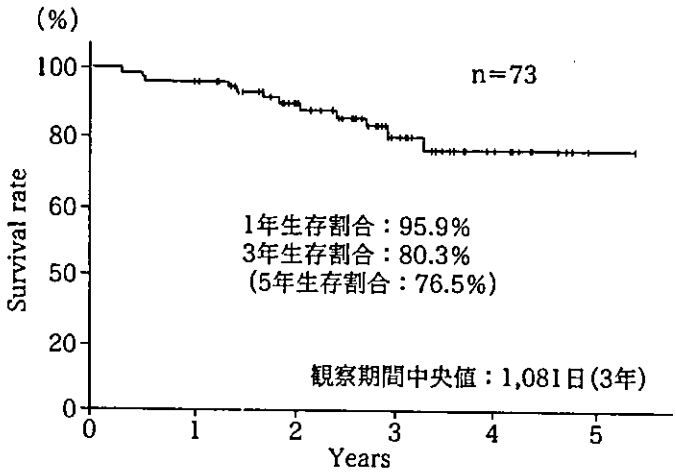

図7 Clinical Stage I食道癌に対する放射線化学療法
(国立がんセンター中央病院 1997～2002年)

CRは，全73例中68例に認められ，Overall CR rateは93.2%であった．また，生存成績は観察期間中央値約3年で，1年96%，3年80%，5年生存割合77%と，同じ術前clinical stage I食道癌手術の成績に劣らない良好な生存成績が得られた(図7)．ほぼ同時期に，JCOG食道がんグループにおいて同様の対象群に対する放射線化学療法の多施設共同臨床第II相試験(JCOG 9708)が行われ，Overall CR rate 95.8%，2年生存割合93%の良好な成績が確認された．

EMR適応外のclinical stage I食道癌症例では，従来，手術療法が標準的治療である．しかし，以上の結果より，根治的放射線化学療法も標準的治療になりえること，そして少なくとも選択肢の一つとして呈示すべき治療法であることが確認された．現在，JCOG食道がんグループと消化器がん内科グループの共同で，clinical stage I食道癌症例に対する手術療法vs放射線化学療法の第III相比較試験を計画中である．

V．放射線化学療法の問題点と今後の展望

本邦における食道癌に対する根治的放射線化学療法の成績に関して，とくに外科医や癌治療に携わったことのない消化器内科医は，当初，かなり疑心暗鬼であった．しかし，近年手術に匹敵する治療成績が明らかになってきて，その認識は大きく変貌しつつある．昨今，ともすればその有効性ばかりがもてはやされ，「本療法がすべて手術にとってかわる」「手術はなくなり，食道外科医はもう必要ない」などの極論すら半ば本気で囁かれたりもした．大きな勘違いと言わざるをえない．なぜなら放射線化学療法症例数の蓄積や長期生存例の増加に伴い，いくつかの問題点が浮き彫りになってきたからである．つまり，放射線化学療法後の遺残・再発例の対応，そして放射線照射による晩期毒性の問題である．

1．放射線化学療法後の遺残・再発

50～60 Gyの根治照射を行った後に手術を行うリスクは以前よりよく知られていた．かつての術前照射隆盛の時代を知る外科医のなかで，放射線照射後の手術で「痛い思い」を経験した者は少なくない．それ故，根治的放射線化学療法後の遺残例や局所再発例に対するsalvage surgeryに一種のアレルギーを感じてしまうのも無理のないことと考える．しかし，遺残・局所再発例を内科的治療により根治せしめることは不可能であり，EMRを含めた切除術でしか根治の手段がないことは紛れもない事実である．そこで，安全確実なsalvage surgeryの手術手技を確立させることが必要と考える．そのためには，遺残・局所再発が明らかになった時点を逃すことなく，できるだけ早いsalvage surgeryの移行を迅速かつ正確に判断することも大事な点である．また，放射線化学療法前の原発巣の深達度が浅いものほど遺残・局所再発例におけるEMRでのレスキュー可能症例は多いの

で，かかる症例では検査頻度を多くするなどして繊細な内視鏡観察を行うことが必要である．しかし，実際，放射線化学療法後の検査をどれくらいの間隔をおいて行うかは未解決の問題である．われわれは，ステージに関係なく最初の1年間は，2〜3カ月ごとに内視鏡と頸部・胸部・腹部CT検査を行っている．

2. 放射線照射に伴う晩期毒性

放射線照射に伴う晩期毒性は，照射野と総照射線量に関係する．程度の軽いものも含めれば，治療開始より半年後から1年後あたりに放射線肺臓炎，胸水貯留，心嚢水貯留をきたす症例は決して少なくない．CRが得られても心毒性として心筋梗塞をきたし死亡した症例もある[17]ので，決して軽んじてはいけない毒性である．放射線化学療法後，とくにCRに入った症例では長期の観察が必要になるので，晩期毒性の存在を常に念頭に意識しておくことが必要である．また，毒性と再発を正確に鑑別することも大事な点である．さらに今後は，晩期毒性軽減が期待できるような新たな照射線量と照射野の設定の構築，つまり根治性を損なわせることなく不必要な照射を避ける治療開発なども行っていくべきと考える．

おわりに

今まで述べてきたように，食道癌に対する根治的放射線化学療法は魅力的な治療戦略である．各ステージで標準的治療である手術に匹敵，凌駕する成績が得られており，今後新たな標準的治療になりえる可能性を秘めている．しかし，まだまだ一般臨床として広く浸透しているとは言いがたい．さらに，遺残・再発例に対してまだsalvage EMR，salvage surgeryが安全確実に広く行われている状況ではなく，晩期毒性に対する理解も十分ではない．未だ発展途上の段階にある治療法であるという認識を持つべきである．

本療法の発展のためには，質の高い多施設共同の臨床試験を通して，安全性と有効性のデータを蓄積させていくことと同時に，各個人が一般臨床で多くの経験を積んでいくことが必要である．

一人の食道癌患者を前にして放射線化学療法を行うにあたり，診断，治療計画，実際の治療，治療後の対応など一連の過程において，内視鏡医，放射線診断医，放射線治療医，消化器内科医，そして外科医，それぞれの立場の医師が協力し一体となって治療に取り組んでいく体制が重要である．

文　献

1) 国立がんセンター，食道疾患研究会 編．全国食道がん登録調査報告　第16号　昭和58・59・60・61・62年症例の治療成績．1997
2) The Japanese Society for Esophageal Diseases. Comprehensive Registry of Esophageal Cancer in Japan(1998, 1999)&Long-term Results of Esophagectomy in Japan(1988-1997)3 rd ed., 2002
3) 室　圭：食道癌に対する放射線化学療法．血液・腫瘍科　40；453-460，2000
4) 室　圭，新井達広，濱中久尚：食道sm 2/sm 3癌に対する放射線・化学療法の治療成績—clinical stage I食道癌に対する放射線・化学療法について．胃と腸　37；1305-1314，2002
5) 室　圭：食道がんの集学的治療．消化器外科NURSING 2002秋季増刊：43-53，2002
6) Isono, K., Sato, H. and Nakayama, K.: Results of a nationwide study on the three field lymph node dissection of esophageal cancer. Oncology　48；411-420, 1991
7) Kato, H., Watanabe, H., Tachimori, Y., et al.: Evaluation of neck lymph node dissection for thoracic esophageal carcinoma. Ann. Thorac. Surg.　51；931-935, 1991

8) Kato, H.：Lymphnode dissection for thoracic esophageal carcinoma；Two-and 3-field lymph node dissection. Ann. Chir. Gynaecol. 84；194-199, 1995
9) 鶴丸昌彦，宇田川晴司，梶山美明，他：手術成績からみた胸部食道癌に対する術式の選択；1) 胸部食道扁平上皮癌に対する拡大郭清の適応と限界．外科 57；1032-1038，1995
10) 平山 克，森 昌造：手術成績からみた胸部食道癌に対する術式の選択；2)拡大郭清と集学的治療について．外科 57：1039-1046，1995
11) 鶴丸昌彦，宇田川晴司，梶山美明，他：胸部食道扁平上皮癌症例における3領域郭清の功罪．日消外会誌 28；947-950，1995
12) 井手博子，江口礼紀，中村 努，他：胸部食道癌の拡大リンパ節郭清の功罪；術前進行度診断に基づく3領域拡大郭清の評価．日消外会誌 28；951-955，1995
13) 安藤暢敏，小澤壮治，辻塚一幸，他：胸部食道癌に対する3領域郭清の功罪．日消外会誌 28；937-941，1995
14) 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
15) 三梨桂子，大津 敦，土井俊彦，他：T4/M1 LYM 食道癌に対する根治目的放射線化学療法(CRT)の長期成績．第57回食道学会学術集会抄録集，2003
16) 室 圭，新井達広，濱中久尚，他：Clinical Stage I 食道癌に対する放射線化学療法の治療成績．第57回食道学会学術集会抄録集，2003
17) Ishikura, S., Nihei, K., Ohtsu, A., et al.：Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the esophagus. J. Clin. Oncol. 21；2697-2702, 2003

Summary

Definitive Chemoradiotherapy for Esophageal Cancer

Kei Muro*, Tatsuhiro Arai*, Takashi Ura*, Ayumu Goto*, Hisaaki Yasui*, Tetsuya Hamaguchi*, Yasuhide Yamada*, Yasuhiro Shimada*, Kuniaki Shirao*, Hiroyasu Igaki**, Yuji Tachimori**, Hoichi Kato**, Yoshinori Ito*3, Atsushi Imai*3 and Yoshikazu Kagami*3

Recently, we have reported that the survival rates from definitive chemoradiotherapy (CRT) are comparable with those of surgical procedures for esophageal cancer in every clinical stage. Definitive CRT for esophageal cancer is a very attractive treatment, considered to be a cureoriented therapy and preserve the esophagus. However, up to this time, the number of cases and the long-term data on CRT are very limited and the analysis of CRT has only been available from retrospective studies in mono-institution, Therefore, the results of this treatment are not reliable. Furthermore, long-term toxicity after definitive CRT has became known as a serious problem. Preventing long-term toxicity, which is occasionally fatal, and providing a suitable treatment are both necessary. In the future, subjects for improvement in the survival rates for CRT are managing long-term toxicity and confirming salvage surgery including endoscopic mucosal resection (EMR), as a safe and reliable procedures for residual or recurrent disease after definitive CRT.

It is necessary for us to have a much experience as possible with CRT in our clinical practices and in prospective clinical trials (e.g. the study of Japan Clinical Oncology Group). If this is done, we can understand the effect of CRT in comparison with surgery for esophageal cancer.

Key words：chemoradiotherapy, clinical stage, Japan Clinical Oncology Group (JCOG), long-term toxicity, salvage surgery

**Division of Gastrointestinal Oncology, **Department of Surgery, *3Division of Radiation Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan*

Diseases of the Esophagus (2003) 16, 261–264

DISEASES OF THE ESOPHAGUS

Case report

Esophageal carcinoma with tracheal stenosis due to tumor invasion and long survival after chemoradiotherapy

Y. Kinoshita, H. Udagawa, K. Tsutsumi, M. Ueno, S. Mine, S. Hukuda, K. Sasaki, S. Matoba, T. Hayakawa, M. Matsuda, M. Hashimoto, T. Sawada, G. Watanabe

Department of Surgery, Toranomon Hospital, Tokyo, Japan

SUMMARY. **For patients who have esophageal carcinoma with tracheal invasion surgery is usually not indicated because operative complications are considerable and the prognosis is poor. We experienced complete regression of a large esophageal carcinoma with tracheal stenosis due to tumor invasion without tracheoesophageal fistula. Irradiation of 68 Gy was delivered to a long T field from the neck to the lower thoracic esophagus, and was combined with chemotherapy using cisplatin and 5-fluorouracil. The tumor decreased markedly in size and the tracheal stenosis resolved. The patient has survived for 4 years, although second primary early esophageal carcinoma and hypopharyngeal carcinoma were detected 2 years after his initial chemoradiotherapy. Although the prognosis of advanced esophageal carcinoma with invasion of other organs is usually poor, the effect of chemoradiotherapy can sometimes be dramatic and a good result can be achieved in such patients.**

KEY WORDS: **5-fluorouracil, chemoradiation, cisplatin, esophageal carcinoma, tracheal invasion.**

INTRODUCTION

It is difficult to perform esophagectomy in patients who have esophageal carcinoma with tracheal invasion. Even if surgical treatment succeeds in such patients, long survival cannot be expected in many cases.[1] However, there have been some reports of long-term survival after multidisciplinary treatment in recent years. We encountered a patient with advanced esophageal carcinoma with tracheal invasion causing tracheal stenosis in whom chemoradiotherapy produced sustained regression, and this case is reported here.

CASE REPORT

A 64-year-old-man presented with hoarseness in October 1997. He was prescribed treatment for the common cold at an otolaryngology clinic. However, dysphagia developed from May 1998, so another otolaryngologist was consulted. When esophagogastroscopy was performed, a protruding tumor of the esophagus was detected, and he was referred to our department in June of the same year. Laboratory tests were normal at the time of hospitalization except for an squamous cell carcinoma (SCC) related antigen level of 3.7 μg/L and a cytokeratin 19 fragment (CYFRA) level of 3.3 μg/L. A barium swallow revealed an advanced esophageal carcinoma of 68 mm in length on the anterior wall in the upper third of the esophagus, and another tumor, 32 mm in length on the right wall in the middle third of the esophagus (Fig. 1a). Esophagoscopy showed two advanced carcinomas at the same positions as detected by esophagography (Fig. 2a). Additionally, 0-IIa + IIc and 0-IIc lesions were seen on the posterior wall at 30 cm from the incisors and on the right-hand wall at 40 cm from the incisors, respectively. Computed tomography (CT) revealed a tumor measuring 40 × 31 mm in the upper esophagus that had caused tracheal stenosis due to invasion of the trachea (Fig. 3a), while another tumor was seen on the right-hand wall of the middle esophagus, and lymph node metastases to the left paratracheal and the middle paraesophageal regions were also detected. On bronchoscopy, the tumor was seen to be invading the trachea, and

Address correspondence to: Dr Yoshihiro Kinoshita, Department of Surgery, Toranomon Hospital, 2-2-2 Minato-ku, Toranomon, Tokyo, 105-8470 Japan. Tel: + 81 3 3588 1111; Fax: + 81 3 3582 7068; Email: yoshihirokinoshita@nifty.com

Fig. 1 (a) Barium swallow shows two esophageal tumors, including one on the anterior wall in the upper esophagus and one on the right wall in the middle esophagus. (b) After chemoradiotherapy, the ulcerated tumor in the upper third of the esophagus has almost disappeared and the other advanced tumor in the middle esophagus is completely gone.

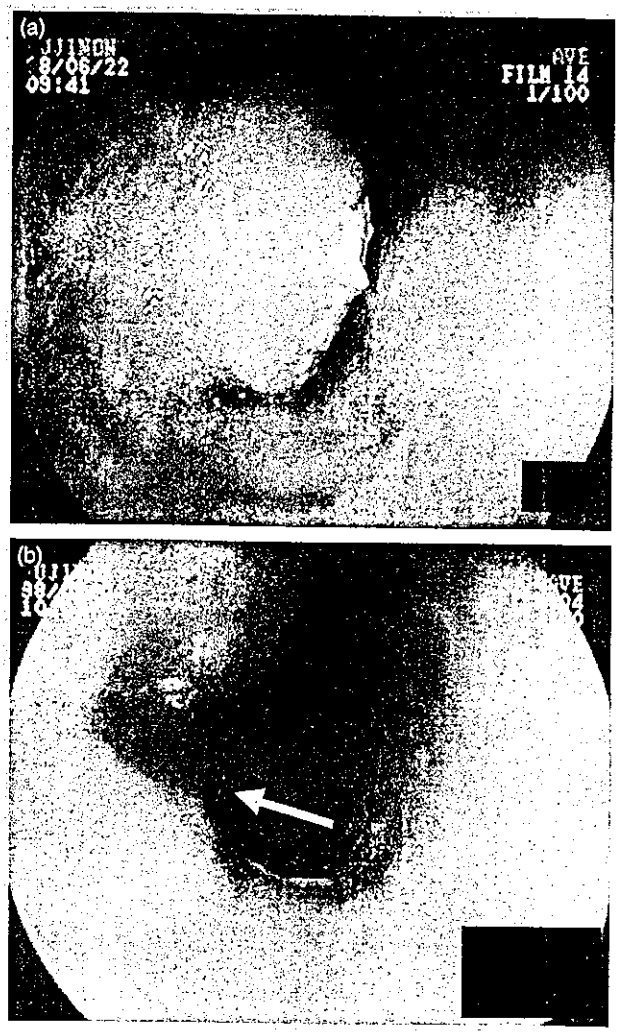

Fig. 2 (a) Esophagoscopy shows advanced carcinoma on the anterior wall of the upper esophagus. (b) Erosive esophagitis due to irradiation extends between 15 cm and 35 cm from the incisors after chemoradiotherapy.

there was at least 60% stenosis with exposed tumor (Fig. 4a). From these findings, we diagnosed multicentric primary esophageal carcinoma, T4 N1 M0, Stage III, and decided to perform chemoradiotherapy.

Irradiation of 68 Gy was delivered to a long T field from the neck to the lower thoracic esophagus, and the treatment was performed from July 2 to August 14, 1998. Because cisplatin therapy requires hydration and there was a risk of exacerbating the esophageal stenosis, chemotherapy was started with 2 weeks of 5-fluorouracil (500 mg/day) alone. The patient was also given prednisolone to control the edema, which was gradually tapered from 40 mg. He was also prescribed 9 mg/day of cisplatin from July 17. However, his white cell count fell to 1900/μL on July 29, so chemotherapy was stopped and his treatment was completed by continuing the radiotherapy alone.

After chemoradiotherapy, a barium swallow showed that the ulcerated tumor in the upper third of the esophagus had almost disappeared, and the other advanced tumor in the middle third of the esophagus had completely disappeared (Fig. 1b). Endoscopy showed that erosive esophagitis due to irradiation was present at 15 cm to 35 cm from the incisors (Fig. 2b). Although a small ulcer was seen at 22 cm, carcinoma was not detected by biopsy. A CT showed that the tumor invading the trachea in the upper mediastinum was markedly reduced and tracheal stenosis was no longer evident (Fig. 3b). The second tumor and the lymph node metastases had also disappeared. Although the tracheal mucosa was irregular on bronchoscopy, tracheal stenosis had completely resolved (Fig. 4b). The patient was discharged on August 29, 1998. The only complications of chemoradiotherapy were grade 3 myelosuppression (leukocytes: 1600/μL, platelets: 5.7×10^4/μL) and grade 2 radiation dermatitis. When re-evaluation was performed in September 1999, no tumor was detected, so complete response was achieved by chemoradiotherapy.

Balloon dilation had to be performed four times for stenosis of the upper third of the esophagus

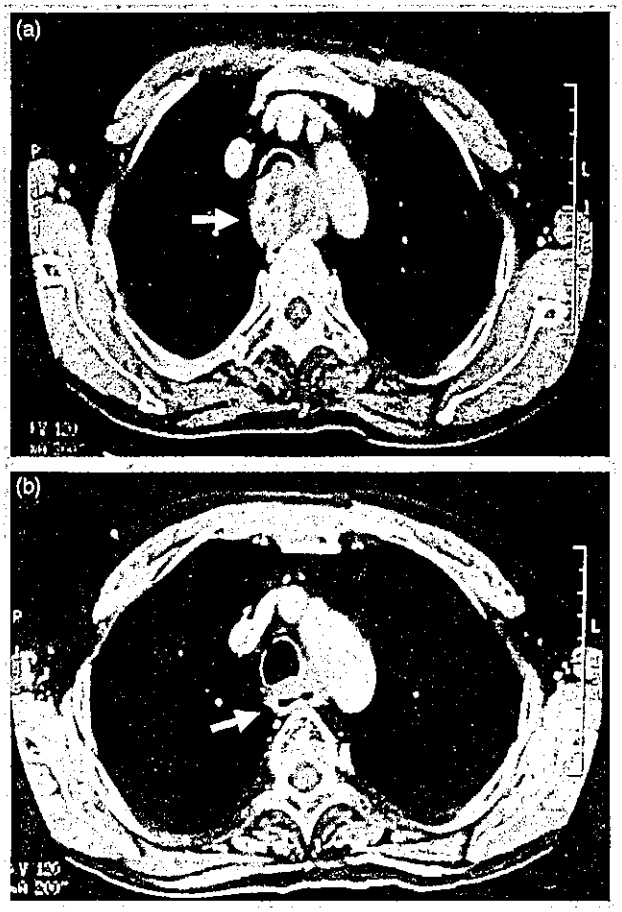

Fig. 3 (a) CT reveals a tumor of 40 × 31 mm in the upper esophagus that has caused tracheal stenosis due to invasion of the trachea. (b) After chemoradiotherapy, CT shows that the tumor with tracheal invasion in the upper esophagus has been markedly reduced, and tracheal stenosis is no longer detected.

within 2 years after discharge from hospital. Superficial esophageal carcinoma was detected 40 cm from the incisors by esophagoscopy in July 2000, about 2 years after treatment and endoscopic mucosal resection was performed (pathological diagnosis: t1a, ly1, v0).[2] Hypopharyngeal carcinoma was also diagnosed simultaneously and was treated with 64 Gy of irradiation to the neck plus cisplatin therapy (10 mg/day, 5 days per week for 5 weeks). It is now 4 years since his first treatment, and the patient is still alive and disease-free.

DISCUSSION

In patients who have esophageal carcinoma with tracheal invasion, surgery is not the treatment of choice since operative complications are considerable and the prognosis is poor, although radical esophageal dissection may be achieved by combined excision of the trachea. Currently, chemoradiotherapy is used to treat esophageal carcinoma invading other organs for the purpose of down-staging before surgery.[3] In

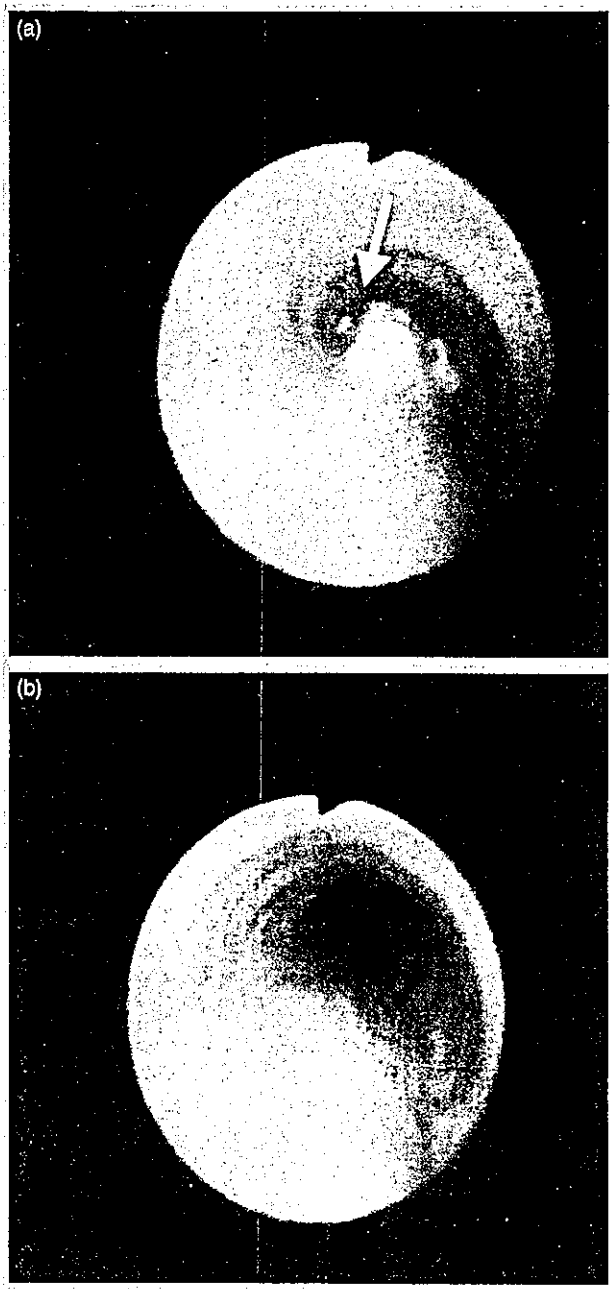

Fig. 4 (a) Bronchoscopy shows the tumor invading the trachea, with at least 60% stenosis. (b) Although the mucosa is irregular, tracheal stenosis has completely disappeared.

our department neoadjuvant chemoradiotherapy has achieved an overall clinical response rate of 65% and a 2-year survival rate of 77.9% in patients undergoing esophagectomy after down-staging of T4 carcinomas.[4] In the present patient, we also considered performing chemoradiation before an operation. However, even if the tracheal invasion with the exposed tumor had been eliminated during treatment, the anatomical structure of the tracheal membrane would have been lost and the possibility of causing tracheal damage during surgery would have been high. Moreover, since it was inside the radiation field, critical complications may have arisen

as a consequence of tracheal damage. Therefore, we chose radical irradiation using a long T field that included the superficial carcinoma in the lower esophagus and the neck, which is a common site of lymph node metastasis from tumors in the upper third of the esophagus. We had planned to perform radical radiotherapy combined with low dose 5-fluorouracil (300 mg/m^2) and cisplatin (6 mg/m^2)[5] but we decided to avoid the early administration of cisplatin because it would have required hydration to prevent renal damage and there was the risk of worsening the tracheal stenosis. Since radiation could also cause edema that might have worsened his stenosis, we administered prednisolone at the beginning of therapy, and we delayed the use of cisplatin for about 2 weeks to confirm the absence of respiratory complications. The side-effects of chemoradiotherapy included grade 3 leukopenia and grade 2 thrombocytopenia (1600/μL, 5.7×10^4/μL, respectively). Use of the long T field for irradiation may have contributed to this. Only chemotherapy was stopped and the myelosuppression improved promptly with administration of granulocyte colony-stimulating factor. It could be argued that radiation should also have been stopped, but radiotherapy was being used for local control of T4 disease, so it was continued. The tumor response was very good and the only long-term side-effect was esophageal stricture that has required balloon dilation four times.

This patient had synchronous multiple primary esophageal carcinoma with four foci. Synchronous multiple esophageal carcinoma is reported to occur in 24% of patients, while asynchronous tumors occur in 15%. Head and neck tumors account for 46.8% of the other carcinomas in patients with asynchronous tumors.[6] Our patient underwent endoscopy every 6 months for follow-up and new tumors were detected in the hypopharynx and the lower esophagus 2 years after the first primary esophageal carcinoma. As both were superficial cancers, chemoradiotherapy was performed for the lesion in the hypopharynx and endoscopic mucosal resection was done for the lower esophageal tumor.

Although we tend to think that advanced esophageal carcinoma with invasion of other organs will have a poor prognosis, chemoradiotherapy can achieve dramatic results in some patients. Of course, careful follow-up is required after remission is achieved.

References

1 Matsubara T, Kuroda J, Tokuchi M *et al.* [Tracheal resection for thoracic esophageal carcinoma with tracheal invasion.] J Clin Surg 2001; 56: 36–42. (In Japanese.)

2 Japanese Society for Esophageal Disease. Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus. Ninth edn. Tokyo: Kanehara Ltd, 2001.

3 Kim J H, Choi E K, Park S B *et al.* Preoperative hyperfractionated radiotherapy with concurrent chemotherapy in respectable esophageal cancer. Int J Radiat Oncol Biol Phys 2001; 50: 1–12.

4 Udagawa H, Tsutsumi K, Kinoshita Y *et al.* Phase II neoadjuvant chemoradiation for clinical T4 esophageal cancer. In: Recent Advances in Diseases of the Esophagus. Italy: Monduzzi, 2001, 605–8.

5 Itoh Y, Fuwa N, Matsumoto A *et al.* [Concurrent chemoradiotherapy using protracted infusion of low dose CDDP and 5-FU and radiotherapy for esophageal cancer.] Nippon Igaku Hoshasengakkai Zasshi 1999; 45: 395–401. (In Japanese.)

6 Makuuchi H, Shimada H, Mizutani K *et al.* Analysis of long-term follow-up patients after endoscopic mucosal resection for early esophageal cancer with special references to metachronous multiple cancers. Stomach Intestines 1996; 31: 1223–33.

別刷

癌と化学療法

VOL.30(2003)

癌と化学療法社

● 原 著 ◐

進行食道癌に対するNedaplatin+5-FU化学放射線療法の治療成績

中村 努*1 井手 博子*1 江口 礼紀*1 林 和彦*1
太田 正穂*1 成宮 孝祐*1 高崎 健*1 三橋 雅夫*2

〔*Jpn J Cancer Chemother* 30(6): 803-807, *June*, 2003〕

要旨 根治切除不能 (stage IV) 食道扁平上皮癌29例に対して，nedaplatin (16～20 mg/m²) +5-FU (700 mg/m²) を4日間と同時に放射線療法30 Gyを1コースとして2コースを施行した。治療効果はCR: 4, PR: 13, NC: 10, PD: 2でCR率14%，奏効率59%であった。50%生存期間は238日で1年生存率は34.5%であった。治療は24例 (83%) が完遂でき，口内炎などの有害反応が少ない傾向にあった。nedaplatin+5-FU化学放射線療法の治療効果はcisplatin+5-FU化学放射線療法と同等であると考えられ，今後，比較(第III相)試験を施行する必要性がある。

Nedaplatin and 5-Fluorouracil Combined with Radiotherapy for Advanced Esophageal Cancer: Tsutomu Nakamura*1, Hiroko Ide*1, Reiki Eguchi*1, Kazuhiko Hayashi*1, Masaho Ota*1, Kosuke Narumiya*1, Ken Takasaki*1 and Masao Mitsuhashi*2 (*1*Dept. of Surgery, Institute of Gastroenterology and* *2*Dept. of Radiology, Tokyo Women's Medical University*)

Summary

We conducted a pilot study of nedaplatin+5-fluorouracil (5-FU) combined with radiotherapy for 29 patients with primary advanced (stage IV) esophageal cancer. A complete remission (CR) was obtained in 4 (14%) and a partial response in 13 patients (response rate: 59%). The median survival time and one-year survival rate were 238 days and 34.5%, respectively. Of the 29 patients, 24 (83%) completed the treatment schedule and toxicity of stomatitis and the like was infrequent. In conclusion, these results suggest that the efficacy of nedaplatin+5-FU combined with radiotherapy might not differ from that of cisplatin+5-FU combined with radiotherapy. Clearly, the usefulness of this combined therapy needs to be assessed in multicenter phase III trials. Key words: Esophageal cancer, 5-FU, Chemoradiotherapy, Squamous cell carcinoma, 245-S (*Received Oct. 25, 2002/Accepted Dec. 26, 2002*)

*2 東京女子医科大学・放射線科

連絡先: 〒162-8666 東京都新宿区河田町8-1 *1 東京女子医科大学消化器病センター・外科
中村 努

0385-0684/03/¥500/論文/JCLS

はじめに

進行食道癌患者に対する初期治療として化学放射線療法が施行されている。化学療法の標準的レジメンであるcisplatin＋5-FUと放射線療法との同時併用療法(chemoradiotherapy)は，術前治療または根治療法として広く行われている[1,2]。わが国でも主に進行食道癌に対して施行され，その治療効果は高い奏効率が示されている[3]。しかし，有害事象が高度で入院期間の長期化を余儀なくされている。また，この標準的治療が始められて10年以上経過しており，新たな有効なレジメンの開発を試みるべきと考えられる。

一方，cisplatinの誘導体nedaplatinは，食道癌症例において単剤のphase II studyで高い奏効率[4]を示しており，5-FUとの併用療法も行われている[5,6]。nedaplatin＋5-FUによる化学放射線療法は症例[7,8]や少数例[9]の報告があるのみである。そこで高度進行（stage IV）食道癌患者に対し，nedaplatin＋5-FUと放射線療法を同時（concurrent）に施行するpilot studyを行ったので，治療成績および有害事象を報告する。

I．対象および方法

1998～2001年に前治療のない根治切除不能の進行食道癌で，内視鏡下生検組織診で扁平上皮癌が確認された29例を対象とした。eligibility criteriaはPS 0～2で，治療前に明らかな食道瘻を伴っていない症例とし，入院時検査で白血球数4,000/mm³以上，ヘモグロビン8.0 g/dl以上，血小板10,000/mm³以上，ビリルビン1.5 mg/ml未満，AST/ALT正常値の3倍未満，クレアチニン・クリアランス60 ml/min以上とした。本療法施行に際し，全症例にinformed consentを文書で得た。stagingは食道造影，内視鏡検査，CTスキャン，腹部頸部超音波検査，超音波内視鏡検査で行い，TNM分類に従った。

II．レジメン

nedaplatin 16～20 mg/m²/日，5-FU 700 mg/m²/日を4日間24時間持続点滴し（days 1～4），同時に放射線療法2 Gy/日を開始し，30 Gyまで（days 1～5，8～12，15～19）を1コースとし，1週間空けて2コース行うこととした（図1）。放射線の照射野は，主病巣およびCT検査において長径1 cm以上でリンパ節転移と診断した部位とした。手術を予定している場合はday 33まで上記レジメンどおり行った。つまり，化学療法2コースと放射線総線量40～50 Gyとした。2コース前の血液検査で白血球数2,000/mm³未満，または血小板50,000/mm³未満であった場合は，2コース目の化学療法は投与しない。白血球数1,500/mm³未満または血小板30,000/mm³未満となった場合は放射線治療を中断し，白血球数3,000/mm³以上または血小板50,000/mm³以上まで回復するまで待ち，2週間以上回復しない場合は治療を中止することとした。

効果判定は，食道癌取扱い規約（第9版）の化学療法および放射線治療の直接効果判定基準に従い行った[10]。また，手術例は同規約の病理組織学的判定基準に従いgrade 3をCR，grade 2をPR，grade 0，1をNCとした。有害反応はNational

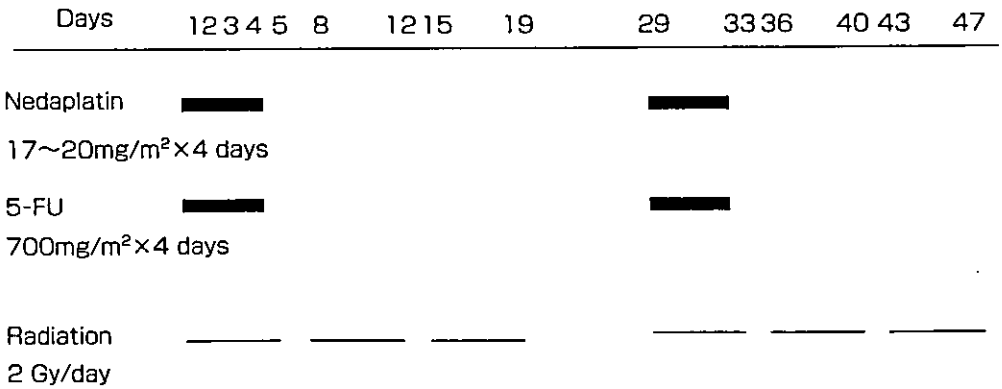

図1 Nedaplatin＋5-FUによる化学放射線療法の治療計画

表1 背景因子

Sex	
Male	25
Female	4
Median age (range)	64 (51～81)
Performance status	
0	12
1	15
2	2
Location	
Ce	3
Ut	5
Mt	19
Lt	2
TNM Stage	
T3M1 (Lym)	2
T4M0	15
T4M1 (Lym)	7
TanyM1 (Org)	5

(n=29)

表2 進行食道癌に対するnedaplatin+5-FUによる化学放射線療法の効果

完遂率	24/29 (83%)	
効果	(食道癌取扱い規約)	
CR	4 (14%)	response rate 59%
PR	13 (45%)	
NC	10 (34%)	
PD	2(6.7%)	

PDの2例は肝・肺転移例

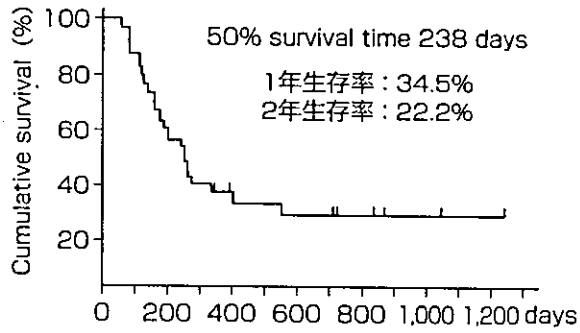

図2 Overall survival curve

Cancer Institute-Common Toxicity Criteria (NCI-CTC) Version 2.0, Japan Clinical Oncology Group (JCOG) 版[11]により判定した。

III. 結 果

1. 背景因子

治療した29例は表1のごとく男性25例，女性4例で，年齢の中央値は62歳で，年齢制限をしていなかったため81歳の症例にも行った。stageはTNM分類によると全例stage IVで，T3N1M1 (lymph): 2例，T4N1M0: 15例，T4N1M1 (lymph): 7例，TanyN1M1 (org): 5例（肺転移2例，肝転移3例）であった。占居部位では頸部食道癌が3例含まれていたが，残りの26例は胸部食道癌であった。

2. 臨床効果

総合評価は29例中4例がCR (CR率14%)で，PRが13例で，奏効率58.6% (95%信頼区間: 40.7～76.5%)であった（表2)。NCは10例，またPDは2例で，いずれも肺・肝転移例であった。計画された治療を完遂できた症例は24例 (83%)で，完遂できなかった症例は5例であった。その原因は原病巣の増悪4例，食道気管支瘻1例であった。

治療開始日よりの生存曲線を図2に示す。経過観察期間は12.6～40.8か月（中央値: 27.5か月）で，50%生存期間は238日（7.9か月）であった。1年生存率は34.5%，2年生存率は22.2%であった。本治療後の経過では食道切除術は7例に行われ，1例は頸部食道癌症例のため喉頭合併切除で，残りの6例は右開胸による胸部食道切除術であった。バイパス手術2例，食道ステント挿入6例，胃瘻2例に施行した。また，nedaplatin+5-FUの化学療法を2例に施行した。PR以上で再発が確認された8例の再発形式は局所再発2例，遠隔リンパ節再発2例，臓器転移4例(肝・腎・脳・骨)であった。

3. 有害反応

血液毒性ではgrade 3, 4の発生率は白血球減少が9例 (31%)，貧血4例 (14%)，血小板減少が3例 (10%)であった。grade 4の血小板減少が1例出現し，血小板輸血など対症療法を行い回復した（表3)。嘔気は1例のみがgrade 3で，口内炎はgrade 3以上は1例もなかった。食道瘻(grade 4)は計5例 (17%)で，うち2例は治療中に出現

表 3 NCI-CTC Version 2.0, JCOG 版による有害反応

	Grade					%Grade 3, 4
	0	1	2	3	4	
WBC	6	2	12	9		31%
Hemoglobin	3	12	10	4		14%
Platelets	9	8	9	2	1	10%
Nausea	5	18	5	1		4%
Stomatitis	19	9	1			
Creatinine	28	1				
Pulmonitis	25	2	2			
Esophageal fistula	24			1	4	17%

し治療中断したが，3例は治療終了後出現した。食道ステントを3例に行い，またバイパス術を1例に施行した。もう1例は治療終了とほぼ同時に食道気管支瘻となり，画像診断で治療効果はCRと判定した。直ちにステントを挿入したが，2か月後ステントが胃内に墜落したため，内視鏡的に取り出しバイパス術を行った。この症例は治療開始より2年経過した現在も再発を認めていない。

治療関連死はなかったが，治療終了後に起こった肺炎1例と胆管炎1例の2例が治療後約3か月後と約2か月後に死亡した。また，治療終了後に胃瘻造設術また食道ステント挿入術を施行された症例のうち，それぞれ1例ずつ吐血で死亡した。

IV. 考　察

食道癌に対するcisplatin＋5-FUの化学放射線療法は1980年代より開始され，今日まで多数の報告がなされている。進行食道癌に対してはCR率10～30%，奏効率60～80%とされているが，治療効果判定基準がそれぞれ異なっているため単純な比較は困難といわざる得ない[1-3]。本研究と同様に食道癌取扱い規約の効果判定基準を用いた報告[12,13]では，奏効率およびCR率ともに本研究と同等と考えられる。また，生存期間で比較してみても，高い奏効率を示しているOhtsuら[3]および前出の報告[12,13]では，stage IV症例における生存期間の中央値は7～9か月であり，本治療はこれらcisplatin＋5-FUを用いた化学放射線療法と同等の治療成績であると考えられた。

nedaplatin＋5-FUの化学療法は，肝転移例に効果があるという報告がある[6,7]。本研究では，肝転移を含む臓器転移を有する進行食道癌症例5例に施行されたが，PR: 2例，NC: 1例，PD: 2例という結果で，最長1年1か月の生存であり，その他の症例は1年未満で死亡している。局所は奏効した症例もあったが，転移巣での効果が総合評価の示すとおりであった。今後，臓器転移症例に対しては化学療法のみを先行させるか，また，化学放射線療法を行う際はnedaplatinの投与量を含め検討が必要である。

nedaplatinの用量を含めた投与法についてはcisplatinと同様に様々で，一定の見解が得られていない。本研究では，nedaplatinの投与量が16～20 mg/m² 4日間とした根拠はIshidaらの研究[12]，またJCOG study 9516でcisplatin 70 mg/m²とされ，16 mg/m² 4日間で総投与量がほぼ一致するためであった。ちなみに，5-FU 700 mg/m² 4日間はこれらの研究と一致させた。過去のnedaplatinを用いた食道癌に対する化学放射線療法の検討[7-9]でも，投与法は様々で一定していない。cisplatin＋5-FUにおいても投与法は様々で，low doseで放射線と連日行われる方法が報告され，第III相試験も現在進行している[14]。また，nedaplatinの投与法に関しても，cisplatinと同様に投与方法および用量を探究する必要がある。

有害反応では，本研究においても骨髄障害や食道瘻が発生し，これらの点に関してはcisplatin＋5-FUによる化学放射線療法[3,13]と差はないと考

えられる。一方，cisplatin＋5-FUによる化学放射線療法では，grade 3以上の口内炎や腎機能障害を認め[3,13]，長期の入院が余儀なくされている。nedaplatinは嘔気・口内炎・下痢など粘膜障害や腎機能障害では，cisplatinよりも軽微であることが報告されている[4-6]。本研究でもその傾向がみられ，口内炎はgrade 2が1例でgrade 3以上はなく，クレアチニンも1例で軽度上昇した(grade 1)のみであった。よって，化学放射線療法期間中の患者のQOLの向上がなされ，早期の退院および通院治療が可能となると考えられる。

今回，進行食道癌患者においてnedaplatin＋5-FUによる化学放射線療法のpilot studyを行った。臨床効果はcisplatin＋5-FUによる化学放射線療法とほぼ同等と考えられ，有害反応は軽微な傾向があった。今後，標準治療であるcisplatin＋5-FUによる化学放射線療法との多施設共同の比較試験を行う必要がある。

文　献

1) Gill PG, Denham JW, Jamieson GG, *et al*: Patterns of treatment failure and prognostic factors associated with the treatment of esophageal carcinoma with chemotherapy and radiotherapy either as sole treatment or followed by surgery. *J Clin Oncol* **10**: 1037-1043, 1992.
2) De Pree C, Aapro MS, Spiliopoulos A, *et al*: Combined chemotherapy and radiotherapy, followed or not by surgery, in squamous cell carcinoma of the esophagus. *Ann Oncol* **6**: 551-557, 1995.
3) 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.
4) 田口鐵男，涌井　昭，鍋谷欣市・他: 254-S(*Cis*-diammine glycolateplatinum)の消化器癌に対する第II相試験．癌と化学療法 **19**: 483-488, 1992.
5) 藤井正人，徳丸　裕，今西順久・他: 頭頸部癌に対するNedaplatinと5-FU併用療法の検討．癌と化学療法 **25**: 53-58, 1998.
6) Yoshioka T, Gamoh M, Shineha R, *et al*: A new combination chemotherapy with cis-diammine-glycolatoplatinum (Nedaplatin) and 5-fluorouracil for advanced esophageal cancers. *Internal Med* **38**: 844-848, 1999.
7) 金子和弘，伊藤紘朗，伊東友弘・他: 食道癌肝転移に対し，Nedapaltin(NDP)＋5-FU＋放射線療法が有効であった1例．癌と化学療法 **28**: 831-834, 2001.
8) Sumi H, Ohtsu A, Boku N, *et al*: A case of inoperative esophageal carcinoma with hepatic and nodal metastases which showed a long-term survival after chemoradiotherapy including nedaplatin. *Jpn J Clin Oncol* **30**: 406-409, 2000.
9) Yamanaka H, Motohiro T, Michiura T, *et al*: Nedaplatin and 5-FU combined with radiation in the treatment for esophageal cancer. *Jpn J Thorac Cardiovasc Surg* **46**: 943-948, 1998.
10) 日本食道疾患研究会・編: 食道癌取扱い規約．第9版，金原出版，東京，1999.
11) 福田治彦，西條長宏: NCI-CTC日本語訳JCOG版—第2版について．癌と化学療法 **28**: 1993-2027, 2001.
12) Ishida K, Iizuka T, Ando N, *et al*: Phase II study of chemoradiotherapy for advanced squamous cell carcinoma of the thoracic esophagus: Nine Japanese institution trial. *Jpn J Clin Oncol* **26**: 310-315, 1996.
13) 小林研二，藤谷和正，辻中利政・他: 高度進行食道癌（初発）に対する化学放射線照射同時併用療法の治療成績．癌と化学療法 **28**: 961-964, 2001.
14) Nishimura Y, Suzuki M, Nakamatsu K, *et al*: Prospective trial of concurrent chemoradiotherapy with protracted infusion of 5-fluorouracil and cisplatin for T 4 esophageal cancer with or without fistula. *Int J Radiat Oncol Biol Phys* **53**: 134-139, 2002.

British Journal of Cancer (2003) 88, 18 – 24

www.bjcancer.com

Definitive chemoradiotherapy for patients with malignant stricture due to T3 or T4 squamous cell carcinoma of the oesophagus

K Kaneko*[,1], H Ito[1], K Konishi[1], T Kurahashi[1], T Ito[1], A Katagiri[1], T Yamamoto[1], T Kitahara[2], Y Mizutani[2], A Ohtsu[3] and K Mitamura[1]

[1]Second Department of Internal Medicine, Showa University School of Medicine, 1-5-8, Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan; [2]Department of Radiology, Showa University School of Medicine, 1-5-8, Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan; [3]Division of Gastrointestinal Oncology/ Digestive Endoscopy, National Cancer Centre Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba 277-8577, Japan

We retrospectively investigated the efficacy and feasibility of concurrent chemoradiotherapy for patients with severe dysphagia caused by oesophageal squamous cell carcinoma. Concurrent chemoradiotherapy was performed in 57 patients with T3 or T4 disease containing M1 lymph node (LYM) disease. Chemotherapy consisted of protracted infusion of 5-fluorouracil (5-FU) 400 mg m^{-2} 24 h^{-1} on days 1 – 5 and 8 – 12, combined with 2-h infusion of cisplatin (CDDP) 40 mg m^{-2} on days 1 and 8. Radiation treatment at a dose of 30 Gy in 15 fractions of the mediastinum was administered concomitantly with chemotherapy. A course schedule with 3-week treatment and a 1 to 2-week break was applied twice, with a total radiation dose of 60 Gy, followed by two or more courses of 5-FU and CDDP. In all, 24 patients (42%) achieved a complete response, and the 3-year survival rate was 19%. Major toxicities were leukocytopenia and oesophagitis, and there were two (4%) treatment-related deaths. In contrast, 22 patients with T3 disease survived longer than 35 patients with T4 disease ($P = 0.001$); however, the survival rate in 15 patients with M1 LYM disease did not differ significantly from that in 42 patients without M1 LYM disease ($P = 0.3545$). Our results indicate that definitive chemoradiotherapy is potentially curative for locally advanced oesophageal carcinoma with malignant stricture. The efficacy and survival of patients treated with this regimen are related to the T factor.
British Journal of Cancer (2003) **88,** 18 – 24. doi:10.1038/sj.bjc.6600684 www.bjcancer.com

Keywords: oesophageal carcinoma; dysphagia; chemoradiotherapy; prognosis

The indications for definitive chemoradiotherapy for patients with severe dysphagia caused by oesophageal carcinoma are poorly defined. Dysphagia is a major symptom that affects the quality of life in patients with unresectable oesophageal tumours. Chemotherapy, radiotherapy, laser therapy, and stent insertion have been reported to relieve symptoms. Recently, metallic stents have become popular in the palliative treatment of patients with dysphagia caused by oesophageal carcinoma (Song *et al*, 1991; Bethge *et al*, 1992; Fleischer *et al*, 1992; Kozarek *et al*, 1992; Schaer *et al*, 1992; Knyrim *et al*, 1993; May *et al*, 1995; Wengrower *et al*, 1998). These stents can be inserted on an outpatient basis and provide rapid relief of symptoms of dysphagia. However, the indications for metallic stent insertion in patient with severe dysphagia caused by oesophageal carcinoma also remain controversial, and the clinical staging has not been evaluated before implantation of metallic stents in these reports.

On the other hand, the effects of chemotherapy combined with radiotherapy on oesophageal carcinoma have been investigated since the 1980s. Several investigators have reported successful results with these modalities, either with or without surgery, against local – regional carcinoma (Leichman *et al*, 1984; Leichman *et al*, 1987; Poplin *et al*, 1987; Coia *et al*, 1991; Frorastiere *et al*, 1993; Poplin *et al*, 1994). The combination of 5-fluorouracil (5-FU) and cisplatin (CDDP) has become a standard regimen, not only because of the clinical outcome but also because of the synergism between the two agents and their radiosensitising effects (Douple *et al*, 1980; Scanlon *et al*, 1986; Byfield, 1990). Recently published results on chemoradiotherapy indicated that it offers various advantages for the treatment of carcinoma of the oesophagus (Frorastiere *et al*, 1993; Coia, 1994). In a prospective randomised trial by the Radiation Therapy Oncology Group, which compared chemoradiotherapy with radiotherapy alone, the combined-modality arm demonstrated a significant improvement of survival (Herskovic *et al*, 1992), with a 5-year survival rate of 27%, compared with 0% for radiotherapy alone (Al-Sarraf *et al*, 1997). With regard to the indications of chemoradiotherapy as a curative treatment for patients with locally advanced diseases, our multicentre study suggested that concurrent chemoradiotherapy was potentially curative even in cases with locally advanced carcinoma of the oesophagus (i.e., T4 and/or M1 lymph node metastasis (LYM) disease) (Ohtsu *et al*, 1999). Of the 54 patients in that study, 18 (33%) achieved a complete response, and the 3-year survival rate was 23%. On the other hand, there are no studies that investigated the effects of chemoradiotherapy in patients with oesophageal stricture

*Correspondence: Dr K Kaneko, E-mail: gikaneko@med.showa-u.ac.jp
Received 23 April 2002; revised 4 October 2002; accepted 8 October 2002

caused by tumours presenting with dysphagia as the principal symptom.

In the present retrospective study, we evaluated the effects of chemoradiotherapy for patients with 'malignant stricture' caused by squamous cell carcinoma of the oesophagus. Definition of tumour stage was based on the 1987 criteria of the tumour-node-metastasis (TNM) classification of the International Union Against Cancer (UICC). Accordingly, T4 was defined as a tumour that invaded contiguous structures and M1 LYM was defined as nodal metastasis beyond the regional lymph nodes. The efficacy and feasibility of chemoradiotherapy were analysed in consecutive patients with malignant stricture caused by oesophageal squamous cell carcinoma.

METHODS AND MATERIALS

Patient population

From May 1996 to March 2000, 70 consecutive patients aged $\leqslant 75$ years were diagnosed at Showa University School of Medicine as having locally advanced oesophageal carcinoma with malignant stricture associated with severe dysphagia. Of the 70 patients, 13 were excluded from the present study for the presence of malignant fistula ($n=1$), distant metastasis (liver metastasis ($n=4$), lung metastasis ($n=2$), bone metastasis ($n=3$)), medical conditions (including ineligible laboratory data as defined below, $n=2$), or concurrent gastric cancer ($n=1$). None of the patients had other malignancies or surgery and chemotherapy for previous diseases. Previous studies indicated that 95% of oesophageal cancers in Japanese patients are squamous cell carcinomas (Japanese Research Society for Esophageal Diseases, 1997). In agreement with that observation, none of the patients enrolled in this study had oesophageal adenocarcinoma; thus, all patients had squamous cell carcinoma of the oesophagus. All patients were enrolled in the present study after registration in the previous study (Ohtsu *et al*, 1999).

Eligibility criteria

Patients who were eligible for this trial had previously untreated, histologically confirmed squamous cell carcinoma of the thoracic oesophagus. The tumours had to show evidence of T3 and T4 disease, containing M1 LYM disease, based on the staging criteria of the UICC. The prestudy clinical evaluation included air contrast barium oesophagography, oesophagoscopy, neck computed tomography (CT), chest CT, abdominal CT, endoscopic ultrasonography, bronchoscopy, and bone scan. However, endoscopic ultrasonography was optional since the endoscope could not be passed through stenotic lesions in most cases (89%). Bronchoscopy was performed in some cases when tracheobronchial involvement was suspected. Adjacent organs were considered to be involved if the tumours extended into the oesophageal lumen, caused deformity of the tracheobronchial tree or if the tumours appeared to be attached to the organs at a $>90^{\circ}$ angle to the thoracic aorta as observed on the CT scan (Picus *et al*, 1983; Takashima *et al*, 1991). T3 or a lesser extent of the disease was determined by endoscopic ultrasonography. In those patients who could not undergo this procedure, T3 was defined based on the lack of any associated abnormal bronchoscopic findings; that is, no deformity of the airway and tracheobronchial tree on the CT scan. Furthermore, we modified the criteria described previously for the definition of T3 disease (Picus *et al*, 1983) to include tumours attached to the organs at a $\leqslant 90^{\circ}$ angle to the thoracic aorta as observed on the CT scan. The patients were considered to have LYM if the tumour was $\geqslant 1$ cm in diameter (Curtin *et al*, 1998). Radiological evaluations for staging were reviewed by two radiologists (TK and YM) and the physicians at Showa University School of Medicine, as was reported in previous studies (Picus *et al*, 1983; Takashima *et al*, 1991; Curtin *et al*, 1998). However, while the UICC staging criteria were adopted in these previous studies, we used a non-standard staging technique in this study, especially when evaluating the depth of tumour infiltration. The clinical staging was also evaluated according to 1983 AJCC staging criteria. The following criteria were used for enrolment for chemoradiotherapy: (1) An Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or less, (2) satisfactory haematologic function (leukocyte count $\geqslant 3000\,mm^{-3}$ and platelet count $\geqslant 100\,000\,mm^{-3}$), (3) satisfactory hepatic function (AST or ALT levels within three times the normal upper limit and a serum bilirubin level of less than $2.0\,mg\,dl^{-1}$), (4) good renal function (creatinine level $\leqslant 1.5\,mg\,dl^{-1}$ and creatinine clearance $\geqslant 50\,ml\,min^{-1}$), (5) satisfactory pulmonary function (PaO_2 $\geqslant 70$ mmHg), (6) normal electrocardiogram, and (7) life expectancy $\geqslant 8$ weeks. Patients with serious complications, such as a history of ischaemic heart disease, pulmonary fibrosis, or active carcinoma at another site were excluded from the study. After explaining the true disease status and predicted complications of the treatment, including the possibility of treatment-related death, each patient gave informed consent for the study. The study protocol was approved by the Human Ethics Review Committee of Showa University School of Medicine.

Treatment schedule

Chemotherapy consisted of protracted infusion of 5-FU at a dose of $400\,mg\,m\,day^{-1}$ on days 1 – 5 and 8 – 12, combined with a 2-h infusion of CDDP at $40\,mg\,m^{-2}$ on days 1 and 8. A 10 MV radiation treatment was administered for 3 weeks (5 days/week) at $2\,Gy\,day^{-1}$, concomitantly with chemotherapy. The targeted area for carcinoma of the upper and middle thirds of the oesophagus included the primary tumours with a 3-cm margin craniocaudally and any metastatic nodes with 1- to 1.5-cm margin, in the supraclavicular fossa and mediastinum. For carcinoma of the lower third of the oesophagus, the field was extended to include the perigastric nodes, while the supraclavicular fossa was excluded if the cervical nodes were found to be negative. The daily fractional dose of radiotherapy was 2 Gy administered 5 days a week. When the planned volume included both the supraclavicular fossa and upper abdominal nodes, a daily dose of 1.8 Gy was allowed. After a dose of 30 Gy, we allowed a 1- to 2-week treatment-free period. Radiotherapy was restarted on day 29 or 36, along with the same schedule of chemotherapy as described above. The treatment course included 3 weeks of radiotherapy followed by a 1- to 2-week break, and the 30 Gy course was administered twice, with a total radiation dose of 60 Gy. The irradiation techniques were initially applied in anterior and posterior opposed fields. At 40 Gy, the radiation portals were reduced to shield the spinal cord and to encompass the primary tumour craniocaudally with a 2- to 3-cm margin, usually by using an oblique opposed field. Metastatic nodes were encompassed with a 1- to 1.5-cm margin. The total radiation dose to the spinal cord was kept at a maximum of 40 Gy. The homogeneity of the dose within the planning volume was within $\pm 10\%$ of the prescribed dose.

Patients who were evaluated for an objective response to the above treatment received additional chemotherapy consisting of a continuous infusion of 5-FU at a dose of $800\,mg\,m^{-2}$ on days 1 – 5 and CDDP at a dose of $80\,mg\,m^{-2}$ on day 1. This treatment schedule of 1-week treatment followed by a 3- to 4-week break was only repeated once in some patients and no further treatment was applied if no disease progression was observed. When a single course consisted of treatment followed by a >5-week break, we defined the latter as interruption. All patients receiving chemoradiotherapy were monitored by neck CT, chest CT, abdominal CT, endoscopy, and air contrast oesophagography every 4 – 5 weeks.

Evaluation of response and toxicity of chemoradiotherapy

For measurable lesions, the response was assessed using the World Health Organization criteria. Briefly, a complete response (CR) was defined as the complete disappearance of all measurable and assessable disease for at least 4 weeks. A partial response (PR) was defined as more than 50% reduction in the sum of the products of the longest perpendicular diameter of measurable disease for a period of at least 4 weeks. Stable disease (SD) was defined as the failure to observe CR, PR, or progressive disease for at least 4 weeks. Progressive disease (PD) was defined as a more than 25% increase in the sum of the products of the longest perpendicular diameter of measurable disease or the appearance of new lesions. To investigate the changes in the grade of dysphagia, the response of the primary tumour was evaluated using modified criteria of the Japanese Society for Esophageal Diseases (1992). For primary tumours, CR was defined as when all visible tumours, including ulceration, disappeared for at least 4 weeks, confirmed by normal endoscopic biopsy specimens. PR represented more than 50% reduction in the area of the primary tumour as observed on oesophagography. PD was considered to be an increase in the area of the tumour of more than 25%. The response was evaluated by oesophagography, oesophagoscopy, and neck, chest and abdominal CT scans during each course.

Toxicity was evaluated using the criteria defined by the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2.0). Toxicity was assessed on a weekly basis during chemoradiotherapy and then biweekly during the subsequent chemotherapy.

The grade of dysphagia was determined by the dysphagia score as described previously (Mellow *et al*, 1985; Knyrim *et al*, 1993). A score of 0 denoted the ability to eat a normal diet, 1 denoted the ability to eat some solid food, 2 denoted the ability to eat semisolids only, 3 denoted the ability to swallow liquids only, and 4 denoted complete dysphagia, even to saliva. Improvement of dysphagia was defined as a decrease in the dysphagia score by at least 1 point. Furthermore, we also used the PS score to evaluate any improvement/deterioration of quality of life in patients under treatment. The PS and dysphagia scores were recorded biweekly by the physician during and after these treatments.

Statistical analysis

Follow-up evaluations after chemoradiotherapy were performed every 3 months for the first 2 years and every 6 months thereafter by endoscopy and CT scan. Differences between the two groups were calculated by the χ^2 test or the Wilcoxon rank-sum test. Survival was calculated from the data at the initiation of treatment by the actuarial Kaplan–Meier method (Kaplan *et al*, 1958). Survival differences between the two groups were assessed by the log-rank test. Multivariate analyses were performed using multiple logistic regression. *P*-values of less than 0.05 were considered significant.

RESULTS

Patient characteristics

The characteristics of the participating 57 patients are listed in Table 1. Of these, 47 patients were men and 10 were women, and the median age was 64 years. Most patients had a good performance status. According to our criteria, the clinical staging was classified as follows: stage II in four patients, stage III in 38, and stage IV in 15. There were 22 patients (39%) with T3 disease, and 35 (61%) with T4 disease. Of 57 patients, 15 (26%) had M1 LYM disease. Clinically involved sites in the 35 cases with T4 disease were thoracic aorta (20 patients), tracheobronchial tree (13 patients), and both sites (2 patients). A single patient had cervical node metastasis, 12 had abdominal nodes, and two had metastases in both nodes. Most (90%) of the primary tumours were more than 5 cm long, with a median length of 7 cm (range, 4–15 cm). All 57 patients had histopathologically confirmed squamous cell carcinoma. In all, 53 patients (93%) completed at least the chemoradiotherapy segment with a total radiation dose of 60 Gy. The remaining four patients did not complete chemoradiotherapy; two experienced disease progression and two died because of treatment-related oesophagoaortic fistula. Of the 53 patients with complete chemoradiotherapay segment, eight and 22 patients had a 1-week break and a 2-week break after a 3-week treatment, respectively. The remaining 23 patients had an interruption during chemoradiotherapy. Of the 46 patients who responded to chemoradiotherapy, 40 (87%) received the additional two or more courses of chemotherapy. However, six patients completed only one course of chemotherapy, because these six patients achieved a CR after one course of chemotherapy.

Table 1 Patient characteristics

No. of patients	57
Sex (male / female)	47/10
Age (range)	64 (45–75 years)
Performance status	
0	41
1	15
2	1
Median tumour length (range)	7.0 (4–15 cm)
Location[a]	
Upper	11
Middle	31
Lower	15
Histopathology	
Well differentiated	6
Moderately differentiated	41
Poorly differentiated	10
Stage (UICC)	
T3 M0	18
T3 M1	4
T4 M0	24
T4 M1	11

[a]Location of the tumour according to the TNM classification; UICC: International Union Against Cancer.

According to the 1983 AJCC criteria, the clinical staging was classified as follows: stage II in none, stage III in 50 patients, and stage IV in seven. There were 32 patients (56%) with T3 disease, and 25 (44%) with T4 disease in AJCC criteria. None of the patients was classified as T2 disease since all patients had dysphagia. Of the 57 patients, T4 disease was predominant in our criteria; however, T3 disease was predominant in AJCC criteria. The frequency of T3 and T4 disease based on our criteria was not significantly different from that in AJCC criteria ($P = 0.0607$). In contrast, 26% of 57 patients had M1 LYM disease based on our criteria; whereas 12% had M1 LYM based on AJCC criteria alone. There was no significant difference between the two groups ($P = 0.0576$). Four patients were classified as stage II (T3N0M0) based on our criteria; however, none of the patients had stage II based on AJCC criteria and all patients were classified as stage III or IV.

Clinical response to chemoradiotherapy

The results of the overall response are summarised in Table 2. Of the 57 eligible patients, 24 (42%) achieved CR. In all, 46 patients, including the 24 CR cases, demonstrated an objective response according to the Japanese evaluation criteria, which resulted in a response rate of 81%. Nine patients showed an SD, and two had a PD. The CR rate was significantly lower in patients with T4 (10 of

Table 2 Response results

	Number of patients	CR		PR		SD		PD	
		n	%	*n*	%	*n*	%	*n*	%
Primary tumour	57	25	44	22	39	10	17	0	0
Overall	57	25	42	22	39	9	16	2	3

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease.

35; 29%) disease than in those with T3 (14 of 22; 64%, $P=0.009$). Furthermore, the CR rate in patients with M1 LYM (4 of 15; 27%) disease was not significantly different from that in patients with M0 LYM (20 of 42; 48%, $P=0.2663$). In 15 patients with M1 LYM disease, the CR rate in those with cervical node metastasis was not significantly different from that in patients with abdominal node metastasis. Of 11 patients with T4M1 disease, two (18%) achieved a CR and one (9%) had over 3-year survival. In multivariate analyses, the CR rate based on our criteria was related to T factor ($P=0.0351$), but not to M factor ($P=0.4413$). In contrast, the CR rate based on AJCC criteria did not correlate with the T ($P=0.0535$) or M factor ($P=0.6805$).

Toxicity

The major side effects of chemoradiotherapy encountered in our patients during treatment are listed in Table 3. These included myelosuppression and oesophagitis. Grade 3 and higher leukocytopenia, anaemia, thrombocytopenia, and oesophagitis occurred in 30, 33, 14, and 25% of the patients, respectively. Two patients (4%) developed sepsis associated with leukocytopenia; however, these patients recovered from sepsis with the use of filgrastim and antibiotics. Of 35 patients with T4 disease, three (9%) developed treatment-related perforation of the oesophageal wall: one developed a mediastinal fistula, while each of the other two developed an aortic fistula. These three patients had T4 disease before treatment, and these events occurred during chemoradiation. One patient showed spontaneous healing of the mediastinal fistula after the disappearance of inflammatory findings, despite continuation of treatment, and achieved a PR. The remaining two patients with oesophagoaortic fistulae died of massive bleeding during two courses and four courses of chemoradiation, respectively. Nausea was not associated with chemoradiotherapy for patients with abdominal metastatic nodes.

Table 3 Major complications appearing during and after chemoradiotherapy

	Grade 1		Grade 2		Grade 3		Grade 4	
	n	%	*n*	%	*n*	%	*n*	%
Leukocytopenia	11	19	23	40	14	25	3	5
Anaemia	3	5	22	39	19	33	0	0
Thrombocytopenia	5	9	6	11	5	9	3	5
Nausea/Vomiting	17	30	5	9	9	16	0	0
Diarrhoea	5	9	11	19	5	9	2	4
Mucositis	6	11	6	11	5	9	0	0
Oesophagitis	23	40	11	19	9	16	5	9
Renal	5	9	11	19	0	0	0	0
Pulmonary[a]	11	19	5	9	0	0	0	0
Cardiac[a]	0	0	6	11	1	2	0	0

[a]Late radiation-related complications.

Treatment was interrupted during the chemoradiotherapy segment in 23 patients for the following reasons: persistent leukocytopenia ($n=17$), fistula ($n=3$), and other complications ($n=3$). The median duration of the interruption because of persistent leukocytopenia was 6 days (1–13 days) after a definite break. All 17 patients could pursue the treatment. There were two (4%) deaths related to treatment: as a result of oesophagoaortic fistula, as mentioned above. However, the patient with mediastinal fistula continued the treatment after a 1-week interruption, since inflammation could be improved with the use of antibiotics. In all patients, treatment had little effect on body weight ($-1.3\pm9.2\%$).

Late radiation-related complications included pneumonitis and pericarditis. Pneumonitis of grade 2 or less occurred in 16 patients (28%), but none of the patients developed grade 3 or higher toxicity. Pneumonitis occurred at a median of 5.5 months from the end of radiotherapy (range, 3–8 months). Grade 3 pericarditis with pericardial effusion was detected in one patient (2%). Dyspnoea owing to pericardial effusion appeared after approximately 6 months from the end of radiotherapy. Histopathologically, no malignant cells were found in pericardial effusion samples. This patient remains disease-free and is still alive after more than 3 years of termination of treatment.

Grade of dysphagia

Table 4 summarises the effects of treatment on the dysphagia score. Most patients had severe dysphagia caused by oesophageal carcinoma. With regard to the primary lesions as evaluated by the Japanese criteria, 47 (83%) of the 57 patients showed improvement of the dysphagia score, including 25 (44%) with CR. These 25 CR cases became dysphagia-free, and 11 (44%) never complained of dysphagia over a 3-year period. Of the remaining 13 patients, dysphagia appeared again after treatment in eight, which was because of local recurrence in five, and compression of metastatic lymph node in three. Implantation of a self-expanding metallic stent was performed in these patients, because these eight patients developed dysphagia caused by malignant stricture after failure of chemoradiotherapy.

The dysphagia score decreased from 3.2 to 1.1 ($P<0.0001$), and dysphagia improved in 46 (81%) of the 57 patients. Of the 47 patients in whom the primary lesion responded to chemoradiotherapy, dysphagia improved in 46, while one patient could not take solid food because of a progressive oesophageal stricture induced by radiation-related fibrotic changes. Of these 46 patients, dysphagia improved in 27 (59%) following a single course of chemoradiotherapy, and in 19 (41%) after two courses. The median duration of dysphagia improvement was 10 months after treatment in these patients. The proportion of PS 0, 1, 2, and 3 before treatment was 41 (72%), 15 (26%), 1 (2%), and 0 (0%),

Table 4 Dysphagia score before and after concurrent chemoradiotherapy

	Before treatment		After treatment	
Dysphagia score	*n*	%	*n*	%
Grade 0	0	0	24	42
Grade 1	0	0	16	28
Grade 2	6	10	8	14
Grade 3	36	65	7	12
Grade 4	15	25	2	4

A score of 0 denotes the ability to eat a normal diet, 1 denotes the ability to eat some solid food, 2 denotes the ability to eat semisolids only, 3 denotes the ability to swallow liquids only, and 4 denotes complete dysphagia, even to saliva.

respectively. The proportion of PS 0, 1, 2, and 3 after treatment was 37 (65%), 16 (28%), 3 (5%), and 1 (2%), respectively. The PS was still 2 or 3 after treatment in some patients with progressive disease; however, most patients had a PS before and after treatment.

Survival

After a median follow-up period of 14 months (range, 1–58 months), 17 (30%) patients were still alive. Survival rates of 1 and 3 years were 61% (35 of 57) and 19% (11 of 57), respectively. Figure 1 shows the survival curves of 57 patients based on the T factor (T3 or T4). The median survival times of 22 patients with T3 disease and 35 patients with T4 disease were 29 and 11 months, respectively; the survival rate of patients with T3 disease was significantly longer than that of patients with T4 disease ($P=0.001$, log-rank test). Furthermore, when the patients were divided into two subgroups of 15 with M1 LYM (four patients with T3 and 11 with T4) and 42 with M0 LYM (18 patients with T3 and 24 with T4), the median survival time of 42 patients with M0 disease (15 months) was not different from that of 15 patients with M1 disease (12 months, $P=0.3545$, log-rank test). Multivariate analyses showed that the survival rate based on our criteria was strongly related to T factor ($P=0.0051$), but not to M factor ($P=0.4615$). In contrast, the proportion of T3 and T4 disease or M0 and M1 disease classified based on our criteria was not similar to that classified by AJCC criteria, although the survival rate based on the AJCC criteria was also related to the T factor ($P=0.0247$) but not to the M factor ($P=0.5128$) in multiple logistic regression (see Figure 2).

DISCUSSION

The value of chemoradiotherapy for the treatment of unresectable oesophageal carcinoma remains controversial, and only a few clinical studies have been published since the 1980s (Leichman *et al*, 1984; Leichman *et al*, 1987; Poplin *et al*, 1987; Coia *et al*, 1991; Herskovic *et al*, 1992; Frorastiere *et al*, 1993; Poplin *et al*, 1994). Most patients in these studies had local–regional disease (UICC stage I or II). Although some reports included patients with T4 disease, the proportion of such patients was usually low and the clinical outcomes were not clearly described. The results of these studies, including CR rates and survival rates, were confusing, since the clinical and pathological backgrounds varied, especially with regard to the stage of the disease. Therefore, stratification by clinical stage should be applied when evaluating the impact of

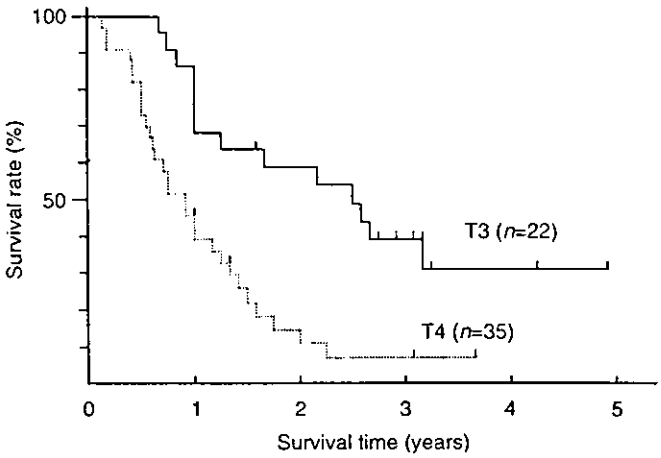

Figure 1 Survival curves of 22 patients with T3 disease and 35 patients with T4 disease.

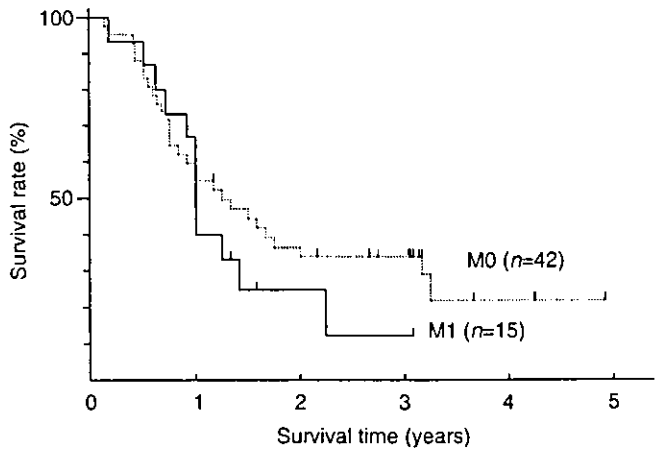

Figure 2 Survival curves of 42 patients with M0 disease and 15 patients with M1 LYM disease.

treatment on survival and response. Coia *et al* (1991) reported long-term results with 5-FU and mitomycin C chemotherapy combined with radiation therapy. In their study, 33 patients with stage III and IV disease were treated with chemotherapy and 50 Gy of radiation therapy with palliative intent; this treatment resulted in a median survival duration of 9 months and a 2-year survival rate of only 3% (Coia, 1994). Zeone *et al* (1992) reported the results of curative nonsurgical treatment that consisted of 5-FU, CDDP, and 64 Gy of radiotherapy combined with neodymium: yttrium-aluminium garnet (Nd:YAG) laser therapy in appropriate patients. They treated 65 patients who had predominantly T1–3 disease, but their study included five patients with T4 disease. Although the 3-year survival rate of the 65 eligible patients was 37%, all five patients with T4 disease died within 18 months. In another large study from Australia, 79 patients with advanced-stage carcinoma, including 25 with systemic metastasis, were treated with 5-FU, CDDP, and 30–35 Gy of radiation therapy (Burmeister *et al*, 1995). A 3-year survival rate of 9% was achieved in patients with advanced disease. However, clinical stages based on the TNM classification were not described; therefore, the stage at which patients survived longer is unknown. A literature search produced no other studies that specifically investigated chemoradiotherapy for locally advanced disease, such as T4 and/or M1 LYM. In our previous study, a CR rate of 33% and a 3-year survival rate of 23% were achieved in patients with unresectable T4 tumours and/or M1 LYM disease (Ohtsu *et al*, 1999), suggesting that concurrent chemoradiotherapy was potentially curative for locally advanced carcinoma. In our present study, a CR rate of 39% and a 3-year survival rate of 19% were achieved in patients with 'severe dysphagia' accompanied by T3 or T4 disease.

With regard to the efficacy and feasibility of chemoradiotherapy, our clinical outcomes in the present study were similar to those in our previous multicentre study. In our previous and present studies, the extended field of irradiation was used to cover the three field dissected areas by extended surgery in Japan. Furthermore, a combination of 5-FU and CDDP has become a standard regimen because of the synergism between the two agents and their radiosensitising effects (Douple *et al*, 1980; Scanlon *et al*, 1986; Byfield, 1990).

Some studies of a continuous irradiation course combined with 5-FU and CDDP indicated that grade 3 and higher leukocytopenia and oesophagitis occurred in 33–54% and 48–50% of patients, respectively (Herskovic *et al*, 1992; Poplin *et al*, 1994). It is likely that severe leukocytopenia and oesophagitis frequently occurred in a continuous irradiation course. Since the presence of severe toxicity because of both the extended field of irradiation and a combination of chemoradiotherapy had been expected, we used a

split course radiation technique with a 1- to 2-week treatment-free period instead of using a continuous irradiation course. In contrast, the periods of recovery from toxicity were not sufficient for a 1-week break in many patients. Therefore, we believed that at least a 2-week break would be required to administer chemoradiotherapy without an interruption. Our results suggested that definitive chemoradiotherapy with a split course radiation technique accompanied by a 2-week break is feasible for locally advanced carcinoma.

In contrast, our results were associated with significant toxicity, consisting predominantly of leukocytopenia and perforation of the oesophageal wall. The high incidence of leukocytopenia and oesophagitis might be because of both the extended field of irradiation and combination of chemoradiotherapy. Fortunately, the leukocytopenia was not a fatal complication, and patients with leukocytopenia-related sepsis could recover with the use of filgrastim and antibiotics. Perforation of the oesophageal wall was an unavoidable significant toxic effect of treatment for T4 disease. However, no perforation occurred in patients with T3 disease. Previous studies reported the development of fistula in 29% of 94 patients with oesophagobronchial involvement who were treated with radiation therapy alone (Roussel *et al*, 1995). Early death occurred in all patients who developed complications, with a median period of 1.7 months. The rate of oesophageal perforation in the present study was 9% (three of 35 patients) in patients with T4 disease, which was lower than that reported by Roussel *et al*. Furthermore, one of the three perforations in our study closed spontaneously following additional chemoradiotherapy after improvement of the inflammatory process, and the patient achieved PR with respect to the primary tumour. Insertion of the metallic stent as a palliative treatment was not performed in our patients despite perforation of the oesophageal wall. However, these results do not support the criticism that chemoradiotherapy should be contraindicated for T4 disease, especially in cases that involve fistula.

In contrast, several reports have proposed that insertion of a metallic stent is effective in the palliative treatment of malignant oesophageal stricture (Song *et al*, 1991; Bethge *et al*, 1992; Fleischer *et al*, 1992; Kozarek *et al*, 1992; Schaer *et al*, 1992; Knyrim *et al*, 1993; May *et al*, 1995; Wengrower *et al*, 1998). However, the indication for metallic stent insertion in patients with malignant stricture caused by oesophageal carcinoma remains controversial. In one study, 21 patients with malignant oesophageal stricture received a self-expanding metallic stent, and all stents were placed successfully with no immediate severe complications (Knyrim *et al*, 1993). Dysphagia improved in 92% of their patients and the dysphagia score decreased from 3 to 1, while the mean survival time was 168 days. In another study, 30 patients with incurable malignant obstruction of the oesophagus and cardia were treated with self-expanding metallic stents (May *et al*, 1995). All stents were placed successfully with no early complications. Dysphagia improved in 83% of the patients within 1 week, and the mean survival time was 108 days (range, 14 – 211 days). In a multicentre study from Israel, 81 patients with malignant obstruction of the oesophagus and gastric cardia were treated with self-expanding metallic coils (Wengrower *et al*, 1998). All coils were placed successfully and dysphagia improved in 96% of the patients, while the dysphagia score dropped from 3.5 to 1.2. The mean survival time was 16 weeks (range, 4 – 56 weeks). In these results (Knyrim *et al*, 1993; May *et al*, 1995; Wengrower *et al*, 1998), the stent was placed successfully and dysphagia improved in approximately 90% of the patients. Furthermore, there seemed to be few fatal complications in the early postinsertion period, although late complications occurred in 22 – 30% of the patients (Knyrim *et al*, 1993; May *et al*, 1995; Wengrower *et al*, 1998). The mean survival time was 4 – 5 months after stent insertion. Efficacy, complications, and survival time are not likely to be different, although different stents are inserted as an initially palliative treatment. Approximately 90% of our patients had severe dysphagia before chemoradiotherapy, however, dysphagia improved in 81% of the patients and the average dysphagia score decreased from 3.1 to 1.1. Most of our patients had a good PS before and after treatment. The change in the grade of dysphagia in our study was not different from those reported by other investigators (Knyrim *et al*, 1993; May *et al*, 1995; Wengrower *et al*, 1998). However, implantation of the metallic stent is unlikely to be curative in patients with severe dysphagia. In contrast, most patients with T3 disease become dysphagia-free following such a procedure. If a metallic stent is initially inserted for patients with severe dysphagia, such patients, especially those with T3 disease, are unlikely to have a complete cure. Assessment of the clinical stage according to the TNM classification should be performed in patients with dysphagia caused by advanced oesophageal carcinoma, and chemoradiotherapy should be provided to patients with T3 or T4 accompanied by M1 LYM disease. Insertion of a metallic stent as a palliative treatment may be of limited value, for example, to patients with oesophageal fistula or systemic metastasis, or those who develop stricture after failure of the primary curative treatment (Kaneko *et al*, 2002).

The development of imaging techniques such as CT scan, magnetic resonance imaging, and endoscopic ultrasonography, has allowed a more accurate clinical staging of oesophageal tumours in recent years. These advances in diagnostic procedures have allowed the selection of optimal treatment modality through clinical staging. Although there are some 'grey zones' with respect to determining T3 or T4 disease by imaging, several studies have reported the successful use of CT scans and/or magnetic resonance imaging with an accuracy rate of $\geqslant 80\%$ (Picus *et al*, 1983; Takashima *et al*, 1991). We adopted their reported criterion to define T3 or T4 disease. Diagnostic radiologists, together with medical oncologists, were responsible for the final staging. With regard to the determination of positive nodes, there are no reliable diagnostic staging criteria to date. Therefore, we used the 1-cm size to indicate a positive node. The positive predictive value of this criterion was only 50% in the study of Curtin *et al* (1998). This low value might explain our good results in cases with M1 LYM disease, although all 15 patients with M1 LYM disease had advanced T3 or T4 disease with severe stricture. Moreover, the patients classified with T3M0 and T4M0 disease would have had occult nodal involvement that was not detected by CT scan. Since the survival rate in patients with M0 disease did not differ significantly from that of patients with M1 LYM disease ($P = 0.3545$), it is likely that any attempt to separate these groups would be rather artificial. In contrast, only 11% of patients had an EUS to define the depth of wall penetration to establish T3 disease. Since our staging criteria for T3 disease used before treatment is not standard, the clinical staging was also performed according to 1983 AJCC staging criteria. The proportions of T3 and T4 based on the AJCC criteria were not similar to that based on our criteria, although no significant differences were noted between the two groups. However, our results suggested that the survival rate was significantly related to T factor in multivariate analyses, when the clinical staging is classified according to either our criteria or AJCC criteria. The prior staging systems (1983 AJCC) were based on clinical information, and the system may remain an important prognostic indicator for patients managed with chemoradiation.

Literature search did not find other reports that recommended chemoradiotherapy for locally advanced carcinoma with severe stricture. In the present retrospective study, we investigated the efficacy and feasibility of concurrent chemoradiotherapy for patients with severe dysphagia caused by advanced oesophageal squamous cell carcinomas of T3 or T4 and M1 LYM disease. Our results, especially with regard to long-term survival, allow us to suggest that definitive chemoradiotherapy is potentially curative for locally advanced oesophageal carcinoma defined by clinical imaging. Thus, proper clinical staging before treatment is

important in patients with dysphagia caused by oesophageal carcinoma, since the efficacy of such treatment correlates with the T factor. Treatment-related fatal complications can occur in patients with T4 disease; however, toxicities including late radiation-related complications were manageable. Further investigation of the combined treatment modality as a curative approach is required particularly for cases with locally advanced oesophageal carcinoma with T4 disease.

ACKNOWLEDGEMENT

This work was supported in part by the Grant-in-Aid for Cancer Research (14 - 3) from the Ministry of Health, Labour and Welfare.

REFERENCES

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

Bethge N, Knyrim K, Wagner HJ, Starck E, Pausch J, Kleist DV (1992) Self-expanding metal stents for palliation of malignant esophageal obstruction: a pilot study of eight patients. *Endoscopy* 24: 411 - 415

Burmeister BH, Denham JW, O'Brien M, Jamieson G, Gill G, Devitt P, Yeoh E, Hamilton CS, Ackland SP, Lamb DS, Spry NA, Joseph DJ, Atokinson C, Walker QJ (1995) Combined modality therapy for esophageal carcinoma: Preliminary results from a large Australian multicenter study. *Int J Radiat Oncol Biol Phys* 32: 997 - 1006

Byfield JE (1990) Combined modality infusional chemotherapy with radiation. In: *Cancer Chemotherapy by Infusion*, Lokich JJ (ed) 2nd edn, pp 521 - 551. Chicago, IL: Percepta Press

Coia LR (1994) Chemoradiation as primary management of esophageal cancer. *Semin Oncol* 21: 483 - 492

Coia LR, Engstrom PF, Paul AR, Stafford PM, Hanks GE (1991) Long-term results of infusional 5-FU, mitomycin-C, and radiation as primary management of esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 20: 29 - 36

Curtin HD, Ishwaran H, Mancuso AA, Dalley RW, Caudry DJ, McNeil BJ (1998) Comparison of CT and MR imaging in staging of neck metastasis. *Radiology* 207: 123 - 130

Douple EB, Richmond RC (1980) A review interactions between platinum coordination complexes and ionizing radiation: implications for cancer therapy. In *Cisplatin: Current Status and New Developments*, Prestayko AW, Crooke ST, Karter SK (eds) pp 125 - 147. Orland, FL: Academic Press

Fleischer DE, Bull-Henry K (1992) A new coated self-expanding metal stent for malignant esophageal strictures. *Gastrointest Endosc* 38: 494 - 496

Frorastiere AA, Orringer MB, Petez-Tamayo C, Urba SG, Zahurak M (1993) Preoperative chemoradiation followed by transhiatal esophagectomy for carcinoma of the esophagus: final report. *J Clin Oncol* 11: 1118 - 1123

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

Japanese Research Society for Esophageal Diseases (1997) *The Report of Treatment Results of Esophageal Carcinoma in Japan*. Tokyo: National Cancer Centre

Japanese Society for Esophageal Disease (1992) *Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus*, 8th edn. Tokyo: Kanehara Shuppan

Kaneko K, Ito H, Konishi K, Kurahashi T, Katagiri A, Katayose K, Kitahara T, Ohtsu A, Mitamura K (2002) Implantation of self-expanding metallic stent for patients with malignant stricture after failure of definitive chemoradiotherapy for T3 or T4 esophageal squamous cell carcinomas. *Hepato-Gastroenterol* 49: 699 - 705

Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53: 457 - 481

Kozarek RA, Ball TJ, Patterson DJ (1992) Metallic self-expanding stent application in the upper gastrointestinal tract: caveats and concerns. *Gastrointest Endosc* 38: 1 - 6

Knyrim K, Wagner HJ, Bethge N, Keymling M, Vakil N (1993) A controlled trial of an expansible metal stent for palliation of esophageal obstruction due to inoperable cancer. *N Engl J Med* 329: 1302 - 1307

Leichman L, Herskovic A, Leichman CG, Lattin PB, Steiger Z, Tapoxoglu E, Rosenberg JC, Arbulu A, Asfaw I, Kinzie J (1987) Nonoperative therapy for squamous-cell cancer of the esophagus. *J Clin Oncol* 5: 365 - 370

Leichman L, Steiger Z, Seydel HG, Dinddogru A, Kinzie J, Toben S, MacKenzie G, Shell J (1984) Preoperative chemotherapy and radiation therapy for patients with cancer of the esophagus: a potentially curative approach. *J Clin Oncol* 2: 75 - 79

May A, Selmaier M, Hochberger J, Gossner L, Mühldorfer S, Hahn EG, Ell C (1995) Memory metal stents for palliation of malignant obstruction of the oesophagus and cardia. *Gut* 37: 309 - 313

Mellow MH, Pinkas H (1985) Endoscopic laser therapy for malignancies affecting the esophagus and gastroesophageal junction: analysis of technical and functional efficacy. *Arch Intern Med* 145: 1443 - 1446

Ohtsu A, Boku N, Muro K, Chin K, Muto M, Yoshida S, Satake M, Ishikura S, Ogino T, Miyata Y, Seki S, Kaneko K, Nakamura A (1999) Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. *J Clin Oncol* 17: 2915 - 2921

Picus D, Balfe DM, Koeler RE, Roper CL, Owen JW (1983) Computed tomography in the staging of esophageal carcinoma. *Radiology* 146: 433 - 438

Poplin E, Fleming T, Leichman L, Seydel HG, Steiger Z, Taylor S, Vance R, Stuckey WJ, Rivkin S (1987) Combined therapies for squamous-cell carcinoma of the esophagus, a Southwest Oncology Group Study (SWOG-8037). *J Clin Oncol* 5: 622 - 628

Poplin EA, Khanuja PS, Kraut MJ, Hersskovic AM, Lattin PB, Cummings G, Gasper LE, Kinzie JL, Steiger Z, Vaitkevicous VK (1994) Chemoradiotherapy of esophageal carcinoma. *Cancer* 74: 1217 - 1224

Roussel A, Cheze S, Jacob JH, Ollivier JM, Macé-Lescc'h J, Henry-Amar M. (1995) Radiation therapy in esophageal carcinoma with broncho-tracheal involvement (BTI): The Center Francois Baclesse (CFB) experience (Abstract). *Proc Am Soc Clin Oncol* 14: 190a

Scanlon KJ, Newman YL, Priest DG (1986) Biochemical basis for cisplatin and 5-fluorouracil synergism in human ovarian carcinoma cells. *Proc Natl Acad Sci USA* 83: 8923 - 8925

Schaer J, Katon RM, Ivancev K, Uchida B, Rosch Y, Binmoeller R (1992) Treatment of malignant esophageal obstruction with silicone-coated metallic self-expanding stents. *Gastrointest Endosc* 38: 7 - 11

Song HY, Choi KC, Cho BH, Ahn DS, Kim KS (1991) Esophagogastric neoplasms: palliation with a modified Gianturco stent. *Radiology* 180: 349 - 354

Takashima S, Takeuchi N, Shiozaki H, Kobayashi K, Morimoto S, Ikezoe J, Tomiyama N, Harada K, Shogen K, Kozuka T (1991) Carcinoma of the esophagus: CT *vs* MR imaging in determining resectability. *Am J Roentgenol* 156: 297 - 302

Wengrower D, Fiorni A, Valero J, Waldbaum C, Chopita N, Landoni N, Judchack S, Goldin E (1998) EsophaCoil: long-term results in 81 patients. *Gastrointest Endosc* 48: 376 - 382

Zeone T, Romestaing P, Lambert R, Gerard JP (1992) Curative non-surgical combined treatment of squamous cell carcinoma of the oesophagus. *Eur J Cancer* 28A: 1380 - 1386