張できるために食事摂取が可能となり，食事の肺への流れ込みも防止できる(図5)．提示した症例は右気管支への瘻孔を認め，経口摂取が不可能であったがステント挿入後，発熱を認めずに経口摂取可能となった．しかし，ステントが壁に密着せず瘻孔の完全な閉鎖が不可能なため経口摂取が再開できない症例，急激な腫瘍の進行を認める症例，腫瘍が気管へ圧迫し，気道狭窄を起こす可能性等もあり，施行する際にはリスクを含めた十分なインフォームドコンセントが重要である．食道および気管・気管支の両者ともステント挿入する方法[13]は両者の間の組織が壊死に陥り，重篤な合併症を引き起こすリスクがあり，積極的には施行していない．Yamamoto らも QOL の改善には有効であるものの45%の症例で重篤な合併症を認めたことを報告している[14]．

バイパス手術はステントの材質，治療技術の発達によりステント挿入が安全に施行できるようになり，その適応範囲は狭くなっている．当科では安全性，手技の容易さという点から Heimlich 反転胃管を用いたバイパス手術[15]を採用していたが，この数年実際に施行した症例はないのが現状である．Aoki らもバイパス手術とステントの比較を行い，症例に応じた治療法の選択が重要としているもステント挿入を第一選択と結論している[16]．

瘻孔形成症例におけるステント挿入後の放射線治療については否定的な意見が多く，当科においても治療可能症例に対しては CDDP，5-FU，ロイコボリン(LV)による化学療法のみを施行している．この3者併用は当科のデータでは奏効率44.4%であり，LV 未使用治療の奏効率17.6%に比し Phase III 試験は行われていないが効果は高いと考えている[17]．しかしながらステント挿入例においては満足できる治療効果は得られておらず，best supportive care に比し生存期間が延長できるという確証も得られていないため，積極的に行うべき治療かどうか QOL の点を含めて今後の検討が必要である．

大動脈に対する T4 に対しては大動脈内にステントを挿入し，出血を予防する方法が報告されている[18]．Adamkiewicz の血管を閉塞し下半身麻痺という重篤な合併症等があるが出血のリスクを軽減しての放射線治療が可能であり，今後の発展が期待される選択肢の1つである．

IV．進行食道癌に対する遺伝子治療

当科では，治療不能進行食道癌に対する新しい治療法の開発の一環として遺伝子治療の基礎的検討を行ってきた．現時点でもっとも効果の期待できるアデノウイルスベクターを用いた p53 癌抑制遺伝子による遺伝子治療臨床研究のプロトコールを新たに作成し，学内の審査委員会，文部科学・厚生労働両省の承認をうけ，2000年12月に第一例目を施行した．対象となる症例は手術不能であり，他の治療に抵抗性の進行食道癌，75歳以下，ベクターを局注可能であることなどが適応基準となっている．評価項目は局所の抗腫瘍効果，安全性，生物学的反応等である．現在まで7例の症例に施行しており，発熱以外の重篤な有害事象は認めておらず，忍容性は良好である．

p53 癌抑制遺伝子は DNA 損傷からアポトーシス，あるいは細胞周期を制御して DNA 修復を行う際にきわめて重要な遺伝子であり，抗癌剤，放射線の感受性に大きく関与していると考えられる．実際，食道癌細胞に遺伝子導入することにより放射線，抗癌剤の感受性の増強を確認しており[19]，現在施行中の方法で安全性が確認され次第，放射線化学療法施行前の基礎治療として p53 癌抑制遺伝子を導入し，感受性の増強，有害事象の減少を計り，T4 食道癌に対して予後の期待できる Grade3 症例を増加させたいと考えている．

おわりに

T4 食道癌の予後は不良であるが，放射線化学療法を中心とした集学的治療の進歩により，とくに前治療の有効であった切除症例において長期生存例が得られるようになり，今後の新たな治療の開発により，さらなる予後の改善が期待される．

また，新たな材質の発達によりステント挿入による姑息的治療もQOLの改善にきわめて有用な治療法として確立されつつある．

文　献

1) Isono K, Sato H, Nakayama K: results of a nationwide study on the three-field lymph node dissection of esophageal cancer. Oncology 48: 411-420, 1991.
2) 松原久裕，落合武徳：胸部食道癌のリンパ節郭清の基本方針と手術手技．消化器外科 22：1327-1334，1999.
3) 小出義雄：胸部食道癌の集学的治療の研究．千葉医学 74：361-371，1998.
4) Comprehensive Registry of Esophageal Cancer in Japan (1998, 1999) 3rd edition. The Japanese Society for Esophageal Diseases, Chiba 2002.
5) 吉永有信，岡住慎一，島田英昭ほか：full scale volume rendering 3D-dynamic CTによる食道癌他臓器浸潤診断．第56回日本食道疾患研究会抄録集 120，2002.
6) 小出義雄，岡住慎一，松原久裕ほか：食道癌における至適切除範囲の検討．日消外会誌 30：2088-2092，1997.
7) al-Sarraf M, Martz K, Herskovic A, et al: Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol 15: 277-284, 1997.
8) Minsky BD, Pajak TF, Ginsberg RJ, 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 20: 1167-1174, 2002.
9) 落合武徳，松原久裕：胸部食道癌手術．消化器外科 25：802-810，2002.
10) 岡住慎一，福長 徹，河野世章ほか：18F-FDG, 11C-methionin による診断．Innevision 14：100-103，1999.
11) 星野敏彦，宮崎信一，島田英昭ほか：3D-EUSによる食道癌放射線化学療法の効果判定法の検討．第56回日本食道疾患研究会抄録集 133，2002.
12) Ohtsu A, Boku N, Muro K, et al: Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. J Clin Oncol 17: 2915-2921, 1999.
13) Colt HG, Meric B, Dumon JF: Double stents for carcinoma of the esophagus invading the tracheo-bronchial tree. Gastrointest Endosc 38: 485-489, 1992.
14) Yamamoto R, Tada H, Kishi A, et al: Double stent for malignant combined esophago-airway lesions. Jpn J Thorac Cardiovasc Surg 50: 1-5, 2002.
15) Cukingnan RA, Carey JS: Carcinoma of the esophagus. Ann Thorac Surg 26: 274-286, 1978.
16) Aoki T, Osaka Y, Takagi Y, et al: Comparative study of self-expandable metallic stent and bypass surgery for inoperable esophageal cancer. Dis Esophagus 14: 208-211, 2001.
17) 松原久裕，外浦 功，落合武徳：治療の実際 V. 食道癌 CF療法，CF+LV療法(入院)．古江 尚(編)；実践・癌化学療法別副作用対策．メディカルレヴュー社 pp104-105，2000.
18) 猶本良夫，羽井佐実，山辻知樹ほか：大動脈浸潤を伴う食道癌治療における大動脈ステントグラフト内挿術．手術 55：415-419，2001.
19) Matsubara H, Kimura M, Sugaya M, et al: Expression of wild-type p53 gene confers increased sensitivity to radiation and chemotherapeutic agents in human esophageal carcinoma cells. Int J Oncol 14: 1081-1085, 1999.

Reprinted from
Jpn J Clin Oncol 2002;32(2)59–63

Advanced Esophageal Cancer with Esophago-bronchial Fistula Successfully Treated by Chemoradiation Therapy with Additional Endoscopic Resection: a Case Report

Masato Morihiro[1], Narikazu Boku[1], Atsushi Ohtsu[1], Shin'ichi Miyamoto[1] and Satoshi Ishikura[2]

[1]Division of Digestive Endoscopy and Gastrointestinal Oncology and [2]Division of Radiation Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

Jpn J Clin Oncol 2002;32(2)59–63

Case Reports

Advanced Esophageal Cancer with Esophago-bronchial Fistula Successfully Treated by Chemoradiation Therapy with Additional Endoscopic Resection: a Case Report

Masato Morihiro[1], Narikazu Boku[1], Atsushi Ohtsu[1], Shin'ichi Miyamoto[1] and Satoshi Ishikura[2]

[1]Division of Digestive Endoscopy and Gastrointestinal Oncology and [2]Division of Radiation Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

Received August 9, 2001; accepted November 14, 2001

Chemoradiation is potentially curative for esophageal cancer in various stages, but local failure is a major problem. The present case was a 49-year-old male diagnosed with advanced esophageal cancer with an esophago-bronchial fistula and lymph node metastasis. Histological diagnosis by biopsy was adenosquamous cell carcinoma. Chemoradiotherapy comprising intravenous infusion of cisplatin and continuous infusion of 5-fluorouracil with concurrent radiation was initiated in July 1997. In December 1997, after four courses of therapy, partial remission was obtained and the fistula closed with a remnant polypoid lesion at the primary site, which remained even after six courses of treatment. In February 1998, endoscopic polypectomy was performed for the remnant lesion and histological examination revealed that it contained adenocarcinoma cells. Thereafter, no additional treatment was performed and the patient has been disease-free for 3.5 years. This case suggests that additional endoscopic resection is an optional treatment for local failure after chemoradiation.

Key words: esophageal cancer – bronchial fistula – chemoradiation – endoscopic resection

INTRODUCTION

Surgical resection has been recognized as a standard treatment for esophageal cancer. In recent years, however, a combination of chemotherapy comprising infusion of 5-fluorouracil (5-FU) with cisplatin (CDDP) and concurrent radiation therapy has been reported to be potentially curative for unresectable esophageal cancer and has a survival comparable to surgery for resectable esophageal cancer (1–4). Complete remission (CR) can be obtained in >50% of patients with T2/3 (UICC–TNM) esophageal cancer (1). The CR rate for T4 disease, however, is ~30% and most of the non-CR cases are due to remaining loco-regional disease (4). Thus, local failure is one of the major problems in chemoradiotherapy.

Progression of the primary tumor usually causes some serious medical conditions such as impaired oral intake, pneumonia and bleeding. Because surgical resection after definitive chemoradiotherapy has various obstacles, mostly due to severe fibrosis, salvage therapy for local failures after chemoradiotherapy has not yet been established.

We report a case of advanced esophageal cancer with a pretreatment esophago-bronchial fistula successfully treated with chemoradiotherapy followed by endoscopic resection.

CASE REPORT

The patient was a 49-year-old male with cough, general fatigue, dysphagia and a weight loss of 5 kg, referred to our hospital in June 1997. Endoscopic examination revealed an advanced esophageal cancer located on the middle thoracic esophagus (Fig. 1A). Histological analysis of the biopsy specimen revealed adenosquamous carcinoma. A computed tomography (CT) scan indicated a thickened esophageal wall that compressed the left main bronchus, suggesting direct invasion (Fig. 1B) and one lymph node 10 mm in diameter located on the middle thoracic paraesophageal region. Esophagography revealed that the lesion was 9 cm in length and associated with an esophago-bronchial fistula (Fig. 1C). CT revealed no evidence of distant metastasis. Thus, the clinical stage was

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

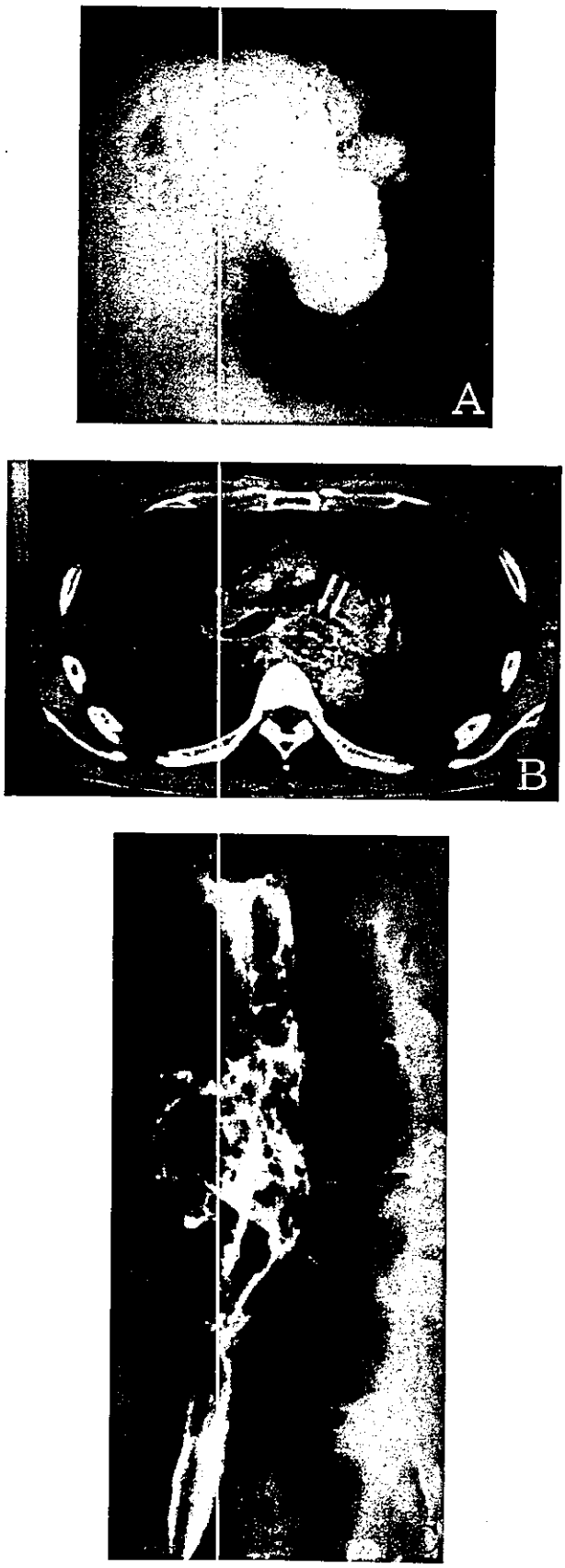

Figure 1. Image diagnosis before initiation of chemoradiation in July 1997: (A) endoscopic picture; (B) computed tomography, direct invasion to the left main bronchus is indicated by arrows; (C) esophagography.

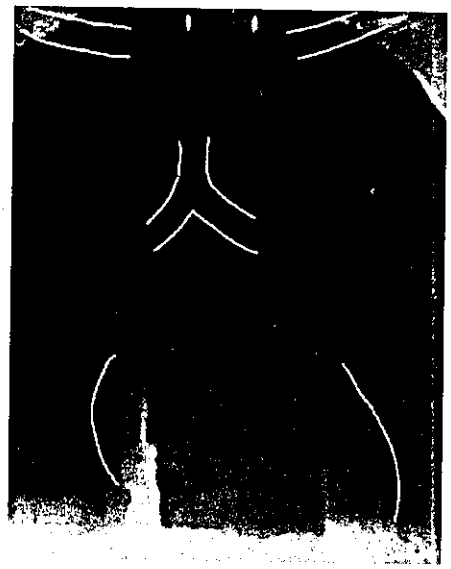

Figure 2. Initial portal film of this case.

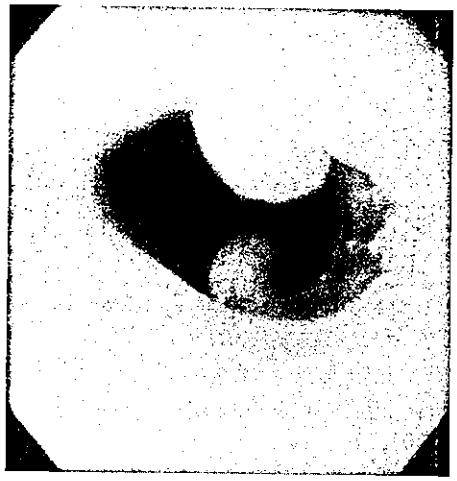

Figure 3. Endoscopic picture of remnant polypoid lesion after six courses of chemoradiation, before endoscopic resection in February 1998.

diagnosed as T4N1M0 according to the UICC classification and this case was considered to be unresectable.

Because of the presence of the esophago-bronchial fistula, the patient was admitted to our hospital and managed under fasting and complete parenteral nutrition via central vein. In July 1997, a combination of chemotherapy and radiation therapy was initiated. The initial treatment schedule comprised two courses of drip infusion of CDDP (40 mg/m^2) on days 1 and 8 and continuous infusion of 5-FU (400 mg/m^2/day) on days 1–5 and 8–12, every 5 weeks.

Radiation therapy was delivered concurrently with chemotherapy to a total dose of 60 Gy in 30 fractions over 8 weeks. It was started with 10 MV X-rays via AP–PA opposed ports up to 40 Gy and a booster dose of 20 Gy was given via bilateral oblique ports with spinal cord shield. The target volume

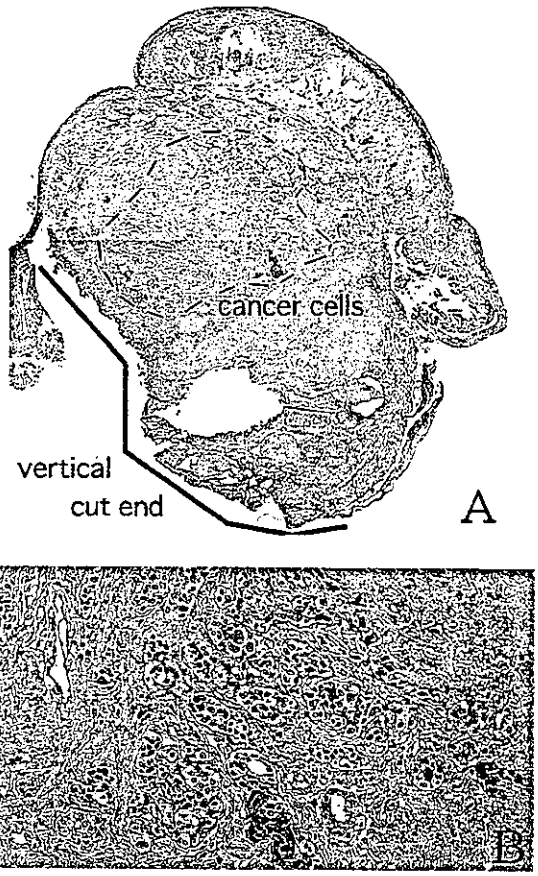

Figure 4. Histology of the resected specimen of the remnant polypoid lesion: (A) macroscopic picture, the vertical cut end is indicated by a solid line and the area of cancer cells is enclosed by an interrupted line; B) microscopic picture (×300).

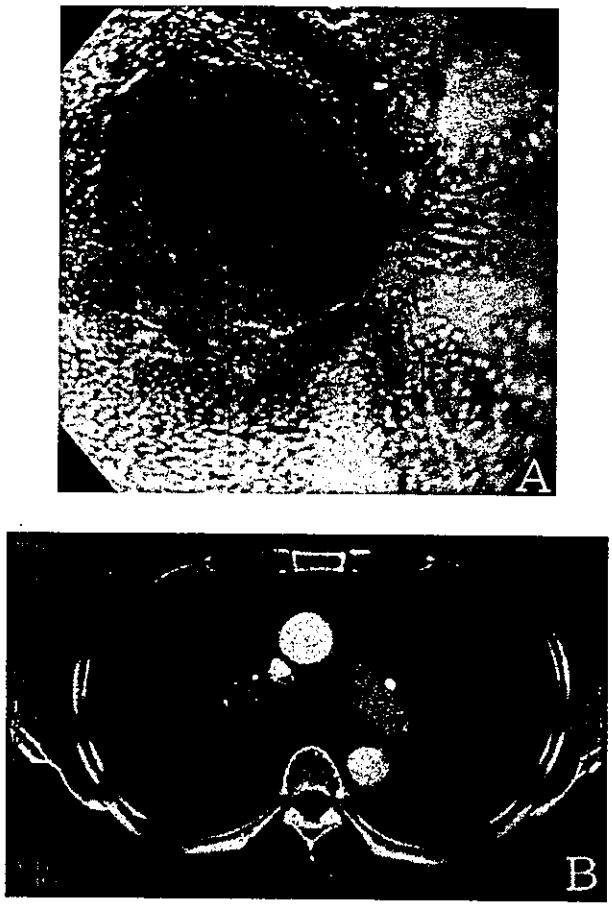

Figure 5. Follow-up examination in February 2001: (A) endoscopy after Lugol staining; (B) computed tomography.

included the primary tumor with a 3 cm margin craniocaudally (Fig. 2). After two courses of the chemoradiotherapy, four courses of chemotherapy with CDDP (80 mg/m^2) on day 1 and 5-FU (800 mg/m^2) on days 1–5 were performed every 4 weeks. The case was complicated with grade 3 stomatitis and grade 1 nausea, with no severe hematological toxicities, bleeding or infection during the treatment. Despite an esophago-bronchial fistula, the patient did not develop pneumonia during this treatment series, although he sometimes complained of a small amount of cough and sputa. Low-grade fever occurred once after three courses, but decreased following administration of antibiotics for 6 days.

After four treatment courses, esophagography in December 1997 indicated closure of the esophago-bronchial fistula. This closure was confirmed by endoscopy. Endoscopic examination revealed a small remnant polypoid lesion, however, which was confirmed histologically as adenosquamous carcinoma in a biopsy specimen taken by ordinary biopsy forceps. After six treatment courses, CT examination detected no thickening of the esophageal wall and no lymph node swelling, but the polypoid lesion showed no change (Fig. 3) in esophagoscopy and the response of chemoradiation was evaluated as non-CR.

After biopsy, two endoscopic examinations confirmed that there were no remnant cancer cells in the mucosa surrounding the polypoid lesion and endoscopic ultrasonography confirmed that the polypoid cancer was limited within the submucosal layer and it also revealed no submucosal tumor except the polypoid lesion, which was diagnosed to be resected by endoscopic polypectomy with minute morbidity. Subsequently, the lesion was resected endoscopically using conventional polypectomy methods in February 1998. No complications occurred during or after this procedure. Histologically, the resected specimen contained poorly differentiated adenocarcinoma and the cancer cells reached near the vertical cut end (Fig. 4A and B).

Thereafter, no additional treatment was performed and follow-up endoscopic examination with biopsy and CT scan examination revealed no local progression and no lymph node or distant metastasis. In August 2001, 4 years after initiation of chemoradiotherapy and 3.5 years after endoscopic resection, the patient is alive with no evidence of the disease (Fig. 5A and B).

DISCUSSION

Ohtsu et al. previously reported that chemoradiation is effective for locally advanced (T4) esophageal cancer (4). However, malignant fistula to the respiratory tract, the mediastinum and large vessels before and after treatment is a serious complication of locally advanced esophageal cancer. Although radiation has generally been regarded to be contraindicated in patients with a malignant fistula, we previously reported that chemoradiotherapy was effective even for far advanced esophageal cancer with a malignant fistula (5). Several reports indicated that 50–91.7% of pre-treatment malignant fistulae were successfully closed by chemotherapy and/or radiation therapy (5–7).

The present patient had advanced esophageal cancer with the histological type of adenosquamous carcinoma. Since adenosquamous cells are a minority in esophageal cancer, no report has specially mentioned its sensitivity to chemoradiotherapy. In many Western studies showing the efficacy of chemoradiotherapy, only a few patients with esophageal adenocarcinoma were included. These studies have shown comparable sensitivities of adenocarcinoma and squamous cell carcinoma. Hence it is considered that adenosquamous cell carcinoma may show the same sensitivity as squamous or adenocarcinoma of the esophagus.

For patients with esophago-bronchial fistula, esophageal stenting using a covered stent may generally be used to protect the respiratory tract from contamination since insertion of a stent is an easy procedure with low morbidity and no mortality. However, it has been reported that an esophageal stent before or during chemoradiotherapy might migrate to the esophageal wall and surrounding tissues and induce necrosis of the tissues, resulting in enlargement of the fistula or rupture of large vessels (5). Stenting may be regarded as a palliative treatment only for the purpose of occlusion of the fistula and it should be used very carefully along with chemoradiotherapy. Moreover, chemoradiotherapy can provide a chance of cure with closure of the fistula even for the patients with malignant fistula. It seems that chemoradiotherapy may be chosen as a first-line therapy aiming at cure and stenting may be only a palliative therapy. For these reasons, we treated the present case with chemoradiotherapy and the fistula was successfully closed after obtaining marked tumor reduction.

In the present case, because a polypoid lesion with cancer cells remained after the completion of therapy, the effect of the therapy was evaluated as a partial remission. In chemoradiation, complete remission rates for T2–3 and T4 esophageal cancer are as high as 60–70% (1,8,9) and 30–40% (4,10) and local recurrence at the primary site is observed in approximately one third of the cases after obtaining complete remission. Hence local control is another major problem with chemoradiation. Although some authors have reported that the down-staging by preoperative chemoradiotherapy contributes to an increase in the curative resection rate of surgery (8,11,12), several studies of preoperative chemoradiotherapy followed by surgery (CRT-S) indicated no survival benefit compared with surgery alone (11,12). Surgery after definitive chemoradiotherapy including a dose of >50 Gy of radiation appears to have substantial obstacles because of severe fibrosis. Moreover, no second-line chemotherapy has been reported to be effective for local failure after chemoradiation. The present case had had an unresectable esophageal cancer at the initiation of therapy, so salvage surgery could not be an option after the completion of chemoradiotherapy. Thus, the chance of a cure for local failure after chemoradiotherapy seemed very small for the present case.

Endoscopic resection for superficial esophageal cancer is commonly used in Japan (13–15). Endoscopic resection is ordinarily indicated for superficial esophageal cancers within the epithelial or mucosal muscle layer because submucosal esophageal cancer is frequently associated with lymph node metastasis (13–15). At the time of polypectomy for the present case, no indication of endoscopic resection for remnant disease after chemoradiotherapy was determined, and the present case was the first endoscopic resection after chemoradiotherapy in our institution. We performed it with the patient's informed consent after explaining the following points. First, CT examination showed complete remission of lymph node metastasis and no distant metastasis, suggesting that local control might offer a small chance of cure. Second, since it was a small polyp diagnosed to be limited within the submucosal layer by EUS, it might be resected endoscopically safely with less morbidity although a risk of perforation could not be estimated. Third, endoscopic resection would not affect the subsequent chemotherapy. The present patient seems to be cured since there has been no recurrence for 4 years after initiation of chemoradiotherapy and for ~3.5 years after endoscopic resection.

Since the remnant disease originating from T4 esophageal cancer is generally considered to extend to the deeper portion of the esophageal wall or beyond it, this case seems to be exceptional. However, the present case suggests that endoscopic resection for the remnant disease after chemoradiotherapy for advanced esophageal cancer might offer a small chance of cure, associated with little morbidity. We suggest that endoscopic resection might be tried for some remnant disease after chemoradiation and that its possible indications may be (1) a small elevated lesion without ulceration, (2) diagnosis to be limited within the submucosal layer, (3) confirmation of no metastatic lesion by image diagnosis and (4) the patient's informed consent. Further study of additional endoscopic resection after chemoradiation for esophageal cancer is warranted.

References

1. Poplin EA, Khanuja PS, Kraut MJ, Herskovic AM, Lattin PB, Vaitkevicius VK, et al. Chemotherapy of esophageal carcinoma. *Cancer* 1994;74:1217–24.
2. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA Jr, Al-Sarraf M, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85–01). Radiation Therapy Oncology Group. *J Am Med Assoc* 1999;281:1623–7.

3. Al-Sarraf M, Martz K, Herskovic A, Leichman L, Brindle JS, Emami B, 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, Nakamura A, 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. Muto M, Ohtsu A, Miyamoto S, Muro K, Boku N, Yoshida S, et al. Concurrent chemoradiotherapy for esophageal carcinoma patients with malignant fistulae. *Cancer* 1999;86:1406–13.
6. Ahmed HF, Hussain MA, Grant CE, Wadleigh RG. Closure of tracheoesophageal fistulas with chemotherapy and radiotherapy. *Am J Clin Oncol* 1998;21:177–9.
7. Malik SM, Krasnow SH, Wadleigh RG. Closure of tracheoesophageal fistulas with primary chemotherapy in patients with esophageal cancer. *Cancer* 1994;73:1321–3.
8. Bates BA, Detterbeck FC, Bernard SA, Qaqish BF, Tepper JE. Concurrent radiation therapy and chemotherapy followed by esophagectomy for localized esophageal carcinoma. *J Clin Oncol* 1996;14:156–63.
9. Girvin GW, Matsumoto GH, Bates DM, Garcia JM, Clyde JC, Lin PH. Treating esophageal cancer with a combination of chemotherapy, radiation and excision. *Am J Surg* 1995;169:557–9.
10. Ando N, Ozawa S, Kitagawa Y, Takeuchi H, Kitajima M. Salvage surgery for T4 esophageal cancer following down-staging by neoadjuvant chemoradiotherapy. *Nippon Geka Gakkai Zasshi* 1997;98:767–72 (in Japanese).
11. Ancona E, Ruol A, Castoro C, Chiarion-Sileni V, Merigliano S, Peracchia A, et al. First-line chemotherapy improves the resection rate and long-term survival of locally advanced (T4, any N, M0) squamous cell carcinoma of the thoracic esophagus: Final report on 163 consecutive patients with 5-year follow-up. *Ann Surg* 1997;226:714–23;discussion 723–4.
12. Yano M, Tsujinaka T, Shiozaki H, Inoue M, Doki Y, Monden M, 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.
13. Noguchi H, Naomoto Y, Kondo H, Haisa M, Yamatsuji Y, Tanaka N, et al. Evaluation of endoscopic mucosal resection for superficial esophageal carcinoma. *Surg Laparosc Endosc Percutan Tech* 2000;10:343–50.
14. Nomura T, Boku N, Ohtsu A, Muto M, Matsumoto S, Yoshida S, et al. Recurrence after endoscopic mucosal resection for superficial esophageal cancer. *Endoscopy* 2000;32:277–80.
15. Kodama M, Kakegawa T. Treatment of superficial cancer of the esophagus: a summary of responses to a questionnaire on superficial cancer of the esophagus in Japan. *Surgery* 1998;123:432–9.

Biopsy Specimen Microvessel Density Is a Useful Prognostic Marker in Patients with $T_{2-4}M_0$ Esophageal Cancer Treated with Chemoradiotherapy[1]

Shuichi Hironaka, Takahiro Hasebe, Tomoyuki Kamijo, Atsushi Ohtsu, Narikazu Boku, Shigeaki Yoshida, Hiroki Saitoh, and Atsushi Ochiai[2]

Pathology Division, National Cancer Center Research Institute East, Chiba 277-8577, Japan [S. H., T. H., T. K., A. Oc.]; Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba 277-8577, Japan [S. H., A. Oh., N. B., S. Y.]; and Second Department of Internal Medicine, Asahikawa Medical College, Asahikawa 078-8510, Japan [H. S.]

ABSTRACT

Purpose: **The purpose of this study was to identify prognostic markers for chemoradiotherapy (CRT) in $T_{2-4}M_0$ esophageal cancer.**

Experimental Design: **We investigated clinicopathological and biological markers in biopsy specimens from 73 $T_{2-4}M_0$ esophageal cancer patients treated with CRT (5-fluorouracil plus cisplatin and 60 Gy of radiation). Expressions of *p53* gene product, Ki-67 labeling index, epidermal growth factor receptor, cyclin D1, vascular endothelial growth factor, microvessel density (MVD), thymidylate synthase, dihydropyrimidine dehydrogenase, and glutathione *S*-transferase π in formalin-fixed biopsy samples of primary tumors before CRT were examined immunohistochemically. Clinicopathological and biological marker expressions were compared in terms of survival.**

Results: **Univariate analysis revealed that performance status and T stage in clinicopathological features had a significant association with survival ($P = 0.007$ and 0.04, respectively) and that patients whose tumors showed high MVD [>median (19.7 vessels)] in biological markers had significantly better survival than those with low MVD (≤median, $P = 0.02$). Also, there were weak associations of p53 and Ki-67 with survival ($P = 0.08$ and 0.07, respectively). Multivariate analysis, using both clinicopathological and biological markers, showed that MVD, T stage, and performance status became independent variables ($P = 0.002$, 0.02, and 0.02, respectively). Kaplan-Meier analysis showed that the patients with high MVD tumors survived longer than those with low MVD tumors (median survival time, not reached and 13 months, respectively; 3-year survival rate, 61% and 33%, respectively), with a significant difference of $P = 0.02$.**

Conclusions: **These results indicate that MVD using pretreatment biopsy specimens is a potentially useful prognostic marker for CRT in patients with $T_{2-4}M_0$ esophageal cancer who are treated with CRT.**

INTRODUCTION

Esophageal cancer is one of the most lethal malignancies among gastrointestinal neoplasms. Although surgery had been performed as the standard treatment for esophageal cancer, a variety of combined modality approaches have been investigated in efforts to improve long-term survival. Chemotherapy combined with radiotherapy for the treatment of esophageal cancer has been investigated since the 1980s, and the combination of 5-FU[3] and CDDP has been regarded as being active and enhancing radiosensitivity (1–3). Recent reports on CRT as a definitive and preoperative treatment have indicated various advantages in managing carcinoma of the esophagus (4–6). We have reported that definitive CRT has curative potential for locally advanced esophageal carcinoma (7), and Chan and Wong (8) reported that combined chemotherapy and radiation appeared to be as effective as esophagectomy in localized esophageal cancer. Thus, CRT is potentially an alternative to surgery, and investigating prognostic factors for esophageal cancer treated with CRT is very important.

Because of recent advances in basic research, many biological markers detected immunohistochemically have been reported in esophageal cancer. For p53, it has been postulated that tumors with p53 mutations may be more susceptible to CRT than tumors with wild-type p53 because of a lack of wild-type p53-induced arrest at G_1-S and reduced time for DNA repair (9, 10). For proliferation-associated markers, such as Ki-67 and EGFR, tumors that respond best to DNA-damaging stimuli such as radiotherapy have been known to display a high proliferation rate (11). For cyclin D1, recent identification of genes involved in cell cycle regulation has also led to an understanding that

Received 1/29/01; revised 10/8/01; accepted 10/8/01.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

[1] Supported in part by Grant-in-Aid 11-12 for Cancer Research from the Ministry of Health and Welfare and by a Grant-in-Aid for the Second Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health and Welfare, Japan.

[2] To whom requests for reprints should be addressed, at Pathology Division, National Cancer Center Research Institute East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan. Phone: 81-471-33-1111; Fax: 81-471-31-4724; E-mail: aochiai@east.ncc.go.jp.

[3] The abbreviations used are: 5-FU, 5-fluorouracil; CRT, chemoradiotherapy; CDDP, cisplatin; DPD, dihydropyrimidine dehydrogenase; EGFR, epidermal growth factor receptor; GST-π, glutathione *S*-transferase π; MST, median survival time; MVD, microvessel density; PS, performance status; TS, thymidylate synthase; VEGF, vascular endothelial growth factor.

Table 1 Panel of primary antibodies

Antibody[a]	Clone	Pretreatment	Dilution	City/nation	Source
p53 (mono)	DO7	MW	1:1000	Newcastle/United Kingdom	Novocastra
Ki-67 (mono)	MIB-1	MW	1:50	Newcastle/United Kingdom	Novocastra
EGFR (mono)	EGFR.113	MW	1:40	Heidelberg/Germany	Santa Cruz
Cyclin D1 (mono)	5D4	EDTA, MW	1:50	Glostrup/Denmark	DAKO
VEGF (poly)		Pepsin	1:500	Newcastle/United Kingdom	Novocastra
CD31 (mono)	JC/70A	Pepsin, MW	1:50	Glostrup/Denmark	DAKO
TS (mono)		MW	1:100	Saitama/Japan	TAIHO
DPD (poly)		MW	1:540	Saitama/Japan	TAIHO
GST-π (poly)		MW	1:2000	Nagoya/Japan	MBL

[a] mono, monoclonal antibody; poly, polyclonal antibody; MW, microwave.

altered expression of these genes in cancer cells may be important in determining drug or radiation sensitivity (12). VEGF induces mitogenesis of vascular endothelial cells, and vascular permeabilization and microvessel formation in a tumor are associated with tumor nutrition and oxygenation. They are associated with drug delivery and radiosensitivity because a well-oxygenated cell is fully radiosensitive (13. TS is a target substrate of 5-FU, and it is reported that resistance to 5-FU is related in part to insufficient inhibition of TS (14). The action of DPD is a critical and rate-limiting step in the catabolism of 5-FU, and intratumoral levels correlate with the response to 5-FU-based regimens (15). GST-π is an enzyme that plays an important role in cellular detoxification, and increases in this enzyme have been associated with resistance to antineoplastic agents such as CDDP (16). However, the precise mechanism of tumor response to CRT is not fully understood. Some markers, including p53 (17, 18), Ki-67 (19), EGFR (20), cyclin D1 (21), MVD (22), and GST-π (23) are reportedly prognostic in patients given CRT for esophageal cancer. However, most of these studies were performed using a small number of subjects, and their results were also controversial because of differences among treatment regimens.

This study was designed to identify useful prognostic markers in $T_{2-4}M_0$ esophageal cancer patients given a combination of 5-FU and CDDP with radiotherapy. We examined the expressions of p53, Ki-67, EGFR, cyclin D1, VEGF, MVD, TS, DPD, and GST-π using an immunohistochemical staining method in biopsy specimens before CRT, and we investigated useful prognostic markers between clinicopathological and biological markers by multivariate analysis.

MATERIALS AND METHODS

Subjects. A total of 209 esophageal cancer patients received CRT between August 1992 and April 1999 at the National Cancer Center Hospital East. Seventy-three of these patients met or fulfilled the following criteria and were included in this study: (*a*) sufficient biopsy specimens obtainable before treatment; (*b*) no previous treatment had been received; (*c*) age $\leq$ 75 years; (*d*) PS on the Eastern Cooperative Oncology Group scale $\leq$ 2; (*e*) adequate bone marrow, hepatic, and renal functions; and (*f*) stage T_{2-4}, any N, M_0 on the International Union against Cancer tumor-node-metastasis (TNM) classification. We excluded patients with M_{1a} disease because of its very poor prognosis (24). All patients were given the same regimen of concurrent chemotherapy and radiotherapy.

Treatment Schedule. Chemotherapy consisted of a protracted infusion of 5-FU (400 mg/m^2/day) on days 1–5 and 8–12, combined with CDDP (40 mg/m^2/day) with adequate hydration and antiemetic coverage on days 1 and 8 (6). This schedule was repeated twice every 5 weeks. Radiation therapy using megavoltage X-rays was started on day 1 concomitantly with chemotherapy. There was a 2-week break after a dose of 30 Gy. Radiation therapy was restarted on day 36, along with the same chemotherapy schedule used before. For patients who showed an objective response to treatment, additional chemotherapy was administered and consisted of a protracted infusion of 5-FU (800 mg/m^2/day) on days 1–5 and a 2-h infusion of CDDP (80 mg/m^2/day) on day 1. This treatment was repeated every 4 weeks for two courses. Additional courses of chemotherapy were optional but limited to a total of four courses. No further treatment was administered if no disease progression was observed.

Survival time was counted from the initiation of the first course of treatment to the date of death or to the final date of confirmation of survival.

Immunohistochemical Examination. One to five biopsies, 1–5 mm in diameter, were taken for each tumor (one specimen, 7 cases; two specimens, 23 cases; three specimens, 33 cases; four specimens, 9 cases; and five specimens, 1 case). All of the biopsies were taken at the initial time of the diagnosis.

Immunohistochemical staining was carried out using the avidin-biotin-peroxidase complex method. Formalin-fixed, paraffin-embedded biopsy materials were cut into 3-μm sections, which were then deparaffinized in xylene, dehydrated in a graded ethanol series, and finally immersed in methanol with 0.3% H_2O_2 for 20 min to inhibit endogenous peroxidase activity. The sections for VEGF and CD31 staining were treated with 0.05% pepsin in 0.01 N HCl for 20 and 5 min at room temperature, respectively. The sections for p53, anti-Ki-67 antibody (MIB-1), EGFR, CD31, TS, DPD, and GST-π staining were heated to 95°C by microwave irradiation twice for 10 min in 10 mM citrate buffer solution (pH 6.0), and the sections for cyclin D1 were immersed in EDTA retrieval fluid (pH 8.0). The sections were then cooled for 30 min at room temperature. After washing in PBS, all sections were blocked from nonspecific binding by preincubation with 5% skim milk (7.5 mg) and 2% BSA (3 mg) in PBS (150 ml) for 30 min. Next, the sections were incubated overnight at 4°C with the primary antibodies listed in Table 1. After washing five times in PBS with 0.1% Tween 20 (washing buffer), slides were incubated with biotinylated sec-

ondary antimouse antibodies for p53, Ki-67, CD31, cyclin D1, and TS and antirabbit antibodies for VEGF, DPD, and GST-π diluted 1:200 with blocking buffer for 30 min. After being washed five times with washing buffer, the sections were incubated with avidin-biotin complex (ABC) reagent (DAKO, Glostrup, Denmark), and a color reaction was developed using 2% 3,3′-diaminobenzidine in 50 mM Tris buffer (pH 7.6) containing 0.3% hydrogen peroxide for 5–10 min. The sections were counterstained with Meyer's hematoxylin. In negative controls, the primary antibody solutions were replaced by the blocking buffer.

Evaluation of Immunostaining. The percentages of p53-, Ki-67-, and cyclin D1-positive tumor cells were calculated by counting the number of brown-stained tumor nuclei/total number of cancer cells in the most highly stained area on a high-power view (×400; 0.196 mm²/field). In each specimen, more than 400 cells for p53, cyclin D1, and Ki-67 were counted. According to the intensity of cell membrane EGFR staining in the whole tumor (median area, 3.14 mm²), all patients could be divided into the following four groups: (*a*) group ±, fainter staining than normal esophageal epithelium; (*b*) group +, the same staining as normal epithelium; (*c*) group ++, moderately stronger staining; and (*d*) group +++, markedly stronger staining. Groups ± and + were defined as negative for EGFR expression, and groups ++ and +++ were defined as positive for EGFR expression. The staining of VEGF was graded as follows: (*a*) +, the staining intensity in cancer cells was stronger than that in the stromal cells; (*b*) ±, the staining intensity in cancer cells was equal to that in stromal cells; and (*c*) −, the staining intensity in cancer cells was weaker than that in stromal cells. The cases graded as + were defined as positive, as described in previous reports (25). The microvessel count was assessed by light microscopy in three of the most extensive areas of neovascularization (termed "hot spots") at a high-power view (×400; ×40 objective and ×10 ocular; 0.196 mm²/field), and we calculated the average number of vessels. We counted intratumoral and stromal vessels with actual lumens around the tumor nests but did not count a single endothelial cell (or cluster) and vessels that existed far from the tumor nests. For TS and DPD staining, positivity was based on a subjective estimation of the intensity (0–3) and extent of tumor staining. Positive staining was defined if >30% of the tumor was stained, and negative staining was defined as staining in ≤30% of the tumor. Intensity levels 0 and 1 were grouped together and considered negative, whereas staining intensities 2 and 3 were considered positive (18). The intensity of GST-π staining was graded as follows: (*a*) ++, strong; (*b*) +, faint; and (*c*) −, no visible staining. For this marker, cases were defined as positive when >20% of all cancer cells in each section showed ++ or + staining (26). Immunohistochemical staining was evaluated independently by two investigators who were blind to the clinical outcomes of the patients. When the evaluation for each antibody differed between investigators, the investigators discussed it, with or without reevaluation, until an agreement was reached.

Statistical Analysis. Subjects were categorized as positive or negative according to the immunohistochemical results. Univariate analysis for survival was performed by using log-rank tests. The influence of each biological variable on patient survival was assessed by the Cox proportional hazards model.

Table 2 Characteristics of patients with T_{2-4} M_0 esophageal cancer

Characteristic	No.
Sex	
Male	60
Female	13
Age (yr)	62 (38–75)[a]
PS	
0	49
1	24
Location	
Upper	5
Middle	50
Lower	18
Histological type	
SCC[b]	
W/D	1
M/D	48
P/D	24
T stage	
T_2	10
T_3	41
T_4	22
N stage	
N_0	26
N_1	47

[a] Median (range).
[b] SCC, squamous cell carcinoma; W/D, well differentiated; M/D, moderately differentiated; P/D, poorly differentiated.

The survival curves were calculated by the Kaplan-Meier method. $P < 0.05$ was considered significant. Statistical calculations were performed using the Statistica package (Statsoft, Tulsa, OK).

RESULTS

Patient Characteristics. Clinicopathological features of the patients in this study are shown in Table 2. In terms of T stage, 10 patients had T_2 disease, 41 patients had T_3 disease, and 22 patients had T_4 disease. In terms of N stage, 26 patients had N_0 disease, and 47 patients had N_1 disease. A total of 71 patients (97%) completed at least the CRT segment with a total radiation dose of 60 Gy, and the other 2 patients received 40 and 45 Gy, respectively. Twenty patients (16%) received one additional course of chemotherapy, and 32 patients (44%), 2 patients (3%), and 3 patients (4%) received an additional two, three, and four courses, respectively.

Immunoreactivity. All 73 specimens were immunohistochemically evaluated for p53, Ki-67, EGFR, cyclin D1, VEGF, CD31, TS, DPD, and GST-π. Representative immunohistochemical p53, EGFR, CD31, and DPD stainings are shown in Fig. 1. Positive p53, Ki-67, and cyclin D1 immunoreactivities were detected in nuclei, whereas VEGF, TS, DPD, and GST-π reactivities were observed in the cytoplasm. EGFR expression was seen both on the cell membrane and in the cytoplasm. Microvessels were detected immunohistochemically using anti-CD31 antibody. We made histograms of the p53, Ki-67, and cyclin D1 results, and they showed bimodal distribution. Then, we decided that the trough of the histogram was the cutoff value for positive *versus* negative or high *versus* low marker levels. Expressions of p53, Ki-67, and cyclin D1 varied from 0–95%, 28–88%, and 0–100% with median values of 71%, 72%, and

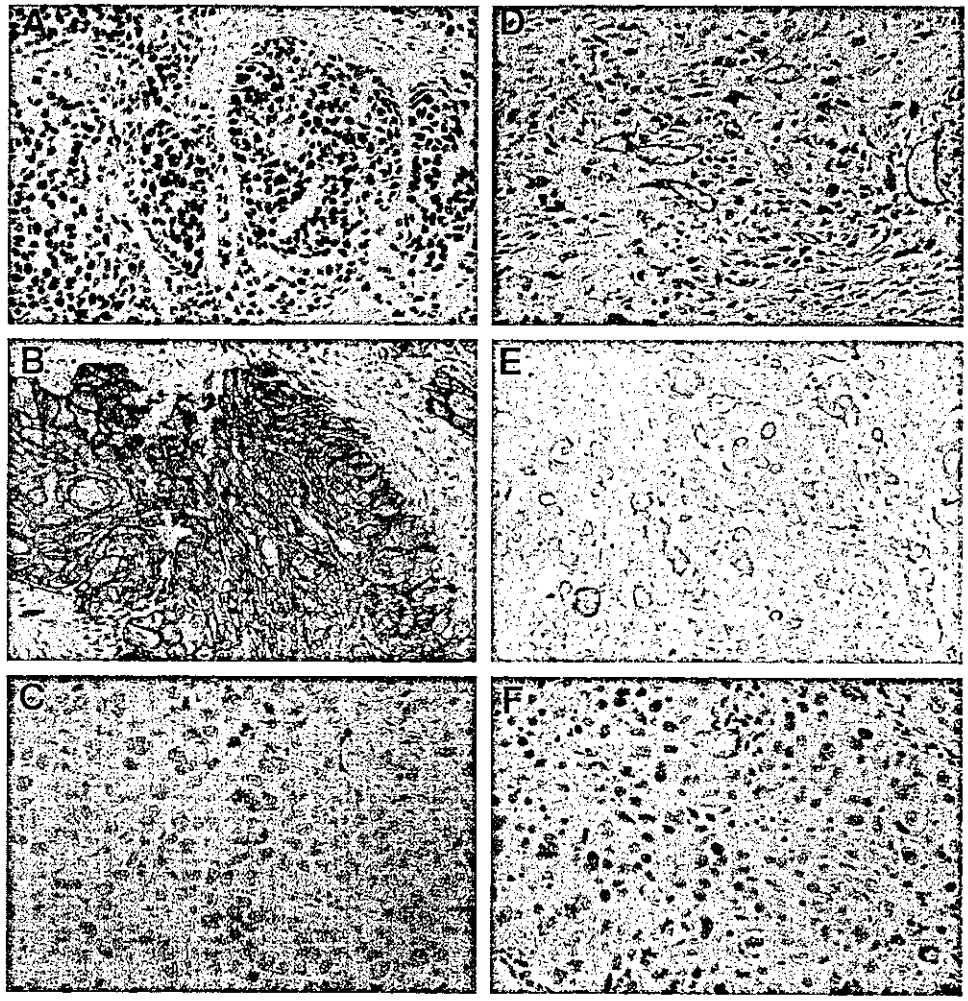

Fig. 1 Representative immunohistochemical p53, EGFR, CD31, and DPD stainings in biopsy specimens before CRT. *A*, p53. p53 immunoreactivity is detected in the nuclear region of tumor cells, as was that for Ki-67 and cyclin D1. *B*, EGFR positive. EGFR immunostaining is seen in the cell membranes of tumor cells. *C*, EGFR negative. Immunostaining is not seen in any cell membranes. *D*, CD31 for microvessels. Microvessels are most numerous at the tumor periphery. *E*, DPD positive. DPD immunostaining was detected in the tumor cell cytoplasm, as was immunostaining for VEGF, TS, and GST-π. *F*, DPD negative. Immunostaining is not seen in any tumor cells.

56%, respectively. We categorized the samples as positive if >20%, >64%, and >40% of the tumor nuclei were stained by anti-p53, anti-Ki-67, and anti-cyclin D1 antibodies, respectively. With regard to MVD, the level varied from 3.7 to 43.7 vessels with a median value of 19.7. We classified tumors into two groups, high MVD and low MVD, based on the number of median value.

Positivity for p53, EGFR, cyclin D1, VEGF, TS, DPD, and GST-π staining was observed in 51, 42, 45, 36, 46, 44, and 46 of 73 cases (70%, 58%, 62%, 49%, 63%, 60%, and 63%), respectively. Fifty-four cases (74%) were determined to have a Ki-67 labeling index of >64, and 36 of 73 (49%) were categorized into the high MVD group.

Univariate Analysis for Survival. Table 3 presents the clinicopathological features of patients and survival. PS and T stage had a significant association with survival ($P = 0.007$ and 0.04, respectively). The relations of other clinicopathological factors, including age, sex, tumor location, histological type, and N stage, with survival were negligible.

Table 4 summarizes biological markers and survival. MVD had the strongest association with survival ($P = 0.02$), and p53 and Ki-67 had weak associations ($P = 0.08$ and 0.07, respectively) with survival. Negligible relations were observed for EGFR, cyclin D1, VEGF, TS, DPD, and GST-π expressions.

Multivariate Analysis for Survival. The effects of clinicopathological and biological variables, including T stage, N stage, PS, MVD, p53, and Ki-67, were examined by multivariate analysis using the Cox proportional hazards model (Table 5). MVD, T stage, and PS were identified as significant and independent variables ($P = 0.002$, 0.02, and 0.02, respectively). A low MVD value yielded a hazard ratio of 3.23, with 95% confidence interval ranging from 1.54–6.78. No other variables were significantly associated with survival on multivariate analysis.

Survival Curves According to MVD by Kaplan-Meier Analysis. The median follow-up period was 34 months. The MST of all patients with $T_{2-4}M_0$ esophageal cancer given CRT was 34 months, and the 3-year survival rate was 44%. Fig. 2 shows the survival curves according to MVD using Kaplan-Meier analysis. The patients with high MVD tumors survived significantly longer than those with low MVD tumors ($P = 0.02$). The MST of the former group was not reached, and their 3-year survival rate after treatment was 61%; the MST and

Table 3 Summary of relation between clinicopathological markers and survival

	n	MST (mo)	*P*
Age			
≤62	33	37	0.36
>62	40	22	
Sex			
Male	60	34	0.90
Female	13	18	
PS			
0	49		0.007
1	24	15	
Location			
Upper or middle	55	30	0.26
Lower	18		
Histological type			
W/D[a] or M/D	49	34	0.41
P/D	24	19	
T stage			
T_{2-3}	51	37	0.04
T_4	22	11	
N stage			
N_0	26	37	0.36
N_1	47	30	

[a] W/D, well differentiated; M/D, moderately differentiated; P/D, poorly differentiated.

Table 4 Summary of relation between biological markers and survival

	n	MST (mo)	*P*
p53(+)	51	23	0.08
p53(−)	22		
KI-67 LI > 64[a]	54	23	0.07
Ki-67 LI ≤ 64	19		
EGFR(+)	42	14	0.74
EGFR(−)	31		
Cyclin D1(+)	45	34	0.94
Cyclin D1(−)	28		
VEGF(+)	36	34	0.94
VEGF(−)	37	30	
High MVD	36		0.02
Low MVD	37	13	
TS(+)	46	37	0.45
TS(−)	27	23	
DPD(+)	44	30	0.80
DPD(−)	29	37	
GST-π(+)	46	37	0.74
GST-π(−)	27	34	

[a] LI, labeling index.

3-year survival rate of the latter group were 13 months and 33%, respectively.

DISCUSSION

In the present study, we examined the usefulness of prognostic factors including clinicopathological and immunohistochemical biological markers in patients with $T_{2-4}M_0$ esophageal cancer who were given CRT. We found MVD, as well as PS, to be an independent prognostic factor for CRT on multivariate survival analysis. We have recently reported that high MVD laryngeal squamous cell carcinomas are more radiosensitive than those with low MVD, and we found that patients with the former survived significantly longer than those with low MVD (27). Basically, tissue oxygen status has been demonstrated to be a very important factor determining radiosensitivity both *in vitro* and *in vivo* (28, 29). Oxygen delivery to tumor tissues appears to rely on a network of microvessels, based on *in vivo* observations of vascular geometry and blood flow in the tumor microcirculation. On the other hand, the tumor microcirculation is clearly an important factor in drug delivery to cancer cells, and the efficacy of drug delivery can be high in richly vascularized tumors. These data are consistent with our present observation that MVD is a favorable prognostic factor in patients who have undergone CRT. In contrast to the present study, it was reported that cancers showing high angiogenesis had a poor prognosis and that this was related to local invasion and distant metastasis (30). There was a statistically significant difference in survival rate in favor of the hypovascular group in surgically resected cases (31, 32). This discrepancy in the usefulness of the MVD of tumor tissues between surgically and CRT-treated cases is potentially interesting. Furthermore, anticancer drugs, especially the 5-FU and CDDP used in our CRT regimen, are regarded as radiosensitizers (1–3). Therefore, a combination of chemotherapy and radiotherapy is a more effective strategy and improved the survival of patients with high MVD tumors more than the survival of those with low MVD tumors because of the point of oxidation and drug delivery to cancer cells. This is in contrast to the previous studies involving surgical cases.

There is another difference in microvessel characterization during microscopic examination from previous reports (22, 31–33). Others counted any brown-stained endothelial cell or endothelial cluster as a single vessel; a vessel lumen was not required for identification of a microvessel. Eric Hall (34) stated that the oxygen diffusion distance in tumor tissue around vessels was approximately 150 μm; *i.e.*, that is to say that cancer cells within a diameter of approximately 150 μm around vessels are involved in the oxygenation area. For this reason, we counted intratumoral and stromal vessels with actual lumens around the tumor nests in consideration of tumor oxidation. We did not count a single endothelial cell (or cluster), and we did not count vessels that existed far from the tumor nests. This evaluation of MVD is thought to be reasonable for studying chemoradiosensitivity and investigating a prognostic marker in patients treated with radiotherapy and/or chemotherapy. Additional studies are needed to confirm the efficacy of this evaluation.

Recently, the effectiveness of CRT for locally advanced esophageal cancer has become clear, and its curative potential is as high as that of surgery (7, 8). In the RTOG 85-01 trial, the MST was 14.1 months, and the 5-year survival rate was 27% after combined CDDP, 5-FU infusion, and radiation (35, 36). In a literature review on the surgical management of esophageal cancer by Müller *et al.* (37), however, the mean respective 3-year and 5-year survival rates after esophagectomy were 25% and 20%. There is no remarkable difference in survival benefit between CRT and surgery for localized esophageal cancer. Esophageal cancer patients may be able to select between CRT and surgery according to the individual characteristics of their tumors. Therefore, it is important to clarify prognostic markers in esophageal cancer patients with operable stage tumors. In this context, our results show MVD to be a potentially useful prog-

Table 5 Multivariate analysis of clinicopathological and biological markers in survival of 73 T_{2-4} M_0 patients treated with CRT

Variable	Category	RR[a]	95% CI	*P*
MVD	High *vs.* low	3.23	1.54–6.78	0.002
T stage	T_{2-3} *vs.* T_4	2.39	1.13–5.07	0.02
PS	0 *vs.* 1–2	2.29	1.16–4.55	0.02
p53	− *vs.* +	2.16	0.97–4.86	0.06
Ki-67 LI	≤64 *vs.* 64<	2.02	0.83–4.93	0.12
N stage	N0 *vs.* N1	1.22	0.58–2.56	0.60

[a] RR, risk ratio; LI, labeling index; CI, confidence interval.

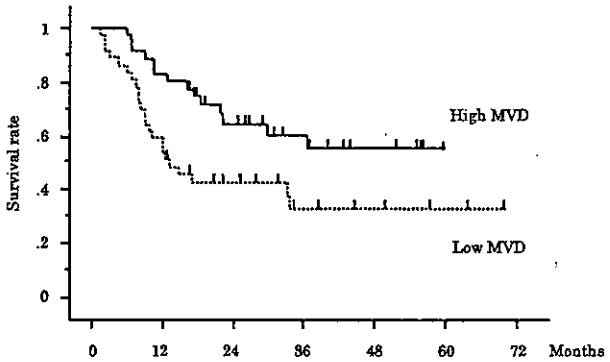

Fig. 2 The survival curves for 73 patients with $T_{2-4}M_0$ esophageal squamous cell carcinoma given CRT, according to MVD. Patients with high MVD tumor survived longer than those with low MVD tumor (MST, not reached and 13 months; 3-year survival rate, 61% and 33%, respectively), with a statistically significant difference ($P = 0.02$).

nostic marker in patients treated with CRT. We also found that the prognostic significance of MVD is opposite that for surgery as described in previous reports. These observations suggest MVD to be a potential marker for choosing between CRT and surgery. Using pretreatment biopsy samples, we are currently investigating clinicopathological and biological prognostic markers including MVD in esophageal cancer patients with $T_{2-3}M_0$ disease who underwent surgery. We hope that MVD will be beneficial for selecting the optimal treatment regimen, thereby prolonging survival for all esophageal cancer patients in the near future.

ACKNOWLEDGMENTS

We thank Dr. Masakazu Fukushima (Taiho Pharmaceutical Co., Ltd.) for providing TS monoclonal antibody and DPD monoclonal antibody. We also thank Mari Nakane and Yuki Yanagisawa for technical assistance.

REFERENCES

1. Byfield, J. E. Combined modality infusional chemotherapy with radiation. *In:* J. J. Lokich (ed.), Cancer Chemotherapy by Infusion, 2nd ed., pp. 521–551. Chicago: Percepta Press, 1990.

2. Douple, E. B., and Richmond, R. C. A review of interactions between platinum coordination complexes and ionizing radiation: implication for cancer therapy. *In:* A. W. Prestayko, S. T. Crooke, and S. K. Karter (eds.), Cisplatin: Current Status and New Developments, pp. 125–147. Orlando, FL, Academic Press, 1980.

3. Scanlon, K. J., Newman, Y. L., and Priest, D. G. Biological basis for cisplatin and 5-fluorouracil synergism in human ovarian carcinoma cells. Proc. Natl. Acad. Sci. USA, *83:* 8923–8925, 1986.

4. Coia, L. R. Chemoradiation as primary management of esophageal cancer. Semin Oncol., *21:* 483–492, 1994.

5. Forastiere, A. A., Orringer, M. B., Perez-Tamayo, C., Urba, S. G., and Zahurak, M. Preoperative chemoradiation followed by trans-hiatal esophagectomy for carcinoma of the esophagus: final report. J. Clin. Oncol., *11:* 1118–1123, 1993.

6. Ohtsu, A., Yoshida, S., Boku, N., Fujii, T., Miyata, Y., Hosokawa, K., Koba, I., Shimizu, W., and Ogino, T. Concurrent chemotherapy and radiation therapy for locally advanced carcinoma of the esophagus. Jpn. J. Clin. Oncol., *25:* 261–266, 1995.

7. Ohtsu, A., Boku, N., Muro, K., Chin, K., Muto, M., Yoshida, S., Satake, M., Ishikura, S., Ogino, T., Miyata, Y., Seki, S., Kaneko, K., and Nakamura, A. Definitive chemoradiotherapy for T_4 and/or M_1 lymph node squamous cell carcinoma of the esophagus. J. Clin. Oncol., *17:* 2915–2921, 1999.

8. Chan, A., and Wong, A. Is combined chemotherapy and radiation therapy equally effective as surgical resection in localized esophageal carcinoma? Int. J. Radiat. Oncol. Biol. Phys., 45: 265–270, 1999.

9. Vogelstein, B., and Kinzler, K. W. p53 function and dysfunction. Cell, *70:* 523–526, 1992.

10. Kastan, M. B., Onyekwere, O., Sidransky, D., Vogelstein, B., and Craig, R. W. Participation of p53 protein in the cellular response to DNA damage. Cancer Res., *51:* 6304–6311, 1991.

11. Raybaud-Diogene, H., Fortin, A., Morency, R., Roy, J., Monteil, R. A., and Tetu, B. Markers of radioresistance in squamous cell carcinomas of the head and neck: a clinicopathologic and immunohistochemical study. J. Clin. Oncol., *15:* 1030–1038, 1997.

12. Hochhauser, D. Modulation of chemosensitivity through altered expression of cell cycle regulatory genes in cancer. Anticancer Drugs, *8:* 903–910, 1997.

13. Suit, H. D., and Suchato, C. Hyperbaric oxygen and radiotherapy of a fibrosarcoma and of a squamous-cell carcinoma of C3H mice. Radiology, *89:* 713–719, 1967.

14. Peters, G. J., van der Wilt, C. L., van Triest, B., Codacci-Pisanelli, G., Johnston, P. G., van Groeningen, C. J., and Pinedo, H. M. Thymidylate synthase and drug resistance. Eur. J. Cancer, *31A:* 1299–1305, 1995.

15. Fischel, J. L., Etienne, M. C., Spector, T., Formento, P., Renee, N., and Milano, G. Dihydropyrimidine dehydrogenase: a tumoral target for fluorouracil modulation. Clin. Cancer Res., *1:* 991–996, 1995.

16. Teicher, B. A., Holden, S. A., Kelley, M. J., Shea, T. C., Cucchi, C. A., Rosowsky, A., Henner, W. D., and Frei, E., III. Characterization of a human squamous carcinoma cell line resistant to *cis*-diamminedichloroplatinum(II). Cancer Res., *47:* 388–393, 1987.

17. Muro, K., Ohtsu, A., Boku, N., Chin, K., Oda, Y., Fujii, T., Hosokawa, K., Yoshida, S., and Hasebe, T. Association of p53 protein expression with responses and survival of patients with locally advanced esophageal carcinoma treated with chemoradiotherapy. Jpn. J. Clin. Oncol., *26:* 65–69, 1996.

18. Yang, B., Rice, T. W., Adelstein, D. J., Rybicki, L. A., and Goldblum, J. R. Overexpression of p53 protein associates decreased response to chemoradiotherapy in patients with esophageal carcinoma. Mod. Pathol., *12:* 251–256, 1999.

19. Kitamura, K., Saeki, H., Kawaguchi, H., Araki, K., Ohno, S., Kuwano, H., Maehara, Y., and Sugimachi, K. 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, *47:* 419–423, 2000.

20. Hickey, K., Grehan, D., Reid, I. M., O'Briain, S., Walsh, T. N., and Hennessy, T. P. Expression of epidermal growth factor receptor and proliferating cell nuclear antigen predicts response of esophageal squamous cell carcinoma to chemoradiotherapy. Cancer (Phila.), *74:* 1693–1698, 1994.

21. Samejima, R., Kitajima, Y., Yunotani, S., and Miyazaki, K. Cyclin D1 is a possible predictor of sensitivity to chemoradiotherapy for esophageal squamous cell carcinoma. Anticancer Res., *19:* 5515–5521, 1999.

22. Torres, C., Wang, H., Turner, J., Shahsafaei, A., and Odze, R. D. Prognostic significance and effect of chemoradiotherapy on microvessel density (angiogenesis) in esophageal Barrett's esophagus associated adenocarcinoma and squamous cell carcinoma. Hum. Pathol., *30:* 753–758, 1999.

23. Tominaga, K., Arakawa, T., Imano, M., Kato, M., Hamaguchi, Y., Watanabe, T., Takaishi, O., Fujiwara, Y., Fukuda, T., Higuchi, K., Osugi, H., Chono, S., and Kuroki, T. Complete regression of recurrent esophageal carcinoma with reduced expression of glutathione *S*-transferase-π by treatment with continuous infusion of 5-fluorouracil and low-dose cisplatin infusion. Am. J. Gastroenterol., *94:* 1664–1668, 1999.

24. Okuma, T., Kaneko, H., Yoshioka, M., Torigoe, Y., and Miyauchi, Y. Prognosis in esophageal carcinoma with cervical lymph node metastases. Surgery, *114:* 513–518, 1993.

25. Boku, N., Chin, K., Hosokawa, K., Ohtsu, A., Tajiri, H., Yoshida, S., Yamao, T., Kondo, H., Shirao, K., Shimada, Y., Saito, D., Hasebe, T., Mukai, K., Seki, S., Saito, H., and Johnson, P. G. Biological markers as a predictor for response and prognosis of unresectable gastric cancer patients treated with 5-fluorouracil and cisplatinum. Clin. Cancer Res., *4:* 1469–1474, 1998.

26. Miyamoto, S., Boku, N., Ohtsu, A., Yoshida, S., Ochiai, A., Okabe, H., and Fukushima M. Study group of S-1 for gastric cancer. Clinical implications of immunoreactivity of thymidylate synthase and dihydropyrimidine dehydrogenase in gastric cancer treated with oral fluoropyrimidine (S-1). Int. J. Oncol., *17:* 653–658, 2000.

27. Kamijo, T., Yokose, T., Hasebe, T., Yonou, H., Sasaki, S., Hayashi, R., Ebihara, S., Miyahara, H., Hosoi, H., and Ochiai, A. Potential role of microvessel density in predicting radiosensitivity of T_1 and T_2 stage laryngeal squamous cell carcinoma treated with radiotherapy. Clin. Cancer Res., *6:* 3159–3165, 2000.

28. Moulder, J. E., and Rockwell, S. Tumor hypoxia: its impact on cancer therapy. Cancer Metastasis Rev., *5:* 313–341, 1987.

29. Rockwell, S., and Moulder, J. E. Hypoxic fractions of human tumors xenografted into mice: a review. Int. J. Radiat. Oncol. Biol. Phys., *19:* 197–202, 1990.

30. Weidner, N., and Folkman, J. Tumor vascularity as a prognostic factor in cancer. *In:* V. T. Devita, S. Hellman, and S. A. Rosenberg (eds.), Cancer, Principle and Practice of Oncology, Pro-updates, Vol. 11, No. 7. Philadelphia: Lippincott-Raven Publishers, 1997.

31. Tanigawa, N., Matsumura, M., Amaya, H., Kitaoka, A., Shimomatsuya, T., Lu, C., Muraoka, R., and Tanaka, T. Tumor vascularity correlates with the prognosis of patients with esophageal squamous cell carcinoma. Cancer (Phila.), *79:* 220–225, 1997.

32. Igarashi, M., Dhar, D. K., Kubota, H., Yamamoto, A., El-Assal, O., and Nagasue, N. The prognostic significance of microvessel density and thymidine phosphorylase expression in squamous cell carcinoma of the esophagus. Cancer (Phila.), *82:* 1225–1232, 1998.

33. Shih, C. H., Ozawa, S., Ando, N., Ueda, M., and Kitajima, M. Vascular endothelial growth factor expression predicts outcome and lymph node metastasis in squamous cell carcinoma of the esophagus. Clin. Cancer Res., *6:* 1161–1168, 2000.

34. Hall, E. J. Predictive assays. *In:* Radiology for the Radiologist, pp. 130–150, 1994.

35. Herskovic, A., Martz, K., Al-Sarraf, M., Leichman, L., Brindle, J., Vaitkevicius, V., Cooper, J., Byhardt, R., Davis, L., and Emami, B. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N. Engl. J. Med., *326:* 1593–1598, 1992.

36. Al-Sarraf, M., Martz, K., Herskovic, A., Leichman, L., Brindle, J., Vaitkevicius, V., Cooper, J., Byhardt, R., Davis, L., and Emami, B. Progress report of combined chemoradiotherapy *versus* radiotherapy alone in patients with esophageal cancer: an intergroup study. J. Clin. Oncol., *15:* 277–284, 1997.

37. Müller, J. M., Erasmi, H., Stelzner, M., Zieren, U., and Pichlmaier, H. Surgical therapy of oesophageal carcinoma. Br. J. Surg., *77:* 845–857, 1990.

Diseases of the Esophagus (2001) 14, 197–201

DISEASES OF THE ESOPHAGUS

Original article

Chemoradiotherapy followed by surgery for thoracic esophageal cancer potentially or actually involving adjacent organs

K. Ikeda,[1] K. Ishida,[1] N. Sato,[1] K. Koeda,[1] K. Aoki,[1] Y. Kimura,[1] T. Iwaya,[1] S. Ogasawara,[1] S. Iijima,[1] R. Nakamura,[2] N. Uesugi,[3] C. Maesawa,[4] K. Saito[1]

[1]Department of Surgery 1, [2]Department of Radiology, [3]Department of Clinical Pathology, and [4]Department of Pathology 2, Iwate Medical University, Morioka, Japan

SUMMARY. **The objective of this study was to evaluate the therapeutic usefulness of chemoradiotherapy (CRT) followed by surgery in patients with clinically T4 (cT4) esophageal cancer involving adjacent organs such as the trachea, main bronchi, and large vessels. Thirty-seven patients with cT4 squamous cell carcinoma of the thoracic esophagus were enrolled in this study. The CRT regimen comprised cisplatin (70 mg/m^2) on day 1, 5-fluorouracil (700 mg/m^2) on days 1–4 and external irradiation (200 cGy/day, total 30 Gy) on either days 8–26 (sequential schedule, $n = 15$) or days 1–19 (concurrent schedule, $n = 22$). Two courses of CRT were given. The results of CRT were complete response in nine patients, partial response in 19, no change in three (minor response in two), and progressive disease in six patients. The median response duration in all responders was 172 days (range: 56–2469, $n = 19$). After CRT, 13 patients received surgery. In 12 of these patients, tumors were completely resected. Histopathologic examination of the resected specimen revealed a discrepancy between clinical response and histopathologic effect. The median duration of survival and the 1-, 2- and 5-year survival rates were 304 days (84–3155), 45%, 35% and 23% in all patients, respectively, 866 days (190–3155), 83%, 83% and 57% in the 13 patients whose tumors were resected, and 187 days (84–2630), 25%, 5% and 5% in the 24 patients whose tumors were not resected. Grade 3 toxicity, especially hematological reactions, was noted in 13.5% (5/37) of the patients. There was one toxicity-related death (sepsis). A good outcome may be obtained with CRT, followed by surgery when feasible. However, CRT can cause toxic reactions, and close monitoring of patients is required.**

INTRODUCTION

Recent advances in surgical technique and postoperative management have improved the outcome in patients with squamous cell carcinoma of the thoracic esophagus.[1–3] However, the locally advanced tumor involving adjacent structures such as the trachea, main bronchi, or large vessels (clinical stage T4; cT4) is often excluded from a primary operation, leading to a poor outcome.[1,4] A combination of cisplatin (CDDP) and 5-fluorouracil (5-FU) (FP therapy) is considered the most potent chemotherapeutic regimen against esophageal cancer.[5,6] Furthermore, FP therapy with external irradiation (chemoradiotherapy; CRT) is useful in terms of controlling cT4 tumors and improving outcome.[7–11] The aim of this study was to evaluate the therapeutic usefulness of CRT followed by surgery in patients with clinically diagnosed cT4 esophageal cancer, which had potentially or actually invaded the tracheobronchial system or large vessels.

Address correspondence to: Dr K. Ikeda, Department of Surgery I, Iwate Medical University, 19–1 Uchimaru, Morioka 020–8505 Japan. Tel.:(+81) 19 651 5111 (ext. 3627); Fax: (+81) 19 651 7166; E-mail: kenikeda@iwate-med.ac.jp

PATIENTS AND METHODS

Patients

Between 1992 and 2000, 361 patients with histologically confirmed squamous cell carcinoma of the thoracic esophagus were admitted to the Department of Surgery 1, Iwate Medical University. In these series, 37 inoperable patients (34 men and three women) were enrolled in this study. All patients had a clinical diagnosis of potential or actual cT4 tumors, invading adjacent structures such as the trachea, main bronchi, or large vessels (aorta, carotid artery, or pulmonary vein), and were considered to be inoperable because of local non-resectability

(Table 1). The mean age of the subjects was 62.0 years (range, 48–77). The diagnosis of cT4 was made on the basis of routine clinical examinations such as esophagography, endoscopy, computed tomography, and ultrasonography. Patients with metastasis to solid organs were excluded. All patients met the following criteria at study entry: performance status, 0–2; normal renal function (serum creatinine, <1.2 mg/dL; blood urea nitrogen, <20 mg/dL; creatinine clearance, >60 mL/min); normal bone marrow function (leukocytes, >4000/mm^3; platelet, >100,000/mm^3); and normal liver function (serum transaminases, <60 IU/l; serum total bilirubin, <1.5 mg/dL). Written informed consent was obtained from all patients, and the study protocol was approved by the Institutional Review Committee.

Treatment schedule for CRT

Before CRT, jejunostomy was performed under lumbar anesthesia to permit enteral nutrition. Central venous catheters were inserted into the subclavian vein, and at least 2500 mL of lactated Ringer's solution was given by intravenous infusion 4–7 days before the start of CRT. CDDP (70 mg/m^2) diluted in 500 mL of 0.9% sodium chloride solution was given intravenously over the course of 2 h on day 1. The CDDP solution was shielded from light during infusion. 5-FU was given as a continuous intravenous infusion for 96 h on days 1–4 at a dose of 700 mg/m^2/day. To maintain sufficient urinary volume, infusions containing sodium chloride, potassium chloride, and frusemide were administered. Antiemetic agents, such as metochlopamide, methylpredonisolone sodium succinate, and 5-HT3 receptor antagonists, were also given intravenously as required. External irradiation (200 cGy/day, five times a week for 3 weeks; total dose 30 Gy) was given either on days 8–26 (sequential schedule, $n = 15$) or days 1–19 (concurrent schedule, $n = 22$).

Table 1. Characteristics ($n = 37$)

Age	62.0 ± 7.9†
Gender (men/women)	34/3
Location of the lesion‡ Ut/Mt/Lt	19/16/2
Invaded organ Tr/MB/LV/Pc/PU/Tv	20/6/16/3/1/1
Degree of LN meta§ cN0M0/N1M0/N1M1a/N1M1b	4/20/5/8

Ut, upper thoracic; Mt, middle thoracic; Lt, lower thoracic; Tr, trachea; MB, main bronchus; LV, large vessels; Pc, pericardium; PU, lung; Tv, thoracic vertebra; LN, lymph node.
†Mean ± standard deviation (SD).
‡According to Guide Lines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus (9th Edition, 1999).
§According to TNM classification (5th Edition, 1997).

Two courses of CRT, separated by a 1-week interval, were given.

Evaluation of clinical response and toxicity

Response to CRT was evaluated about 2 weeks after the completion of two courses. Clinical response was evaluated according to the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus, issued by the Japanese Society of Esophageal Disease.[12] A complete response (CR) was defined as the complete disappearance of all apparent disease for ≥4 weeks. A partial response (PR) was defined as a reduction of >50% in the sum of the products of the two greatest perpendicular diameters of all measurable lesions, lasting for ≥4 weeks without the appearance of new lesions. A minor response (MR) was defined as a reduction of 25–50% in the sum of the products of the two greatest perpendicular diameters of all measurable lesions, lasting for ≥4 weeks without the appearance of new lesions. No change (NC) was defined as either a reduction or an increase of <25% in the sum of the products of the two greatest perpendicular diameters of all measurable lesions, lasting for ≥4 weeks without the appearance of new lesions. Progressive disease (PD) was defined as an increase of >25% in tumor measurements or the appearance of any new lesions. Toxicity of therapy was evaluated according to the Toxicity Grading Criteria of the Japan Clinical Oncology Group (JCOG).[13]

Surgical treatment

Patients who showed a CR to CRT were, in principle, followed up without further treatment. The patients who responded to CRT and met the following conditions underwent surgery: (1) complete resection of the tumor was expected; (2) very good general condition enabling the patient to tolerate operation; (3) written informed consent was obtained. The operative procedure was total esophagectomy with reconstruction using a gastric tube, performed via a right thoracolaparotomy with cervical manipulation. Lymphadenectomy in the mediastinum and upper abdomen was also performed, either with or without lymphadenectomy in the cervical region.

Analysis of survival and response duration

Survival curves were calculated using the Kaplan–Meier method, and statistical significance was evaluated by the log-rank test (two-tailed). The results of all analyzes were as at 31 March, 2001 and were calculated using the software package STAT VIEW-J 4.5 (Abacus Concepts, Berkeley, CA, USA) for the Macintosh.

Table 2. Operative results of 13 resected patients

Patient number	Gender	Age (years)	Location of tumor†	Clinical response†	Histopathologic effects†	pT‡	pN‡	M‡	pStage‡	Survival duration (days)§
1	W	72	Ut	CR	Grade 2	T2	N0	M0	IIA	572
2	M	56	Mt	CR	Grade 2	T2	N0	M0	IIA	866¶
3	M	65	Ut	CR	Grade 2	T2	N1	M0	IIB	929
4	M	60	Mt	CR	Grade 2	Tis	N0	M0	0	3155
5	M	74	Mt	MR	Grade 3	T0	N0	M0	–	1482
6	M	58	Mt	PR	Grade 1	T4	N1	M1b	IVB	190¶
7	M	77	Ut	PR	Grade 2	T2	N0	M0	IIA	159
8	W	62	Mt	PR	Grade 1	T3	N0	M0	IIA	266¶
9	M	48	Ut	PR	Grade 1	T0	N0	M1b	IVB	443
10	M	64	Mt	PR	Grade 1	T3	N1	M0	III	845
11	M	64	Ut	PR	Grade 2	T1	N0	M0	I	1105
12	M	51	Mt	PR	Grade 2	T2	N0	M0	IIA	1447
13	M	64	Ut	PR	Grade 2	T2	N0	M0	IIA	1671

M, men; W, women; Mt, middle thoracic; Ut, upper thoracic; CR, complete response; PR, partial response; MR, minor response.
†According to Guide Lines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus (9th Edition, 1999).
‡According to TNM classification (5th Edition, 1997).
§As of 31 March, 2001.
¶Died of cancer.

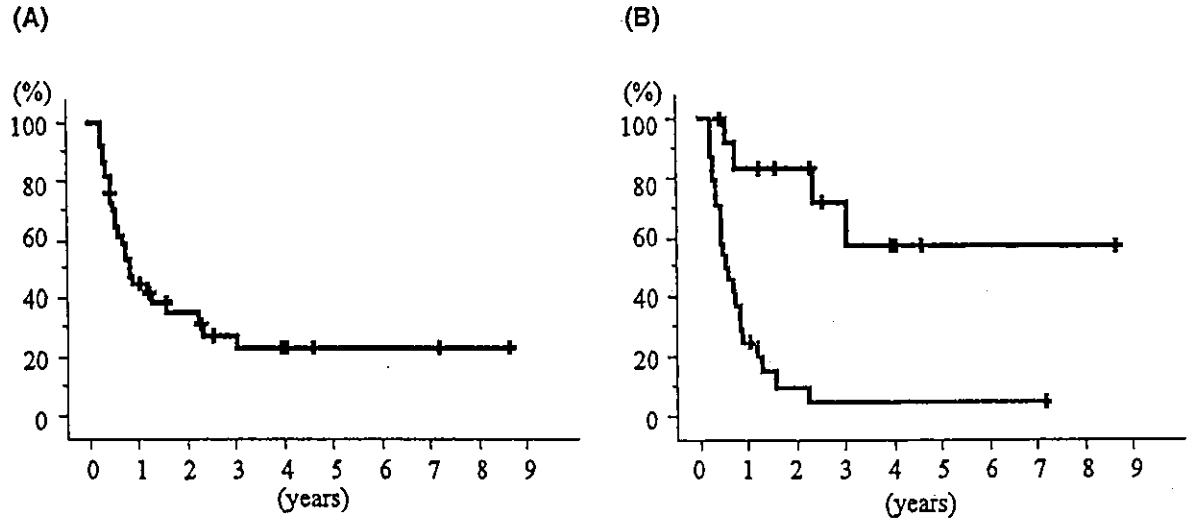

Fig. 1 Survival curves. (A) Overall survival. (B) Survival by resection. Overall survival rates at 1-, 2- and 5-years were 45%, 35% and 23%, respectively. Survival rates in resected patients were statistically significantly higher than in non-resected patients ($P < 0.001$, log-rank test). Black line, resected patients; Gray line, non-resected patients; +, censored case.

RESULTS

All 37 patients were evaluated for clinical response and toxicity of CRT. The result of treatment was CR in nine patients, PR in 19, NC in three (MR in two), and PD in six patients. The overall response (CR + PR) rate and CR rate were 76% (28/37; 95% confidence interval, 57–89%) and 24% (9/37; 9–40%), respectively. Among the nine patients with CR, two continue to show CR after 377 and 2630 days, respectively. Five patients had local recurrence: two subsequently underwent a curative operation, one received endoscopic mucosal resection, one received chemotherapy, and one died without treatment. The two patients with CR (patients 1 and 2, Table 2) requested and received a curative operation 19 and 34 days after the completion of CRT, respectively. Of the 19 patients with PR, eight underwent an operation and 11 have had recurrence of their cancers. Recurrence involved local lesions in six patients, mediastinal lymph nodes metastasis in two, abdominal lymph nodes metastasis in two, axillary lymph nodes metastasis in one, and distant organ metastasis in three patients (one liver, one pulmonary, and one bone). The median duration of response was 172 days (range, 56–2469; $n = 19$) in all responders (CR + PR). In the seven CR and 12 PR patients, the median duration of response was 301 days (76–2469) and 111 days (56–293), respectively.

A total of 13 patients received esophagectomy, including four CR (two with recurrent status), eight PR, and one MR (Table 2). In 12 of these patients, complete resection with no residual tumor was possible. The remaining patient had small multiple

Table 3. Toxicity

Toxicity	Grade†		
	1	2	3
Hemoglobin	13	12	5
Leukocytes	3	23	5
Nausea/vomiting	26	4	0
Diarrhea	6	10	2
Stomatitis	4	1	0
Pharyngitis/esophagitis	9	5	0
Transaminase	1	1	1

†According to Toxicity Grading Criteria of Japan Clinical Oncology Group.

liver metastases, but these were not detected before operation. Histopathologic examination of the resected specimen revealed a discrepancy between the clinical response and the histopathologic effect. In patient 5, the clinical response was evaluated as MR, although no cancer cells were detected on histopathologic examination. The incidence of postoperative complications was relatively high in the 13 patients who underwent esophagectomy. The most frequent complication was related to immunosuppression. Five patients had mild respiratory tract infections (four caused by methycillin-resistant *Staphylococcus aureus* and one caused by *Pseudomonas aeruginosa*). Two suture abscesses and one late-onset idiopathic intrapelvic abscess also occurred.

The median duration of survival was 304 days (range, 84–3155) in all patients, 866 days (190–3155) in the patients whose tumors were resected ($n = 13$), and 187 days (84–2630) in the patients whose tumors were not resected ($n = 24$). Overall 1-, 2- and 5-year rates of survival were, respectively, 45%, 35% and 23% in all patients receiving CRT (including 11 survivors), 83%, 83% and 57% in the 13 patients whose tumors were resected (nine survivors), and 25%, 5% and 5% in the 24 patients whose tumors were not resected (two survivors) (Fig. 1).

Toxic reactions related to CRT are shown according to grade in Table 3. Grade 3 toxicity, involving mainly hematological variables, occurred in 13.5% (5/37) of all patients. Recombinant human granulocyte stimulating factor (rhG-CSF) was given to nine of the 37 patients. There was one toxicity-related death (TRD; sepsis); two cases of interstitial pneumonitis, one case of bacterial pneumonia, and one case of giant subcutaneous abscess were also observed. Furthermore, two esophago-bronchial fistulas, two esophago-vascular fistulas, and one esophago-mediastinal fistula occurred; expandable stents were inserted to close these fistulas in four patients.

DISCUSSION

Despite considerable progress in diagnostic techniques in recent years, many patients are still given a diagnosis of cT4 cancer of the thoracic esophagus. Surgical resection alone cannot improve outcome and quality of life in such patients.[1] In this study, we gave CRT, consisting of FP therapy with external irradiation, to patients with cT4 cancer of the esophagus to assess its therapeutic usefulness and the response to subsequent surgery. The overall response (CR + PR) rates and CR rates were extremely high (76% and 24%, respectively). Moreover, the survival rate in the patients whose tumors were resected was high. However, several problems associated with CRT remain to be solved.

First, we often found a discrepancy between clinical response and histopathological response in patients who underwent resection. This finding suggested that clinical response is not identical to microscopic response. The clinical response of patient 5 was underestimated. In contrast, the clinical response of patients 1 and 2 was overestimated. Although these patients had a CR, histologic examination of the resected specimen revealed a microscopic cancer nest in the muscularis. Such microscopic evidence of cancer cannot be detected by conventional clinical examination. The risk of underestimation or overestimation of the response to treatment during follow-up is thus an important concern. Improved diagnostic techniques and more accurate criteria for evaluating the clinical and microscopic response to treatment are required.

Another problem of CRT is severe adverse effects, especially immunosuppression during or after CRT (or both). Although patients were given recombinant rhG-CSF to control leukocytopenia, one patient died of severe sepsis; pneumonitis, pneumonia, and a giant subcutaneous abscess were also observed. Many patients with cT4 esophageal cancer cannot orally ingest adequate amounts of food because of tumor stenosis, and their nutritional and immune status is often poor. Furthermore, bowel rest as a result of fasting can cause unfavorable complications such as bacterial translocation.[14] In such patients, CRT worsens immunosuppression. To improve this situation, we gave enteral nutrition during treatment, but it was very difficult to restore immune status. Recently, a combination of low-dose CDDP and 5-FU has been shown to be effective and safe.[15] In a previous pharmacokinetic study, we showed that changing the administration schedule of CDDP in FP therapy affects therapeutic response and toxicity.[16] It is important to develop an optimal schedule for giving CDDP and 5-FU with external irradiation.[17] Other measures to improve immune status, such as treatment with glutamine or immune-enhancing agents, should be developed for patients who receive CRT and subsequently undergo tumor resection.[18]

The final problem of CRT is the duration of response. Although many patients initially respond to CRT, the duration of response is often unsatisfactory.

In only one patient with CR was the disease considered to have been cured (duration of response, 2175 days). In the patients whose tumors were not resected, disease recurred within 1 year even when there was no evidence of residual tumor. These findings imply that there is no effective way to inhibit tumor growth in outpatients. Achievement of this goal must await further research.

CONCLUSIONS

CRT is effective against cT4 esophageal cancer, and patients whose tumors can be completely resected have a good chance of a cure. CRT may be beneficial when used as neoadjuvant therapy against locally advanced esophageal cancer. However, CRT can cause severe toxic reactions and immunosuppression, the outcome of which is rarely lethal. Careful management during and after CRT is mandatory.

Acknowledgment

This work was supported in part by a grant-in-aid for Cancer Research (S8–1 and S8–13) from the Ministry of Health and Welfare, Japan.

References

1. Iizuka T, Isono K, Kakegawa T, Watanabe H. Parameters linked to ten-year survival in Japan of resected esophageal carcinoma. Japanese Committee for Registration of Esophageal Carcinoma Cases. Chest 1989; 96: 1005–11.
2. Iizuka T. Surgical adjuvant treatment of esophageal carcinoma: a Japanese Esophageal Oncology Group experience. Semin Oncol 1994; 21: 462–6.
3. Sato N, Murakami K, Ishida K, Ikeda K, Saito K. Pulmonary hypertension and polymorphonuclear leukocyte elastase after esophageal cancer operations. Ann Thorac Surg 1991; 51: 754–8.
4. Ilson D H, Kelsen D P. Combined modality therapy in the treatment of esophageal cancer. Semin Oncol 1994; 21: 493–507.
5. 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 1992; 22: 172–6.
6. Kies M S, Rosen S T, Tsang T K *et al.* Cisplatin and 5-fluorouracil in the primary management of squamous esophageal cancer. Cancer 1987; 60: 2156–60.
7. al-Sarraf M, Martz K, Herskovic A *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.
8. Forastiere A A, Heitmiller R F, Kleinberg L. Multimodality therapy for esophageal cancer. Chest 1997; 112: 195S–200S.
9. Poplin E, Fleming T, Leichman L *et al.* Combined therapies for squamous-cell carcinoma of the esophagus, a Southwest Oncology Group Study (SWOG-8037). J Clin Oncol 1987; 5: 622–8.
10. Ishida K, Iizuka T, Ando N, Ide H. Phase II study of chemoradiotherapy for advanced squamous cell carcinoma of the thoracic esophagus: nine Japanese institutions trial. Jpn J Clin Oncol 1996; 26: 310–5.
11. Ishida K, Koeda K, Sato N *et al.* Problems in neoadjuvant chemoradiotherapy preceding surgery for advanced squamous cell carcinoma of the thoracic esophagus. Jpn J Thorac Cardiovasc Surg 1999; 47: 262–6.
12. Japanese Society for Esophageal Diseases Guide Lines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus. Tokyo: Kanehara (in Japanese), 1999.
13. Tobinai K, Kohno A, Shimada Y *et al.* Toxicity grading criteria of the Japan Clinical Oncology Group. The Clinical Trial Review Committee of the Japan Clinical Oncology Group. Jpn J Clin Oncol 1993; 23: 250–7.
14. Mercadante S. Parenteral versus enteral nutrition in cancer patients: indications and practice. Support Care Cancer 1998; 6: 85–93.
15. Shirasaka T, Shimamoto Y, Ohshimo H *et al.* Mechanism for synergistic antitumor effect in the combination of 5- fluorouracil with cisplatin in vivo tumor models: from the view of biochemical modulation of 5-fluorouracil. Gan Kagaku Ryoho 1991; 18: 403–9 (in Japanese).
16. Ikeda K, Terashima M, Kawamura H *et al.* Pharmacokinetics of cisplatin in combined cisplatin and 5-fluorouracil therapy: a comparative study of three different schedules of cisplatin administration. Jpn J Clin Oncol 1998; 28: 168–75.
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. Bai M X, Jiang Z M, Liu Y W *et al.* Effects of alanyl-glutamine on gut barrier function. Nutrition 1996; 12: 793–6.