment Failure

Acute and late toxicity from this treatment regimen have been described previously (7). Briefly, there were three treatment-related deaths (2%), one each due to renal failure, septic shock or pneumonia. Seven patients (5%) without cancer recurrence died due to late cardiopulmonary toxicity, which was manifested as acute myocardial infarction, radiation pneumonitis or chronic heart failure. Sudden death of unknown origin occurred in three patients without disease failure. Another eight patients died of intercurrent disease. In summary, 19 patients (14%) died from causes other than treatment failure.

DISCUSSION

We have proposed new endoscopic CR criteria for the primary site in the treatment of esophageal cancer. The development of cicatrical stenosis of the esophagus with this treatment often prevents observation of the entire esophagus. Therefore, 'observation of the entire esophagus' is considered to be necessary for endoscopic evaluation of the response to treatment. In common with the RECIST criteria, 'disappearance of tumor lesion' and 'absence of cancer cells in biopsy specimens' are indispensable to confirm CR after chemoradiotherapy. When we first began to evaluate CR by endoscopy, it was problematic how to deal with granular protruded lesions, erosions, ulceration and lugol voiding lesions. Granular protruded lesions were often observed with this treatment (Fig. 3). In the course of careful observation and obtaining repeat biopsy specimens from these lesions, local relapse was not observed. Therefore, this granular protruded lesion was considered as a hypertrophic cicatrix and would not prevent determination of a CR. After chemoradiotherapy, local relapses were often detected by endoscopy as ulceration (slough) of the esophagus. Therefore, 'disappearance of ulceration (slough)' is indispensable to confirm not only CR but also no recurrence. Chromoendoscopy using iodine solution is the most effective method of detecting squamous cell mucosal cancer (T1a) in the esophagus, which is an appropriate candidate for endoscopic mucosal resection (9,10). Iodine staining is based on a chemical reaction between iodine and glycogen. Glycogen-rich granules are mainly included in the prickle-cell layer of the normal stratified squamous epithelium. Therefore, esophagitis, cicatrix due to an ulcer scar and cancerous lesions that are immature and lose glycogen-rich granules at the prickle-cell layer can be recognized as an uncolored layer which is said to be a 'lugol voiding lesion' (Fig. 4). Because biopsy of the lugol voiding lesion makes it possible to distinguish between cancer, erosion due to esophagitis and cicatrix due to ulcer scar, the existence of a 'lugol voiding lesion' would not prevent application of the primary-CR criteria.

The main goal of objective confirmation of the response in clinical trials is to avoid overestimating the observed response rate. However, RECIST described that repeat studies to confirm changes in tumor size may not always be feasible or may

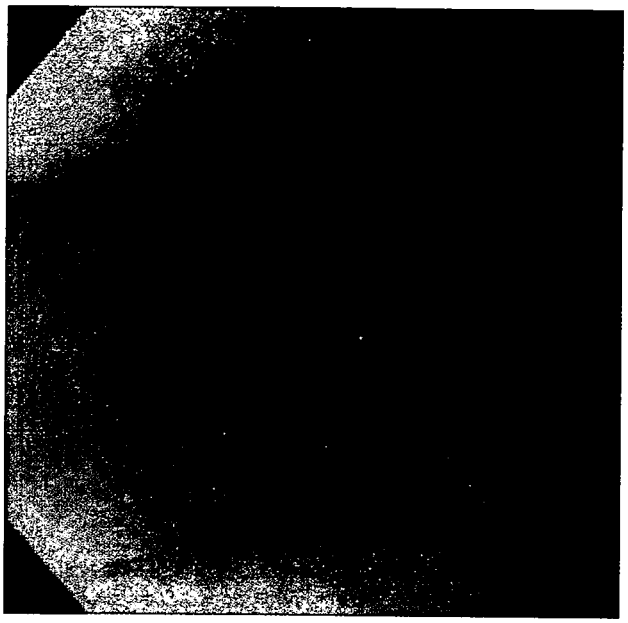

Figure 3. Granular protruded lesion.

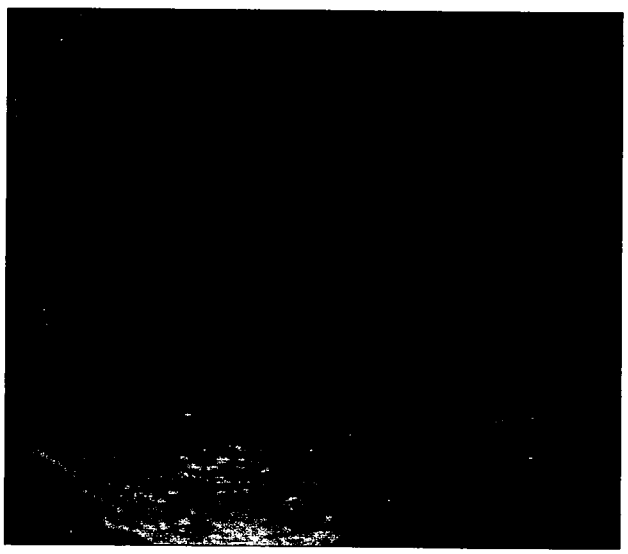

Figure 4. Lugol voiding lesion.

not be part of standard practice in protocols where progression-free survival and overall survival are the key end-points (6). In chemoradiotherapy for locally advanced esophageal cancer, a key end-point is survival. Therefore, repeat assessments were not essential in applying this criterion to confirm primary-CR after the criteria for response are first met.

For a surrogate end-point to be an effective substitute for the clinical end-point, the effects of the intervention on the surrogate must reliably predict clinical benefit or harm based on epidemiological, therapeutic, pathophysiological or other scientific evidence (11,12). Furthermore, these surrogate end-points have been used to reduce the cost and duration of clinical trials. Surrogate end-points are rarely, if ever, adequate substitutes for definitive clinical outcomes in phase III trials. Among several explanations for this failure is the possibility that the disease process could affect the clinical outcome through several causal pathways that are not mediated through the surrogate, with the intervention's effect on these pathways differing from its effect on the surrogate. Even more likely, the intervention might also affect clinical outcome by unintended, unanticipated and unrecognized mechanisms of action that operate independently of the disease process (11).

Tumor response frequently has been used as a surrogate end-point in therapeutic trials of advanced cancer. Unfortunately, tumor response is not a reliable replacement outcome for survival (13). Many of the trials that have established treatment effects on this surrogate end-point have not shown any change in mortality rates. Some of the factors contributing to the failure of a surrogate end-point are a low proportion of CRs rather than just partial responses, a low proportion of responses that are truly durable long-term effects and a high likelihood that unintended mechanisms of action from these aggressive and toxic cancer therapies adversely affect survival. When administering chemoradiotherapy for locally advanced esophageal cancer, any cause of death other than from treatment failure was recognized as an unintended mechanism of action that adversely affects survival (11). Therefore, it is reasonable to propose that an adequate surrogate end-point for CR criteria in esophageal tumors should include the following: (i) simple procedure; (ii) short duration to determine a CR; (iii) possibility to predict long-term survival; (iv) low incidence of disease failure; and (v) acceptable incidence of death from causes other than treatment failure.

RECIST has recommended that utilization of endoscopy for objective determination of tumor response should be restricted to purposes of validation in specialized centers (6). No special endoscopic technique is required for meeting the following criteria by endoscopic examination of the entire esophagus: (i) disappearance of the tumor lesion; (ii) disappearance of ulceration (slough); and (iii) absence of cancer cells in biopsy specimens. Therefore, these criteria should be recognized as involving only a simple procedure and should gain wide acceptance.

With this chemoradiotherapy as scheduled, 4 months are needed for completion, and the first evaluation of the primary site for complete response is performed approximately 5 months from the start of therapy. In this study, most of the patients (89%) were evaluated as having primary-CR within 6 months from the start of therapy. This finding suggests that these criteria can be met in a short period of time not only from the start of therapy (mostly within 2 months) but also after completion of therapy (mostly within 2 months) to declare primary-CR.

A remarkable difference in the 5-year survival rate between patients evaluated as having primary-CR and non-CR was observed in this study. Furthermore, persistence of disease was the greatest cause of treatment failure. Therefore, we could predict long-term survival for patients with locally

advanced esophageal cancer treated with definitive chemoradiotherapy according to these criteria.

In trials of cisplatin-based concurrent chemoradiotherapy for esophageal cancer, data on clinical outcomes for comparison with the present study were available from only two trials, which were the RTOG 85-01 and INT 0123 trials. The incidence of locoregional failure, distant failure and death from causes other than treatment failure in this study were similar to those in the above trials (3,14), suggesting that the clinical outcomes in this study were acceptable.

The accuracy of endoscopic ultrasound (EUS) for initial staging of esophageal cancer is widely accepted. After chemoradiotherapy, however, EUS examination is not helpful in patient management because it cannot accurately identify patients with pathological CR (15–17). This is largely because EUS cannot distinguish between residual tumor and the post-inflammatory changes that characterize effective chemoradiotherapy. EUS is of limited utility in guiding clinical decision making after chemoradiotherapy.

Recently, a retrospective study showed that EUS and EUS-guided fine needle aspiration biopsy (FNA) have the potential of identifying residual lymphadenopathy after pre-operative chemoradiotherapy (18). However, this result was very controversial because EUS-guided FNA was performed in only eight patients.

[^{18}F]Fluorodeoxyglucose ([^{18}F]FDG) positron emission tomography (PET), an emerging imaging technology based on differences in glucose uptake between neoplastic and surrounding normal tissue, has improved the accuracy of clinical staging of untreated esophageal cancer by detecting otherwise occult metastases (19–23). Many studies have reported that [^{18}F]FDG PET is a valuable tool for non-invasive assessment of histopathological tumor response after the completion of neoadjuvant therapy for locally advanced esophageal cancer (24–26). Furthermore, some studies indicated that changes in [^{18}F]FDG uptake or changes in standard uptake value (SUV) were predictive of disease-free survival and overall survival (25–27).

Furthermore, PET/CT is a new imaging modality that provides simultaneous functional and anatomic information. PET/CT has been reported to increase diagnostic confidence compared with either PET or CT imaging alone (28–30). PET/CT also helps in target volume delineation during planning for radiotherapy treatment of esophageal cancer (31,32). Better characterization of the target may improve local control as well as spare normal tissues from radiotherapy sequelae. After therapy, subtle metabolic findings on [^{18}F]FDG PET may result in detection of residual disease after correlation with simultaneously acquired morphologic data. Alternatively, equivocal CT findings, which could represent either recurrent tumor or post-therapy fibrosclerosis, now can be distinguished with the additional information provided by [^{18}F]FDG PET data. In the post-therapy setting, PET/CT might improve the accuracy of PET imaging in distinguishing recurrent disease from benign post-therapy changes. Radiation-induced esophagitis, however, results in false-positive [^{18}F]FDG uptake. Furthermore, because of the limited spatial resolution of PET, lesions <0.5 cm may be undetectable. For these reasons, [^{18}F]FDG PET cannot differentiate partial response from complete response and is of limited utility in guiding clinical decision making after chemoradiotherapy. As PET/CT systems are not yet in widespread use, further studies including comparison with the proposed endoscopic CR criteria or differential evaluation are necessary to establish its role in the evaluation of the response to therapy.

In order to improve local control, many attempts including intensification of radiation dose and accelerated or hyperfractionation radiation methods were made, but all of these methods failed to improve local control or survival (14,33–35). The addition of new agents, other than 5-FU plus cisplatin, may be promising. The addition of paclitaxel to the standard chemoradiotherapy regimen increased the response rate of locally advanced esophageal cancer, with a pathological complete response rate of 38% and an actuarial 3-year survival of 41%, which warrant further investigation (36). The addition of cetuximab, a monoclonal antibody to epidermal growth factor receptor, to high-dose radiation in locoregionally advanced squamous cell head and neck carcinoma resulted in a statistically significant and clinically meaningful improvement in locoregional control and overall survival (37). The use of molecular targeting agents in combination with chemoradiotherapy will be a major focus in future studies, because their toxicity profiles are clearly different from those of cytotoxic agents.

The survival of patients who have residual or recurrent tumor after chemoradiotherapy is dismal, and salvage treatment for such patients is indicated to improve the overall survival. Although some small studies have shown the feasibility and efficacy of salvage surgery, the high mortality associated with salvage surgery after chemoradiotherapy is another important issue. Although the optimal timing and modes of salvage treatment should be investigated in the future, early detection of residual or recurrent tumor that was limited to within the submucosal layer enabled endoscopic mucosal resection (EMR) as a substitute for salvage surgery (38). Photodynamic therapy (PDT) is an experimental cancer treatment modality that selectively destroys cancer cells by the interaction between absorbed light and a retained photosensitizing agent (39). In our experience, PDT was a safe and effective salvage treatment with a CR rate of 62% (40). A phase II trial of PDT for residual or recurrent esophageal cancer after definitive chemoradiotherapy is ongoing at our hospital.

In conclusion, the proposed endoscopic CR criteria appear to represent an appropriate surrogate end-point because they are convenient, require a short period of time (mostly within 6 months) to declare primary-CR, predict favorable survival and are associated with an acceptable frequency of disease failure and death from causes other than treatment failure. The proposed criteria would be of major importance in the process of evaluation of new treatment strategies. Since persistence of disease was the greatest cause of treatment failure

for locally advanced esophageal cancer after chemoradiotherapy, it is important to evaluate accurately the tumor response. In the treatment of locally advanced esophageal cancer, moreover, the fact that RECIST does not refer to CR criteria for primary lesions in detail prevents not only appropriate clinical evaluation of response but also the fulfillment of requirements of a clinical trial. We feel that the RECIST criteria do not provide information to evaluate the primary sites of esophageal cancer. It is recommended that the precise endoscopic findings of primary lesions in esophageal cancer be added to the CR criteria in RECIST.

References

1. Coia LR. Chemoradiation as primary management of esophageal cancer. *Semin Oncol* 1994;21:483–92.
2. Herskovic A, Martz K, al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992;326:1593–8.
3. al-Sarraf M, Martz K, Herskovic A, Leichman L, Brindle JS, Vaitkevicius VK, et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. *J Clin Oncol* 1997;15:277–84.
4. Ohtsu A, Boku N, Muro K, Chin K, Muto M, Yoshida S, et al. Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. *J Clin Oncol* 1999;17:2915–21.
5. Slabber CF, Nel JS, Schoeman L, Burger W, Falkson G, Falkson CI. A randomized study of radiotherapy alone versus radiotherapy plus 5-fluorouracil and platinum in patients with inoperable, locally advanced squamous cancer of the esophagus. *Am J Clin Oncol* 1998;21:462–5.
6. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–16.
7. Ishikura S, Nihei K, Ohtsu A, Boku N, Hironaka S, Mera K, et al. Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. *J Clin Oncol* 2003;21:2697–702.
8. Kaplan EL MP. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–81.
9. Endo M, Takeshita K, Yoshida M. How can we diagnose the early stage of esophageal cancer? Endoscopic diagnosis. *Endoscopy* 1986;18 (Suppl 3): 11–8.
10. Inoue H, Rey JF, Lightdale C. Lugol chromoendoscopy for esophageal squamous cell cancer. *Endoscopy* 2001;33:75–9.
11. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med* 1996;125:605–13.
12. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther* 2001;69:89–95.
13. Moertel CG. Improving the efficiency of clinical trials: a medical perspective. *Stat Med* 1984;3:455–68.
14. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol* 2002;20:1167–74.
15. Beseth BD, Bedford R, Isacoff WH, Holmes EC, Cameron RB. Endoscopic ultrasound does not accurately assess pathologic stage of esophageal cancer after neoadjuvant chemoradiotherapy. *Am Surg* 2000;66:827–31.
16. Zuccaro G Jr, Rice TW, Goldblum J, Medendorp SV, Becker M, Pimentel R, et al. Endoscopic ultrasound cannot determine suitability for esophagectomy after aggressive chemoradiotherapy for esophageal cancer. *Am J Gastroenterol* 1999;94:906–12.
17. Pfau PR, Kochman ML. Pretreatment staging by endoscopic ultrasonography does not predict complete response to neoadjuvant chemoradiation in patients with esophageal carcinoma. *Gastrointest Endosc* 2000;52:583–6.
18. Agarwal B, Swisher S, Ajani J, Kelly K, Fanning C, Komaki RR, et al. Endoscopic ultrasound after preoperative chemoradiation can help identify patients who benefit maximally after surgical esophageal resection. *Am J Gastroenterol* 2004;99:1258–66.
19. Flamen P, Lerut A, Van Cutsem E, De Wever W, Peeters M, Stroobants S, et al. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. *J Clin Oncol* 2000;18:3202–10.
20. Block MI, Patterson GA, Sundaresan RS, Bailey MS, Flanagan FL, Dehdashti F, et al. Improvement in staging of esophageal cancer with the addition of positron emission tomography. *Ann Thorac Surg* 1997;64:770–6; discussion 6–7.
21. Lerut T, Flamen P, Ectors N, Van Cutsem E, Peeters M, Hiele M, et al. Histopathologic validation of lymph node staging with FDG-PET scan in cancer of the esophagus and gastroesophageal junction: a prospective study based on primary surgery with extensive lymphadenectomy. *Ann Surg* 2000;232:743–52.
22. Choi JY, Lee KH, Shim YM, Lee KS, Kim JJ, Kim SE, et al. Improved detection of individual nodal involvement in squamous cell carcinoma of the esophagus by FDG PET. *J Nucl Med* 2000;41:808–15.
23. Kim K, Park SJ, Kim BT, Lee KS, Shim YM. Evaluation of lymph node metastases in squamous cell carcinoma of the esophagus with positron emission tomography. *Ann Thorac Surg* 2001;71:290–4.
24. Flamen P, Van Cutsem E, Lerut A, Cambier JP, Haustermans K, Bormans G, et al. Positron emission tomography for assessment of the response to induction radiochemotherapy in locally advanced oesophageal cancer. *Ann Oncol* 2002;13:361–8.
25. Brucher BL, Weber W, Bauer M, Fink U, Avril N, Stein HJ, et al. Neoadjuvant therapy of esophageal squamous cell carcinoma: responseevaluation by positron emission tomography. *Ann Surg* 2001;233:300–9.
26. Kato H, Kuwano H, Nakajima M, Miyazaki T, Yoshikawa M, Masuda N, et al. Usefulness of positron emission tomography for assessing the response of neoadjuvant chemoradiotherapy in patients with esophageal cancer. *Am J Surg* 2002;184:279–83.
27. Downey RJ, Akhurst T, Ilson D, Ginsberg R, Bains MS, Gonen M, et al. Whole body 18FDG-PET and the response of esophageal cancer to induction therapy: results of a prospective trial. *J Clin Oncol* 2003;21:428–32.
28. Yau YY, Samman N, Yeung RW. Positron emission tomography/computed tomography true fusion imaging in clinical head and neck oncology: early experience. *J Oral Maxillofac Surg* 2005;63:479–86.
29. Rusthoven KE, Koshy M, Paulino AC. The role of PET–CT fusion in head and neck cancer. *Oncology (Huntingt)* 2005;19:241–6; discussion 6, 9–50, 53.
30. Syed R, Bomanji JB, Nagabhushan N, Hughes S, Kayani I, Groves A, et al. Impact of combined (18)F-FDG PET/CT in head and neck tumours. *Br J Cancer* 2005;92:1046–50.
31. Konski A, Doss M, Milestone B, Haluszka O, Hanlon A, Freedman G, et al. The integration of 18-fluoro-deoxy-glucose positron emission tomography and endoscopic ultrasound in the treatment-planning process for esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 2005;61:1123–8.
32. Vrieze O, Haustermans K, De Wever W, Lerut T, Van Cutsem E, Ectors N, et al. Is there a role for FDG-PET in radiotherapy planning in esophageal carcinoma? *Radiother Oncol* 2004;73:269–75.
33. Girinsky T, Auperin A, Marsiglia H, Dhermain F, Randrianarivelo H, Kac J, et al. Accelerated fractionation in esophageal cancers: a multivariate analysis on 88 patients. *Int J Radiat Oncol Biol Phys* 1997;38:1013–8.
34. Jeremic B, Shibamoto Y, Acimovic L, Matovic Z, Milicic B, Milisavljevic S, et al. Accelerated hyperfractionated radiation therapy and concurrent 5-fluorouracil/cisplatin chemotherapy for locoregional squamous cell carcinoma of the thoracic esophagus: a phase II study. *Int J Radiat Oncol Biol Phys* 1998;40:1061–6.
35. Wang Y, Shi XH, He SQ, Yao WQ, Guo XM, Wu GD, et al. Comparison between continuous accelerated hyperfractionated and late-course accelerated hyperfractionated radiotherapy for esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 2002;54:131–6.
36. Meluch AA, Greco FA, Gray JR, Thomas M, Sutton VM, Davis JL, et al. Preoperative therapy with concurrent paclitaxel/carboplatin/infusional 5-FU and radiation therapy in locoregional esophageal cancer: final results of a Minnie Pearl Cancer Research Network phase II trial. *Cancer J* 2003;9:251–60.
37. Bonner J, Harari P, Giralt J, Azarnia N, Cohen R, Raben D, et al. Cetuximab (ErbituxTM) prolongs survival in patients with locally advanced squamous cell carcinoma of the head and neck: a phase III study of high dose radiation

therapy with or without cetuximab. *Proc Am Soc Clin Oncol* 2004;22:319a (abstr 4022).
38. Hattori S, Muto M, Ohtsu A, Boku N, Manabe T, Doi T, et al. EMR as salvage treatment for patients with locoregional failure of definitive chemoradiotherapy for esophageal cancer. *Gastrointest Endosc* 2003;58:65–70.
39. Manyak MJ, Russo A, Smith PD, Glatstein E. Photodynamic therapy. *J Clin Oncol* 1988;6:380–91.
40. Yano T, Muto M, Minashi K, Hattori S, Ohtsu A, Yoshida S. Photodynamic therapy as salvage treatment for local failures after definitive chemoradiotherapy for esophageal cancer. *Gastrointest Endosc* 2005 (in press).

ORIGINAL ARTICLE

Photodynamic therapy as salvage treatment for local failures after definitive chemoradiotherapy for esophageal cancer

Tomonori Yano, MD, Manabu Muto, MD, Keiko Minashi, MD, Atsushi Ohtsu, MD, Shigeaki Yoshida, MD

Kashiwa, Japan

Background: Although definitive chemoradiotherapy for esophageal cancer shows a high response rate, persistent or recurrent locoregional disease remains a major problem. Salvage esophagectomy is the only curative intent treatment option; however, it carries higher morbidity and mortality rates than primary esophagectomy. Response to second-line chemotherapy is quite dismal.

Methods: From December 2002 to November 2003, we applied salvage photodynamic therapy to 13 patients with local failures after completion of chemoradiotherapy, 4 patients had local recurrence after achieving a complete response, and 9 had a persistent tumor after chemoradiotherapy. The decision to treat was based on patients' refusal of salvage surgery or chemotherapy. After the intravenous administration of 2 mg/kg of Photofrin, photoradiation treatment with an excimer dye laser was performed for 48 hours and 72 hours after the injection. Written informed consent was obtained from all patients.

Results: Eight patients (62%) achieved a complete response. After a median follow-up period of 12 months after photodynamic therapy, 6 patients were still free of disease, and the overall survival rate at 1 year was 68.4%. There were no treatment-related deaths.

Conclusions: Our results show that salvage photodynamic therapy could be a promising curative intent treatment option with low morbidity and mortality rates. (Gastrointest Endosc 2005;62:31-6.)

Although definitive chemoradiotherapy (CRT) is now commonly used for the treatment of esophageal cancer, persistent or recurrent locoregional disease occurs in more than 40% of patients and remains one of the major unsolved problems.[1] The survival of the patients who did not achieve complete response (CR) is dismal. Most of them (over 80%) would die within 1 year.[2] Esophagectomy as a salvage treatment has a curative potential; however, it is a more difficult and risky procedure than primary esophagectomy.[3] Postoperative mortality rates within 30 days of surgery also are higher.[3,4] Moreover, there are no curative chemotherapy protocols currently available for treatment of residual tumor.

Some patients with persistent or recurrent locoregional disease have truly local failures without distant metastasis. In such patients, local treatment seems to be sufficient. We have previously reported that EMR could be a salvage option.[5] In that paper, the 3-year survival rate from the initial EMR for all 16 patients was 56%, and there were no serious complications.[5] However, the application of salvage EMR is limited by its requirement for tumor recurrence that is focal in nature, and a high skill level is required for this procedure.

Photodynamic therapy (PDT) is a potential alternative, nonsurgical treatment that eliminates superficial esophageal cancer.[6,7] This method uses a photosensitizing chemical agent that is activated by light to selectively destroy the neoplastic cells.[8-10] Theoretically, PDT may cure T1 and possibly T2 tumors, as classified by the TNM classification,[11] and this procedure is relatively simple to perform. Therefore, we postulated that PDT could be a more effective salvage option than EMR. However, there have been no reports published to date that use this method to treat local failures after definitive CRT. Herein, we report our experience of esophageal cancer patients treated with salvage PDT for local failure after completion of definitive CRT.

PATIENTS AND METHODS

Between December 2002 and November 2003, 13 patients underwent salvage PDT at the National Cancer Center Hospital East, Kashiwa, Japan. All patients initially

0016-5107/$30.00
PII: S0016-5107(05)00545-6

were treated with definitive CRT at our hospital. The CRT consisted of 60 Gy irradiation, along with two cycles of continuous infusion with 5-fluorouracil (5FU) and cisplatin (CDDP) or nedaplatin (NED). The 5FU (400 mg/m^2, 24-hour intravenous infusion) was administered on days 1 to 5 and 8 to 12. CDDP (40 mg/m^2, 2-hour intravenous infusion) was administered with hydration on day 1 and day 8. This schedule was repeated twice, every 5 weeks. Radiotherapy was initiated concurrently on the first day of the first and second course of chemotherapy and was delivered in 30 fractions of 2 Gy for a total of 60 Gy. In addition, two courses of chemotherapy were added for the patients who showed good initial response to treatment. In the cases with renal insufficiency or cardiovascular disease, we used NED instead of CDDP, because NED did not require hydration and showed a low risk of renal toxicity.[12]

Baseline staging of esophageal cancer was determined by the TNM classification of the International Union Against Cancer.[11] Clinical T stage was evaluated by endoscopy and EUS, and clinical N and M stage were evaluated mainly by CT of the neck, the chest, and the abdomen. The definition of complete response after CRT was determined as follows: (1) disappearance of tumor lesion or ulcer of primary site with confirmed cancer negative histology, and (2) disappearance of measurable or assessable metastatic lesion confirmed by CT.

Although all persistent or recurrent tumors were surgically resectable, the decision to undergo nonsurgical treatment was based on the patients' refusal of surgery. All patients gave written informed consent. The criteria for salvage PDT were specific and included the following: (1) no lymph node or distant metastases was detected; (2) tumor staging by a 20-MHz US probe (UM-3R; Olympus Optical Co, Ltd, Tokyo, Japan) was limited to the following categories of uT1 or uT2, uT1 when the tumor invasion was within mucosal and/or submucosal layer, or uT2 when the tumor invaded into the muscularis propria layer; (3) other nonsurgical treatments, e.g., EMR, were not indicated for reasons of difficulty or noncurability; and (4) written informed consent was obtained from the patient.

The PDT procedure commenced with intravenous administration of 2 mg/kg of Photofrin (Wyeth K. K., Tokyo, Japan) followed by dye laser irradiation. The 630-nm-wavelength laser beam was emitted by an excimer dye laser (EDL-1; Hamamatsu Photonics, Hamamatsu, Japan). The laser treatment was performed 48 and 72 hours after injection of the drug. The excimer dye laser was delivered via a microlens fiber introduced into the operative channel of the fiberscope (GIF-Q20; Olympus) and was positioned in the esophagus. The distal tip of the fiber was maintained to keep the distance about 1 cm from the surface of the lesion. The total light density was 75 J/cm^2, with 4 mJ/pulse maximum pulse energy and 40 Hz pulse frequency.

All patients were instructed to avoid direct exposure to sunlight for 1 month after the injection of Photofrin for the purpose of protection from skin photosensitization. Patients were examined endoscopically 7 to 8 days after treatment to confirm the development of tissue necrosis. To evaluate the response and the luminal toxicity of PDT, endoscopic examination with biopsy was repeated at least every month until confirmation of the response. The response to PDT was classified as a CR if there was no macroscopic or microscopic evidence of cancer, or non-CR if a tumor was seen at endoscopy and was confirmed histologically. Recurrence was defined as a relapse after achieving CR. CT was used to evaluate the distant organ or lymph-node metastasis at 3, 6, and 12 months after PDT.

The progression-free survival was measured from the date of PDT to the date of confirmation of the recurrence or the progression of the disease. Overall survival was measured from the date of PDT to death or at last follow-up visit. Survival time was calculated by the Kaplan-Meier method. In addition, we assessed the period of hospital stay, antibiotics usage, and fasting after salvage PDT. If the toxicity occurred within 7 days after PDT, we defined it as acute toxicity. In contrast, if it occurred 8 days after PDT, it was defined as a late toxicity. All information was collected from medical records and was provided by the patient's physicians.

Capsule Summary

What is already known on this topic

- Persistent or recurrent loco-regional disease occurs in more than 40% of esophageal cancers after chemoradiotherapy.
- Photodynamic therapy (PDT) may cure T1 or T2 esophageal tumors and may be a salvage option.

What this study adds to our knowledge

- In an uncontrolled case series from Japan, salvage PDT with curative intent was used in 13 patients, achieving 62% complete response and a 68% 1-year survival.

RESULTS

Baseline patient and lesion characteristics before CRT and those before PDT are summarized in Table 1. Median age was 67 years (range 51-75 years). There were 12 men and one woman. The baseline clinical stage before CRT was as follows: T1, T2, T3, and T4 in 0, 4, 9, and 0 patients, respectively; N0 and N1 in 5 and 8 patients, respectively; and stage I, stage IIA, stage IIB, stage III, and stage IV in 0, 5, 1, 6, and 1 patients, respectively. Nine patients were treated with 5FU, CDDP, and radiation; and 4 patients were treated with 5FU, NED, and radiation. Four patients suffered local recurrence after achieving CR, and the remaining 9 patients had persistent tumor after completion of CRT. Six patients

TABLE 1. Patient and lesion characteristics

Patient	Age (y)	Gender	Baseline TNM stage*†	Tumor status after CRT	TNM stage before PDT†	Histologic confirmation of residual cancer	Tumor length before PDT (cm)
1	64	Male	T2N0M0	Recurrent	T1N0M0	Positive	1
2	59	Male	T3N1M0	Persistent	T1N0M0	Positive	2
3	74	Male	T3N0M0	Persistent	T2N0M0	Positive	4
4	51	Male	T2N0M0	Recurrent	T1N0M0	Positive	2
5	58	Male	T3N1M0	Persistent	T2N0M0	Positive	2.5
6	74	Male	T2N1M1a	Persistent	T1N0M0	Positive	4
7	68	Male	T3N1M0	Persistent	T2N0M0	Negative	7
8	75	Male	T3N1M0	Recurrent	T2N0M0	Positive	3
9	61	Female	T3N0M0	Persistent	T1N0M0	Negative	2
10	71	Male	T2N1M0	Recurrent	T1N0M0	Positive	2
11	64	Male	T3N0M0	Persistent	T2N0M0	Positive	5
12	67	Male	T3N1M0	Persistent	T2N0M0	Positive	6
13	69	Male	T3N1M0	Persistent	T2N0M0	Negative	5

CRT, Chemoradiotherapy; *PDT*, photodynamic therapy.
*Based on the criteria of the TNM classification of malignant tumors by the International Union Against Cancer.
†The tumor stage was evaluated by EUS.

had uT1 tumors (all of them were assessed as having massive submucosal invasion), and 7 patients had uT2 tumors. Three patients were judged to have persistent tumor without histologic confirmation of carcinoma according to the endoscopic and EUS findings of submucosal tumor-like lesions. The median length of tumor before salvage PDT was 3 cm (range 1-7 cm). Seven patients had ulceration on the lesions before PDT.

Clinical outcomes after salvage PDT are summarized in Table 2. The median total delivered light dose was 750 J (range 300-1000 J). A response of the tumors to salvage PDT was seen in all patients. CR was attained in 8 (62%) of the 13 patients. Among the cases with histologically confirmed residual cancer, the CR rate was 60% (6/10). We show the representative case of a patient who achieved CR after salvage PDT in Figure 1. All patients with uT1 tumors achieved CR, whereas two of 7 patients with uT2 also achieved CR. The median time to confirm CR was 3 months (range 1-4 months). Two patients experienced local recurrence after salvage PDT and were re-treated with PDT; however, their recurrent lesions did not disappear. They died of esophageal cancer progression. Of the 5 patients who did not achieve CR, 3 patients were re-treated with PDT, and the remaining two were followed with appropriate best-supportive care. At a median follow-up period of 12 months (range 6-19 months) after application of salvage PDT, 9 patients were still alive and 6 of them were free of disease. The overall survival rate after salvage PDT after 1 year was 68.4% (Fig. 2).

In all cases, intravenous injection of the Photofrin was well tolerated. There were no allergic reactions or injection site irritation. For all 13 patients, the median hospital stay was 13 days (range 6-20 days), the fasting period was 1 day (range 0-6 days), and the antibiotics-required period was 4 days (range 0-10 days). As for acute complication within the 7 days after salvage PDT, high fever (>38.5°C), and chest pain that needed pain killers was observed in 4 and 7 patients, respectively. White blood count (WBC) and C-reactive protein (CRP) were elevated after initial salvage PDT. Median WBC and CRP at 2 days after salvage PDT were 9400/mm^3 (range 5300-15900/mm^3) (normal 4500-8500/mm^3) and 11.2 mg/dL (range 2.3-18.8 mg/dL); (<0.5 mg/dL), respectively. Six patients experienced significant complications: one mediastinitis, one esophagotracheal fistula, 3 stenosis that required repeated balloon dilation, one cutaneous phototoxicity, and one increase of radiation-induced pericardial effusion that required drainage. The patient who developed mediastinitis was cured by intravenous administration of antibiotics and fasting for 1 week. The patient who developed a fistula died of the progression of esophageal cancer. There were no occurrences of treatment-related death.

DISCUSSION

Definitive CRT is considered the standard non-surgical treatment for esophageal cancer, because it shows