TABLE 2. Clinical outcome after salvage PDT

Patient	Total light dose (J)	Best response for PDT	Time to confirm CR (mo)	Recurrence after PDT (site)	Treatment to persistent or recurrent tumor	Major complications	Outcome	Tumor status	Survival from PDT (mo)
1	600	CR	1	No	—	—	Alive	Disease free	19
2	1000	CR	4	Yes (primary)	PDT	—	Dead	With disease	14
3	840	Non-CR	—	—	Palliation	Fistula	Dead	With disease	3
4	750	CR	3	No	—	Stenosis	Alive	Disease free	15
5	750	Non-CR	—	—	Palliation	Mediastinitis	Dead	With disease	8
6	450	CR	3	No	—	Increase of PE	Alive	Disease free	15
7	900	CR	2	Yes (primary)	PDT	—	Dead	With disease	5
8	525	Non-CR	—	Yes (brain)	PDT	—	Dead	With disease	6
9	300	CR	2	No	—	—	Alive	Disease free	13
10	450	CR	2	No	—	—	Alive	Disease free	11
11	825	Non-CR	—	Yes (primary)	PDT	Stenosis	Alive	With disease	6
12	900	Non-CR	—	Yes (primary)	PDT	—	Alive	With disease	9
13	625	CR	3	No	—	Stenosis, phototoxicity	Alive	Disease free	8

PDT, Photodynamic therapy; *CR*, complete response; *NON-CR*, non-complete response; *PE*, pericardial effusion.

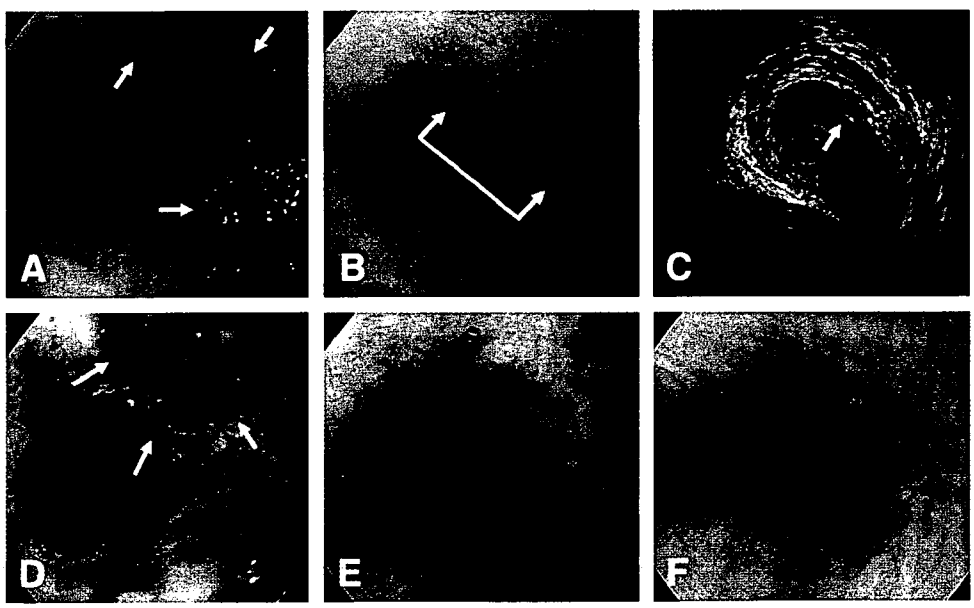

Figure 1. Endoscopic pictures of the patient with esophageal cancer. Baseline clinical stage was assessed as cT2N0M0. **A,** Depressed tumor with surrounding mound *(arrows)* is seen before definitive CRT. **B,** After completion of CRT, a submucosal tumor-like elevation *(arrows)* was persistent at the primary site, and residual cancer was confirmed by biopsy specimen. **C,** EUS image showed a hypoechoic lesion both in the mucosal and submucosal layer *(arrow)*; then, the depth of the residual tumor was assessed as uT1. **D,** At the primary site, tumor necrosis can be recognized by ischemic changes in color *(arrows)*; ulcerative change also can be seen in the background mucosa at 3 days after salvage PDT. **E,** Primary site still shows deep ulceration at 1 month after salvage PDT; however, no cancerous tissue was found by biopsy specimen. **F,** Primary site showed a scar of ulceration at 3 months after salvage PDT; no residual cancer could be found in the biopsy specimen.

comparable survival results to esophagectomy. However, the long-term follow-up results of the prospective randomized trial (Radiation Therapy Oncology Group 85-01) showed that persistence of disease and locoregional failure after definitive CRT were 25% and 13%, respectively.[13] In our previous report, local failure occurred in 34% (18/53)

of the patients treated with definitive CRT.[14] Therefore, improvement of local control is one of the major factors in producing better survival for patients who are treated with definitive CRT.

In our case series, 8 of 13 patients (62%) achieved CR by salvage PDT. Furthermore, the overall survival rate after salvage PDT at 1 year was 68.4%, whereas our previous report showed that overall survival data for patients with non-CR at 3 years was 6%.[2] While, all tumors were assessed as having massive invasion to the submucosal layer or invasion to the muscularis propria layer in this study, salvage PDT showed a relatively high CR rate and excellent short-term survival. These results indicate that carefully selected patients might have a chance of cure by salvage PDT even though they had persistent or recurrent tumor after definitive CRT.

We also previously reported that the overall survival rate of the patients treated by salvage EMR for locoregional failure after definitive CRT was 56% at 3 years.[5] These results might suggest that local treatment by endoscopic modalities such as EMR and PDT could be a treatment option for selected patients.

From a technical point of view, PDT seems to be superior to EMR. If the persistent or the recurrent lesion has an ulceration or severe fibrosis or stenosis, salvage EMR is quite difficult or impossible to perform. If the depth of the residual tumor is limited within the submucosal layer, salvage EMR is relatively difficult and has a risk of being incomplete. Even in such cases, salvage PDT could be indicated in addition to the primary treatment.

Generally, most locoregional failures after definitive CRT are detected at an advanced stage. Endoscopic treatment may not be indicated in such cases because it lacks curative potential. To date, surgical resection is considered to be the only curative treatment in these cases. However, Swisher et al[3] reported that the patients treated by salvage esophagectomy had a significantly higher incidence of anastomotic leaks (39% vs. 7%) and a longer hospital stay (29 days vs. 18 days) than those treated with planned esophagectomy. To treat malignant neoplasms, early detection is very important to cure the patient. Indeed, in our experience, all of the uT1 cases achieved CR. To detect the locoregional failure at earlier stage, the appropriate follow-up schedule after definitive CRT needs to be clarified.

As for the complications of salvage PDT, most of them were manageable with medical treatments. However, one patient developed an esophagotracheal fistula. It is unknown whether the fistula was PDT related or because of the natural progression of disease. Because the tumor in this case was non-CR, we could not deny the possibility of the latter. An esophagotracheal fistula could develop by PDT even for naïve early esophageal cancer cases, and an incidence of 6.5% has been previously reported.[7] Sanfilippo et al[15] reported two patients with esophageal cancer who had developed a fistula after PDT. One received prior external beam irradiation, and the other had intraluminal brachytherapy.[15] Similarly, the reason for mediastinitis or the increase in pericardial effusion occurring after salvage PDT is unknown. One possibility is that radiation-induced esophageal damage and heart disease,[16,17] are potentiated by PDT and that structural damage occurs by transmural necrosis. Nevertheless, it is important to elucidate their mechanism to prevent the potential complications of PDT.

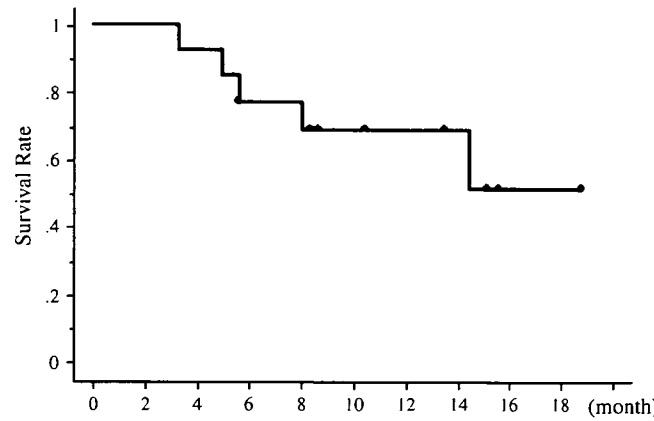

Figure 2. Overall survival of all patients from initiation of salvage PDT.

We have shown the acceptable short-term safety and worthwhile curative properties of salvage PDT when applied to the local failures after definitive CRT. Although further long-term follow-up studies will be required, salvage PDT represents a potentially new and promising treatment option. Large studies will be necessary to define the population of patients who are most likely to benefit from this treatment. Furthermore, we should confirm the efficacy of PDT as a salvage treatment for local failure after definitive CRT.

REFERENCES

1. Herskovic A, Martz K, Al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 1992;326:1593-8.
2. Ishikura S, Nihei K, Ohtsu A, Boku N, Hironaka S, Mera K, et al. Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol 2002;21: 2697-702.
3. Swisher SG, Wynn P, Putnam JB, Mosheim MB, Correa AM, Komaki RR, et al. Salvage esophagectomy for recurrent tumors after definitive chemotherapy and radiotherapy. J Thorac Cardiovasc Surg 2002;123: 173-83.
4. Urschel JD, Ashiku S, Thurer R, Sellke FW. Salvage or planned esophagectomy after chemoradiation therapy for locally advanced esophageal cancer: a review. Dis Esophagus 2003;16:60-5.
5. Hattori S, Muto M, Ohtsu A, Boku N, Manabe T, Doi T, et al. EMR as salvage treatment for patients with locoregional failure of definitive chemoradiotherapy for esophageal cancer. Gastrointest Endosc 2003; 58:65-70.

6. Sibille A, Lambert R, Souquet JC, Sabben G, Descos F. Long-term survival after photodynamic therapy for esophageal cancer. Gastroenterology 1995;108:337-44.
7. Savary JF, Grosjean P, Monnier P, Fontolliet C, Wagnieres G, Braichotte D, et al. Photodynamic therapy of early squamous cell carcinoma of the esophagus: a review of 31 cases. Endoscopy 1998;30:258-65.
8. Manyak MJ, Russo A, Smith PD, Glatstein E. Photodynamic therapy. J Clin Oncol 1988;6:380-91.
9. Pass HI. Photodynamic therapy in oncology: mechanism and clinical use. J Natl Cancer Inst 1993;85:443-56.
10. Dolmans DEJGJ, Fukumura D, Jain RK. Photodynamic therapy for cancer. Nat Rev Cancer 2003;3:380-7.
11. UICC (International Union Against Cancer). TNM classification of malignant tumors. 5th ed. New York: Wiley-Liss; 1997.
12. Ishikura S, Ohtsu A, Shirao K, Muro K, Kagami Y, Nihei K, et al. A phase I/II study of nedaplatin and 5-fluorouracil with concurrent radiotherapy in patients with T4 esophageal cancer: Japan Clinical Oncology Group study (JCOG9908-DI) [abstract]. Proc Am Soc Clin Oncol 2003; 22:276.
13. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA, Al-Sarraf, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG85-01). JAMA 1999;281:1623-7.
14. Hironaka S, Ohtsu A, Boku N, Muto M, Nagashima F, Saito H, et al. Nonrandomized comparison between definitive chemoradiotherapy and radical surgery in patients with $T_{2-3}N_{any}M_0$ squamous cell carcinoma of the esophagus. Int J Radiat Oncol Biol Phys 2003;57: 425-33.
15. Sanfilippo NJ, Hsi A, Denittis AS, Ginsberg GG, Kochman ML, Friedberg JS, et al. Toxicity of photodynamic therapy after combined external beam radiotherapy and intraluminal brachytherapy for carcinoma of the upper aerodigestive tract. Lasers Surg Med 2001;28:278-81.
16. Stewart JR, Fajardo LF, Gillette SM, Constine LS. Radiation injury to the heart. Int J Radiat Oncol Biol Phys 1995;31:1205-11.
17. Veinot JP, Edwards WD. Pathology of radiation-induced heart disease: a surgical and autopsy study of 27 cases. Hum Pathol 1996; 27:766-73.

Received September 18, 2004. Accepted March 8, 2005.

Current affiliations: Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan.

Reprint requests: Manabu Muto, MD, Division of Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital, 6-5-1, Kashiwanoha, Kashiwa, 277-8577 Japan.

By the Numbers

All of the previously published biostatistical articles are now available in a grouped format through a link, *By the Numbers,* under *Features* at www.mosby.com/gie.

● 原 著 ●

根治切除不能進行食道癌に対するNedaplatin/Adriamycin/5-FU (NAF) 併用療法のPhase I Study

平尾 素宏 藤谷 和正 辻仲 利政*

〔*Jpn J Cancer Chemother* 32(1): 53-56, *January*, 2005〕

Phase I Study of the Combination of Nedaplatin (NED), Adriamycin (ADM), and 5-Fluorouracil (5-FU) (NAF) for Treatment of Unresectable Advanced Esophageal Cancer: Motohiro Hirao, Kazumasa Fujitani, Toshimasa Tsujinaka (*Dept. of Surgery, Osaka National Hospital*)

Summary

Background: Esophageal cancer has a poor prognosis. Several strategies including chemotherapy (CDDP+5-FU), either alone or with radiotherapy, have been used to improve the prognosis. However, since CDDP itself has substantial toxicities, including renal and gastrointestinal toxicities, newer platinum analogues, such as nedaplatin (NED) have been developed, and it is of interest to test this new platinum analogue in a combination chemotherapy. Methods: We conducted a phase I-II study using a combination of NED (3 levels, 60-80 mg/m² on day 1), ADM (30 mg/m² on day 1), and 5-FU (700 mg/m² on day 1-5) for treatment of previously untreated advanced esophageal squamous cell carcinoma. Cycles were repeated every 28 days. The objectives were to determine dose-limiting toxicity (DLT), maximum-tolerated dose (MTD), recommended dose (RD) for a phase II study, and to determine antitumor effects. Results: Phase I: 12 patients (pts) (male/female=11/1) were evaluable. The median age was 65 (range 46-74), PS 0/1=7/5. At level 1, 1 pt developed DLT (grade 4, neutropenia). At level 2, 2 pts developed DLT (grade 4 neutropenia and grade 3 diarrhea). Level 2 (70 mg/m²) was determined as the MTD, and a level 1 dose (60 mg/m²) was recommended. Phase II: 7 pts (male/female=4/3) are at RD of level 1 at the present time. Median age 62 (range 46-75). The median number of cycles on phase II study at RD was 2 (range 1-3). 4 PRs were obtained. The response rate was 57.1%. Median survival time (MST) was not reached at the time. Conclusions: This combination therapy appears to be highly effective and generally well tolerated for advanced esophageal cancer. Key words: Nedaplatin, Esophageal cancer, Phase I-II (*Received May 1, 2004/ Accepted Jul. 7, 2004*)

要旨 今回われわれは，NED/ADM/5-FU併用療法(NAF療法)に着目し，予後不良な切除不能食道癌に対するfirst-lineとして，この併用化学療法の安全性および有効性の検討を計画した。key drugであるNEDを増量していき，step 2: 70 mg/m²で2例のdose limiting toxicity (DLT) (grade 4血液毒性とgrade 3非血液毒性)が出現したためstep 2を最大耐用量，step 1の60 mg/m²をNEDの推奨投与量とした。grade 1の悪心・嘔吐が最も多い非血液毒性であり，grade 1の腎毒性はstep 2で1例経験したが，すべて保存的に軽快した。また，step 1でのgrade 4好中球減少のDLT症例のみG-CSFを使用した。以上の第I相試験で明らかとなったNED 60 mg/m²，ADM 30 mg/m² day 1，5-FU 700 mg/m²/日 day 1～5の持続点滴静注を推奨投与とした現在までの第II相での奏効率は57.1%と良好な結果が得られており，安全かつ有効なregimenとして十分期待できる。

はじめに

今回われわれは，予後不良な進行食道癌患者を対象としてnedaplatin (NED)，adriamycin (ADM)，および5-fluorouracil (5-FU)とのNAF併用療法(NAF療法)の安全性および有効性の検討を目的にこの研究を行った[1,2]。臨床第I相として[2]，first-line NAF療法の安全性を検討し，NEDをkey drugとした本療法の推奨用量，用法の結果を報告する。また，現在進行中の第II相として，第I相で決定された推奨用量，用法における有効性

連絡先: 〒540-0006 大阪市中央区法円坂2-1-14 * 独立行政法人国立病院機構大阪医療センター・外科
平尾 素宏

0385-0684/05/¥500/論文/JCLS

および安全性を評価し，本併用療法の feasibility を明らかにする。当研究は当センターIRBにて承認され，患者には十分なインフォームド・コンセントを得てから行っている。以下の記載は，食道癌取扱い規約第9版に準じる。

I. 対　象

2003年1月から2004年3月までの期間，当院消化器科および外科を受診した前治療歴のない根治切除不能進行食道扁平上皮癌。根治切除不能進行食道癌とは，T4もしくはT4疑い，N4，M1，または腹部または頸部の2領域以上に及ぶ明らかなリンパ節転移が認められる症例。評価測定可能病変を有し，年齢は20歳以上75歳以下，performance status (PS): 0～1 (ECOG分類)，十分な心，骨髄，腎，肝機能を有し，重複癌のない患者を対象に施行。なお，選択基準や除外基準の詳細の記述は省略する[2]。

食道癌に対する補助化学療法としてのFAP (5-FU/ADM/CDDP) 併用療法の投与量はそれぞれ50 mg/body，100 mg/body，1,000 mg/body (day 1～5または7持続) と報告されている[3]。今回，NEDの投与量はNED単剤での至適投与量が100 mg/m²であることを考慮し，60 mg/m²を第一投与量とした。ADM，5-FUの投与量はそれぞれ30 mg/m² (day 1)，700 mg/m² (day 1～5持続) とし1日量はほぼ同量としたが，5-FUは5日間の持続投与とし，総投与量として減量した。この理由としてNEDはcisplatin (CDDP) より骨髄障害が強いため，5-FUの総投与量を減らすと同時に，患者のQOLを考えたためである。

II. 方　法

ADM 30 mg/m² day 1，5-FU 700 mg/m²/日 day 1～5の持続点滴静注で4週ごとに投与し，key drugであるNEDの投与量は以下に従い増量する。step 1: 60 mg/m²，step 2: 70 mg/m²，step 3: 80 mg/m²。step 1より試験を開始し，各stepのコースでのdose limiting toxicity (DLT) の発現頻度を評価し，以下に示した基準で投与量stepを移行する。1）同一投与量stepの3例にDLTが認められない場合は，次のstepに移行。2）3例中1例にDLTが認められた場合は3例追加し6例とする。①追加後の3例にDLTが認められない場合には，次のstepに移行する。②追加後の3例中1例にDLTが認められた場合は，その投与量stepを最大耐用量(MTD)とする)。MTDが判明したのち，MTDより1段階低い投与量stepをRD（推奨投与量）とする。またDLT基準は以下のとおりである。①grade 4の白血球減少または好中球減少が出現，②38°C以上の発熱を伴うgrade 3の好中球減少が出現，③25,000/mm³未満の血小板減少，④悪心・嘔吐，食欲不振，疲労および脱毛を除く，grade 3以上の非血液毒性が出現した場合。中止基準を満たさない限り2コース以上行い，前コースでの発現副作用により減量基準も設けた[2]（詳細省略）。

Table 1　Patient characteristics on phase I study

Total number of patients (step 1/step 2)	12 (6/6)
Sex (M/F)	11/1
Age (years)	65 (46-74)
Stage (III/IV a/IV b)	4/3/5
Performance status (0/1)	7/5

第II相として，第I相で決定された推奨用量，用法における有効性を評価するためSimonのminimax designに従い，期待奏効率を50%，閾値率を30%として ($\alpha=0.05$, $\beta=0.20$)，目標必要症例数を40例に設定した。評価病変に対する臨床的治療効果（腫瘍縮小効果）および奏効度の表現はWHO criteriaに従った。

III. 結　果

第1相は男性11例，女性1例の計12例（平均年齢65歳，46～74歳）が登録(Table 1)。進行度とPSもTable 1を参照されたい。各step 6例ずつでstep 2まで増量。step 1で1例のDLT (grade 4の好中球減少)，step 2で2例のDLT（grade 4の好中球減少とgrade 3の下痢）出現のためstep 2をMTD，step 1の60 mg/m²をNEDの推奨投与量とした（Table 2)。好中球減少のnadirは投与第1日目から9～22日（中央値17日）で，回復に3～4日を要した。grade 1の悪心・嘔吐が最も多い非血液毒性であり，grade 1の腎毒性はstep 2で1例経験したが，すべて保存的に軽快した。また，step 1でのgrade 4好中球減少のDLT症例のみG-CSFを使用した。また，進行中の第II相では，NEDの推奨用量をstep 1の60 mg/m²とし，現在のところ7例（男性4例，女性3例）（平均年齢62歳，46～74歳）を登録。施行コース数中央値は2（1～3）で，PR 4例，NC 3例であり，現在までの奏効率は57.1%であった（Table 3)。生存期間も追跡中である。

IV. 考　察

近年，手術手技の向上，術後管理の進歩，早期癌症例発見の増加などの理由で食道癌全体の治療成績は以前より改善したが，高度進行食道癌や再発食道癌は依然とし

Table 2 Hematologic and nonhematologic toxicities by dose level in the first cycle on phase I

Dose step	No. of patients	Neutropenia				Thrombocytopenia				Anemia				Nausea/vomiting				Diarrhea				Elevation of creatinine				Elevation of transaminase			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
1	6	1	1	2	1	0	0	1	0	3	2	1	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	6	2	1	1	1	0	0	0	0	4	1	0	0	3	0	0	0	1	0	1	0	1	0	0	0	0	0	0	0

Table 3 Phase II study on going

Pt #	Gender	Age	TNM	Stage	No. of courses	Response	Evaluable sites
1	F	70	T 4	IV a	2	PR	Main tumor
2	M	54	H 1	IV b	2	PR	Liver
3	M	46	M 1 (brain)	IV b	3	NC	Brain
4	M	74	T 4	IV a	2	NC	Main tumor
5	F	68	T 4, M 1 (lung)	IV b	2	PR	Main tumor, Lung
6	M	60	H 1	IV b	2	NC	Liver
7	F	61	T 4	IV a	1	PR	Main tumor

て予後不良である。1980年代以降の高度進行食道癌や再発食道癌に対する化学療法成績をみると，単剤での奏効率は2～4剤の併用療法よりも低いことは判明している。当初，胃癌に対する効果からADMと5-FUとの併用が期待されたが，1984年のCDDP登場以来，それをkey drugとした多剤併用療法が中心となり効果をあげてきた[4]。1987年以後食道癌の標準併用化学療法となった5-FU/CDDP（FP）は，1992年Japanese Esophageal Oncology Group（JEOG）で行った進行食道癌を対象にしたFP療法の第II相臨床試験にてもその効果が認められ，わが国においても現在標準治療となっている[5]。同時にADMとCDDPの併用効果についても報告されるようになり，ADM，5-FUにCDDPを加えた3剤併用のいわゆるFAP療法の比較的良好な成績が報告されている[3]。しかし，key drugであるCDDPの腎毒性や消化器毒性などの副作用が強いため，QOLの改善が望まれている。

NEDはわが国で開発されたプラチナ誘導体であり，単剤で行われた第II相臨床試験でCDDP同様幅広い抗腫瘍スペクトルを有していることが示され，特に扁平上皮癌（頭頸部癌[6]，食道癌[7]，子宮頸癌[8]）に対する有効性が高いと評価された。また，CDDPに比較し，腎毒性が少なく，消化器障害の程度も低く，患者のQOL向上が期待できる。一方，NEDのDLTは骨髄抑制（白血球減少，血小板減少）であり，MTDは120 mg/m²であった。NED単剤での第II相臨床試験における食道癌に対する奏効率が51.7%（15例/29例）得られている。さらに，NED/5-FU併用療法が基礎的検討からも併用効果が証明されて以来[9]，NED/5-FU併用療法の良好な報告がされている[10]。食道癌と同様にFP療法が標準療法とされる頭頸部癌における報告[11]では，NED+5-FUはCDDP+5-FUと比較して奏効率はほぼ同等で血小板減少の頻度は高いが，腎毒性，悪心・嘔吐の消化器毒性が低いと報告されている。

また，ADMを加えたFAP/N療法の清水らの報告では，高度進行食道癌（高度リンパ節転移およびT4）に対し，抗腫瘍効果50%（FP療法5.9%）で，手術切除率92%（FP療法47%），根治率73%（FP療法25%）と，かなり良好な成績が得られ，毒性ではgrade 2～3の白血球減少と口内炎を認めたが腎毒性や消化器毒性はなく，いずれも保存的に対処可能であったとされている[12]。

taxane系を加えたnew regimenもでているなか[13]，食道癌の標準的治療として現実にはFP療法が行われており，欧米では40～60%の奏効率が報告されている[14,15]が，JEOGにおけるstudyでは奏効率33%（CR 1例+PR 11例/36例）であり，予想を下回る結果であった。以上より，今回われわれは，NED/ADM/5-FU併用療法（NAF療法）に着目し，切除不能進行食道癌に対するfirst-lineとして，この併用化学療法の安全性および有効性の検討を計画した。

NED 60 mg/m²，ADM 30 mg/m² day 1，5-FU 700 mg/m²/日 day 1～5の持続点滴静注を推奨投与法とした，現在までの第II相試験での奏効率は57.1%であり良好な結果が得られた。grade 4の血液毒性がみられたが，保存的に十分対応可能であり，CDDPにみられるような消化器，腎毒性はほとんどなかった。奏効度，安全性およびQOLの面からも期待できるregimenと思われる。治療後予後または生存期間はまだ解析中であるが，今後

症例を登録追加し，さらなる検討を進めたい。

文　献

1) Hirao M, Tsujinaka T and Fujitani K: Phase I-II study of the combination of nedaplatin (NED), adriamycin (ADM), and 5-fluorouracil (5-FU) for treatment of previously untreated advanced esophageal cancer. *Proc ASCO* **23**: 349, 2004.
2) Hirao M, Fujitani K and Tsujinaka T: Phase I study of the combination of nedaplatin, adriamycin, and 5-fluorouracil for treatment of previously untreated advanced esophageal cancer. *Dis Esophagus* **17**(3): 247-250, 2004.
3) 甲　利幸，安田卓司，古河　洋・他: 食道癌の化学療法. 消化器科　**25**(2): 148-153, 1997.
4) 栗原　稔: 食道癌化学療法の現況. 消化器癌　**2**(1): 57-62, 1992.
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* **22**(3): 172-176, 1992.
6) 犬山征夫，三宅浩郷，堀内正敏・他: 頭頸部癌に対する新白金錯体254-Sの後期第II相臨床試験. 癌と化学療法　**19**(6): 871-877, 1992.
7) 田口鐵男，涌井　昭，鍋谷欣市・他: 254-Sの消化器癌に対する第II相臨床試験. 癌と化学療法　**19**(4): 483-488, 1992.
8) 加藤　俊，西村治夫，薬師寺道明・他: 婦人科癌に対する254-Sの臨床第II相試験. 癌と化学療法　**19**(5): 695-703, 1992.
9) Takeda Y, Kasai H, Uchida N, *et al*: Enhanced antitumor efficacy of nedaplatin with 5-fluorouracil against human squamous carcinoma xenografts. *Anticancer Res* **19**: 4059-4064, 1999.
10) 石橋　悟，標葉隆三郎，宮崎修吉・他: 高度進行・再発食道癌に対するNedaplatin/5-FU併用療法の効果--Cisplatin/5-FU併用療法と比較して. 日消外会誌　**34**(8): 1269-1276, 2001.
11) Fujii M, Ohno Y, Tokumaru Y, *et al*: Comparison of nedaplatin plus 5-FU versus CDDP plus 5-FU for head and neck squamous cell carcinoma. *Proc ASCO* **18**: 405 a, 1999.
12) 清水孝王，西巻　正，小杉伸一・他: 高度進行食道癌に対する術前FAP/N(5-FU+ADM+CDDP/Nedaplatin)療法の効果. 日癌治療会誌　**36**(2): 761, 2001.
13) Ajani JA: Docetaxel for gastric and esophageal carcinomas. *Oncology* **16**(6): 89-96, 2002.
14) Kies MS, Rosen ST, Tsang T, *et al*: Cisplatin and 5-FU in the primary management of squamous esophageal cancer. *Cancer* **60**: 2156-2160, 1987.
15) Bleiberg H, Jacob JH, Bedenne L, *et al*: Randomized phase II trial of 5-FU and CDDP versus CDDP alone in advanced oesophageal cancer. *Proc ASCO* **10**: 447, 1991.

日常診療の指針

進行食道癌治療への挑戦

Tactics for advanced esophageal cancer

松原 久裕 落合 武徳*
MATSUBARA Hisahiro *OCHIAI Takenori*

はじめに

食道癌は予後不良の癌の1つであったが，頸部リンパ節郭清を含めた3領域リンパ節郭清を伴う胸部食道切除術が安全に行われるようになり，予後の向上を認めた．手術施行例における詳細なリンパ節転移の検討から頸部リンパ節転移の頻度は少なくなく，主占居部位がLtで深達度sm症例を除き，頸部リンパ節郭清がR2手術をさけるためには必要であることが判明してきた．一方，内視鏡的粘膜切除術(EMR)により早期食道癌の治療は侵襲も少なく，予後も良好であり満足すべき治療結果が得られている．このため術前診断はきわめて重要となり，壁深達度LPMまではEMRの絶対適応としてコンセンサスが得られている．

近年，切除範囲が広くても一括切除可能なESDも行われるようになってきており，分割切除のEMRに比し局所再発が減少するとの報告が多い．壁深達度に関してはさらに，MM-SM1まで適応拡大している施設も増加してきている．SM2以深の癌は前述のLt，SMを除き3領域リンパ節郭清の対象となる．MM-SM1については今後の解析を待つ必要があるが，少なくともSM2以深の癌は治療法がきわめて異なり，進行食道癌の範疇に含まれると判断する．取扱い規約(第9版)による早期食道癌の定義は原発巣が粘膜層にとどまりリンパ節転移を認めない症例と規定されている．

1．進行食道癌の治療

UICCのTNM分類に従うと，頸部リンパ節転移はすべてM1(LYM)となる．当科の解析では主占居部位がUtで47.1%，Mt 31.1%，Lt 19.8%とそれぞれの縦隔内リンパ節転移が43.5，50.6，41.3%であることを考慮すると，頸部リンパ節転移をすべてM1と規定するにはその転移頻度があまりにも高率である．さらに頸部リンパ節郭清を行うことにより，R2の手術とならず良好な予後が期待できる．今後，術前診断の進歩により頸部郭清を省略できる症例は期待できるが，現状ではリンパ節転移診断には限界があり，積極的に行うべきだと考えている．当科の検討や，梶山らの検討においても多くのリンパ節転移は1 cm以下のリンパ節に認められ，その診断は今後の重要な検討課題である．

化学放射線治療はその進歩により，多くの症例に行われるようになった．治療が長期間となり，有害事象も少なくなく，放射線肺臓炎，胸水，心嚢炎など晩期合併症を考慮する必要もあり，侵襲については決して少なくないが，臓器温存の面から治療後のQOLに関しては有利な治療法である．SM癌に対して多施設による手術との第III相臨床試験が計画されているが，あまりにもmodalityが違う治療のため参加する被験者が少ないとの予測が懸念されている．

98年から当科では統合化した低侵襲化手術を行っている．皮膚を縦切し広背筋温存開胸，後縦隔経路再建，メチルプレドニゾロンの使用(Day 0：250 mg，Day 1，2：125 mg i.v.)により手術死亡は認めておらず，9割以上の症例で当日抜管，術後在院日数は中央値18日である．後述の高度進行食道

千葉大学大学院医学研究院先端応用外科学教室 講師 *教授
Key words：進行食道癌／集学的治療／術前化学放射線治療／遺伝子治療／重粒子線治療

0433-2644/05/¥50/頁/JCLS

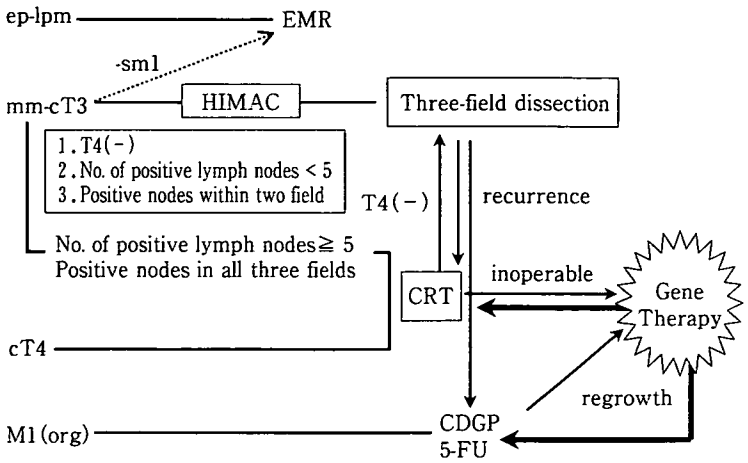

図1 Strategy for Esophageal Cancer

癌を除いた術前未治療症例の5年生存率は68.1%であり，組織学的進行度ではStage II以上が68.8%を占めていることを考慮すると良好な成績である．放射線化学療法が6週間要することと比較しても，術前未治療手術治療は治療を受ける側にとっても有用な治療法であると考えられる．

短期死亡症例の解析ではR2の1例を除きリンパ節転移が5個以上の症例であり，そのほとんどは腹部リンパ節転移の診断が不十分な症例であった．術前診断の進歩が今後さらなる予後の改善に必要である．

2．高度進行食道癌の治療

当科では1983年から3領域郭清を施行してきたが，術式は安定し安全に手術可能となった．予後不良症例について解析したところ，頸部・胸部・腹部の3領域すべてにリンパ節転移を認めた症例，リンパ節転移を5個以上認めた症例，T4症例の3群は3領域リンパ節郭清を施行しても有意に予後不良であった．当科では98年からこれらの3群を高度進行食道癌として術前化学放射線治療を施行した後，3領域リンパ節郭清を伴う食道切除を行っている．術前治療の侵襲を考慮し，手術は放射線照射終了後3週間の間隔をあけている．手術死亡は認めておらず，術後合併症については呼吸器合併症がやや多かったが有意差を認めず，安全に施行可能であった．

従来15%未満であった予後不良群の5生率が42.5%まで改善された．T4症例についてはR2手術の予後が非切除症例の予後と差がないことから実際の臨床上他臓器浸潤を否定できない症例に対しては積極的に化学放射線治療を施行し，T4が解除された症例については積極的に切除を行うことが望ましいと考えている．原発巣のみならずとくにリンパ節転移の残存の有無に関する術前診断は困難であり，癌が残存していないことの証明がきわめて難しい現時点の医療レベルでは，残存した癌に対する保存的な治療でのコントロールは難しいことを考慮し，根治照射後のサルベージ手術ではなく術前化学放射線治療後予定手術として積極的に手術をすることが望ましいと考えている．

再発症例に対し，切除，抗癌剤，放射線と施行可能な治療法をすべて考慮し，再発巣に応じ適切に選択して治療を積極的に行っている．また，当科では切除不能，他治療抵抗性進行食道癌に対する癌抑制遺伝子p53をアデノウイルスベクターを用いて局注する臨床試験を実施した．局所効果は著効例を認めなかったが多くの症例がSDであり，安全に施行可能であった．現在，最長3年5ヵ月生存中の症例も認めている．手技はきわめて容易であり，有害事象は従来の化学療法より少ないので，今後の発展が期待される結果であった．

また，放射線医学総合研究所の協力を得て，術前短期(2週間)重粒子線照射の第I/II相臨床試験を計画し，現在実施中である．今後の解析によりその有用性を検討したい．

Original Paper

Chemoradiotherapy With and Without Esophagectomy for Advanced Esophageal Cancer

Tsutomu Nakamura MD, Masaho Ota MD, Kazuhiko Hayashi MD, Reiki Eguchi MD
Hiroko Ide MD, Ken Takasaki MD, Norio Mitsuhashi MD[1]
Department of Surgery, Institute of Gastroenterology and [1]Department of Radiology
Tokyo Women's Medical University, Tokyo, Japan
Corresponding Author: Tsutomu Nakamura, MD, Department of Surgery
Institute of Gastroenterology, Tokyo Women's Medical University, 8-1, Kawada-cho, Shinjuku-ku
Tokyo, 162-8666, Japan
Tel: +81 3 3353 8111, Fax: +81 3 5269 7507, E-mail: tsutomu@ige.twmu.ac.jp

ABSTRACT

Background/Aims: To evaluate the impact of surgery on survival after chemoradiotherapy, we analyzed the long-term outcome of patients with advanced esophageal cancer.

Methodology: Data on 92 consecutive patients with T3 or T4 esophageal cancer who were initially treated by chemoradiotherapy were reviewed retrospectively. Of 82 patients who completed the planned schedule, 35 patients underwent esophagectomy (CRT+E Group) and 47 patients received definitive chemoradiotherapy (CRT Group).

Results: A response to chemoradiotherapy was obtained in 71% of all 92 patients. The 1- and 3-year survival rates in the patients with T3M0 were 87 and 44 percent respectively, while these in the patients with T4 and/or M1(Lymph) disease were 47 and 20 percent. Although there was no difference in overall survival between the CRT+E Group and the CRT Group, the survival of responders in the CRT+E Group was significantly higher than that of those in the CRT Group ($P=0.0448$). The locoregional recurrence rate of responders in the CRT Group was higher than that in the CRT+E Group. Multivariate analysis showed that the independent prognostic factors were response, M(Lymph), and esophagectomy.

Conclusions: Although this study was retrospective and nonrandomized, esophagectomy after chemoradiotherapy might improve the survival of responders for locoregional control.

KEY WORDS: Chemoradiotherapy; Squamous cell carcinoma; Esophagectomy; Combined modality

INTRODUCTION

Combined modality therapy, including chemotherapy, is necessary to treat advanced esophageal cancer, which can be widely disseminated at the time of diagnosis (1). Recent surgical results for advanced esophageal cancer have been improved by the use of three-field lymphadenectomy and by better postoperative management, but patients with residual tumor (R1-2) still do not survive for over 3 years after surgery (2). Combined modality therapy, consisting of chemoradiotherapy and surgery, has been developed for squamous cell carcinoma of the esophagus and has improved the outcome (3,4). Potentially curative resection is also possible after downstaging by chemoradiotherapy in patients with advanced esophageal cancer (5,6). However, several studies have shown that the survival of patients who received definitive chemoradiotherapy (bimodal therapy) was not different from that of patients who received chemoradiotherapy followed by surgery (trimodal therapy) (7,8). In contrast, other studies have revealed that patients with advanced esophageal cancer who received chemoradiotherapy followed by surgery survive for longer than those without surgery (9,10). Therefore, it is not clear whether esophagectomy can improve survival after chemoradiotherapy, or what is the appropriate timing of surgery.

In this study, we examined the results of all patients with clinical T3 or T4 esophageal cancer who were treated initially with chemoradiotherapy, including those having surgery. Their results were compared with published data on patients with and without surgery. To assess the value of surgery after chemoradiotherapy, we compared the long-term outcome between the patients with and without esophagectomy.

METHODOLOGY

Patients

From 1992 to 2001, 103 consecutive patients with newly diagnosed T3 or T4 esophageal cancer received chemoradiotherapy as their primary treatment at the Institute of Gastroenterology of Tokyo Women's Medical University, Japan. Seven patients who had distant organ metastases or esophageal fistula and four patients aged over 80 years were excluded. The remaining 92 patients with histologically proven squamous cell carcinoma on pretreatment endoscopic biopsy were evaluated in this study. Seventy-eight patients were men and 14 patients were women, and their ages ranged from 43 to 79 years (median age: 62 years). The Eastern Cooperative Oncology Group (ECOG)

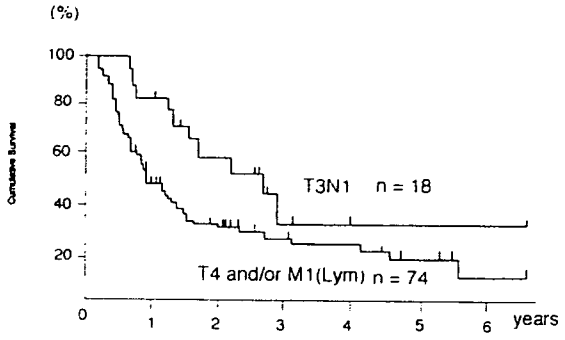

FIGURE 1 Cumulative overall survival of all patients with advanced esophageal cancer initially treated with chemoradiotherapy. The median survival and 3-year survival rate was 27 months and 44% in the18 patients with T3N1M0 (stage III) disease versus 11 months and 20% in the 74 patients with T4 and/or M1(Lymph) (stage IV) disease.

performance status was 0 in 34 patients, 1 in 55 patients, and 2 in 3 patients. The patients were staged clinically based on barium swallow, endoscopy, CT, and endoscopic ultrasonography findings according to the TNM classification. Eighteen patients had T3N1M0 (stage III) disease, while the others had stage IV disease (14 were T3M1, 41 were T4N1M0, and 19 were T4M1). All patients provided written informed consent before starting chemoradiotherapy.

Chemoradiotherapy Schedule

Thirty-one patients received sequential chemotherapy and radiation regimen consisted of cisplatin (70mg/m^2, days 1 and 36) and 5-FU (700mg/m^2/day, days 1-4 and 36-39) according to the schedule used in a phase II study (11). A concurrent chemoradiotherapy, using was the same chemotherapy and radiotherapy doses as protocol A, was given to 20 patients. The concurrent chemoradiotherapy regimen, consisting of low-dose cisplatin (3-5mg/m^2/day), 5-FU (200-300mg/m^2/day) and irradiation, was given to 18 patients. A different concurrent chemoradiotherapy regimen (12), consisting of nedaplatin, an analog of cisplatin, (20mg/m^2/day) and 5-FU (700mg/m^2/day) on days 1-4, days 29-32, and irradiation, was given to 23 patients.

Radiotherapy (30-40Gy) was administrated using anterior and posterior opposed equally weighted beams from 10-MV linear accelerator in 30-40 fractions of 2Gy, after which an additional 20-30Gy (a total of 60-70Gy) was administered via two parallel oblique fields or multiple fields to avoid damage to the spinal cord. The primary tumors and metastatic lymph nodes were included in the radiation fields.

Characteristics	With esophagectomy N=35	Without esophagectomy N=47
Median age (range)	62 (50-74)	63 (43-79)
Men: Women	28 : 7	44 : 3
Performance Status 0/ 1/ 2	15/ 19/ 1	19/ 27 /1
Tumor Location		
Cervical	5 (14%)	7 (15%)
Upper third	4 (11%)	10 (21%)
Middle third	18 (51%)	24 (51%)
Lower third	8 (23%)	6 (13%)
UICC TNM clinical stage		
T3N1M0	10 (29%)	8 (17%)
T3 N1M1 (Lymph)	4 (11%)	8 (17%)
T4 N1M0	14 (40%)	22 (47%)
T4 N1M1 (Lymph)	7 (20%)	9 (19%)
Response to the chemoradiotherapy		
Complete response	9 (26%)	9 (19%)
Partial response	18 (51%)	28 (60%)
No change	7 (20%)	9 (19%)
Progressive disease	1 (3%)	1 (2%)

Evaluation of Response and Toxicity

The clinical response of the tumor was determined in accordance with the criteria for assessment of the response to non-surgical treatment of the Japanese Society for Esophageal Diseases (13). For the primary esophageal lesion, response was assessed from the two-dimensional reduction rate on barium swallow, endoscopy, and tissue biopsy findings. For metastatic lesions, the response was assessed on neck, chest, and abdominal CT scans. In the patients who underwent esophagectomy after chemoradiotherapy, response was evaluated on the basis of examination of the esophagectomy specimens according to the histopathologic criteria for assessing the effects of radiation and/or chemotherapy (13). When no viable cancer cells evident (Grade 3) were detected was classified as complete response (CR). Viable cancer cells accounting for less than 1/3 of the tumor (Grade 2) was classified as partial response (PR). Viable cancer cells accounting for 1/3 or more of the tumor tissue (Grade 1) and no discernible therapeutic effect on the tumor (Grade 0) were classified as no change (NC). If a new lesion detected was detected, this was classified as disease progression (PD). Toxicity was evaluated using the criteria of the National Cancer Institute-Common Toxicity Criteria-Notice of Modifications (NCI-CTC), version 2 (14).

Esophagectomy

Thirty-five patients underwent esophagectomy within three months after completion of their planned chemoradiotherapy schedule (CRT+E group). Esophagectomy was performed via right thoracotomy in 25 patients, via left thoracotomy in 2 patients, and via transhiatal approach in 4 patients. Three-field lymph node dissection was done in 18 patients and two-field dissection was done in 13 patients. Reconstruction was performed using a gastric tube in 28 patients, and using the colon in 3 patients. Pharyngo-laryngo-esophagectomy was performed in 4 patients with cervical esophageal cancer.

Data Analysis

Differences in percentage data were evaluated by the two-sided chi-squared test or Fisher's exact test. Survival was calculated from the first day of the chemoradiotherapy schedule. All survival data were analyzed with JMP, version 4, software (SAS Institute, Cary, NC). Survival curves were constructed according to the Kaplan-Meier method and were compared using the log-rank test. The Cox proportional hazards model was used to determine the treatment features affecting survival.

RESULTS

Chemoradiotherapy

Of all 92 patients, 20% (18/92) had a CR, 51% (47/92) had a PR, 26% (24/92) showed NC, and 3% (3/92) had PD. The overall response rate was 71% (95% confidence interval, 64-76%). Toxicity of Grade 3 or worse of leukopenia, anemia, and thrombocytopenia occurred in 35%, 12%, and 35% of the patients, respectively. No differences were found in response and toxicity among chemoradiotherapy regimens. Six (6.5%) patients did not complete chemoradiotherapy schedule and four (4.3%) patients developed treatment related diseases after chemoradiotherapy.

With and Without Esophagectomy

Among a total of 82 patients who completed the planned chemoradiotherapy schedule, 35 patients had chemoradiotherapy followed by esophagectomy (CRT+E group) and 47 patients had the definitive chemoradiotherapy (CRT group). The clinical characteristics of the both groups are shown in **Table 1**. No significant differences were found between the two groups with respect to age, sex, performance status, tumor location, TNM stage, and response to chemoradiotherapy. The mean radiation dose was 45.3Gy in the CRT+E group, smaller than the dose of 62.7Gy in the CRT group ($P<0.0001$; Student's t test). Thirty-five patients underwent esophagectomy between 19 days and 85 days (median: 30 days) after chemoradiotherapy (CRT+E Group). Curative resection (R0) was done in 25 patients (71%), R1 resection was done in 6 patients (17%), and R2 resection was done in 4 patients (12%). There was no 30-day mortality, but one patient died of pneumonia at days 128 postoperatively.

Survival

For all 92 patients, the median follow-up period was 36 months (range; 11 to 81 months) **(Figure 1)**. The median survival time of the 18 patients with T3N0M0 (stage III) disease was 27 months, while the 1-, 2-, and 3-year survival rates were 83%, 56%, and 44%, respectively. The median survival time of the 74 patients with T4 and/or M1 disease was 11 months, while 1-, 2-, and 3-year survival rates were 47%, 30%, and 20%, respectively.

The survival of the 35 patients in the CRT+E group was longer than that of the 47 patients in the CRT group, without a significant difference ($P=0.0995$) **(Figure 2)**. Among the responders, the survival of the CRT+E group was significantly better than that of the CRT group patients ($P=0.0448$) **(Figure 3A)**, but no difference was found between both groups among the non-responders **(Figure 3B)**. No differences in survival between the CRT+E and CRT groups were demonstrated among the patients with

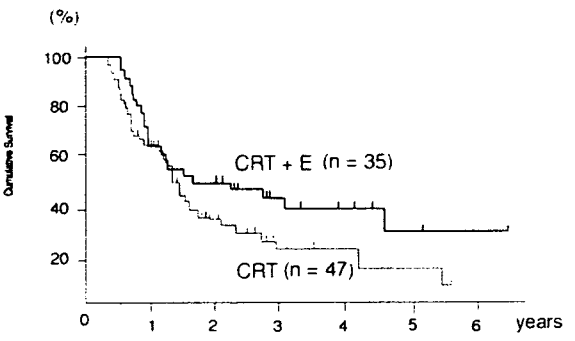

FIGURE 2 Cumulative overall survival of the 82 patients with advanced esophageal cancer who completed planned chemoradiotherapy. The probability of survival was not significantly different between the 35 patients who received chemoradiotherapy followed by esophagectomy (CRT+E) (solid line) and the 47 patients who received definitive chemoradiotherapy (CRT) (broken line) ($P=0.0995$; log-rank test).

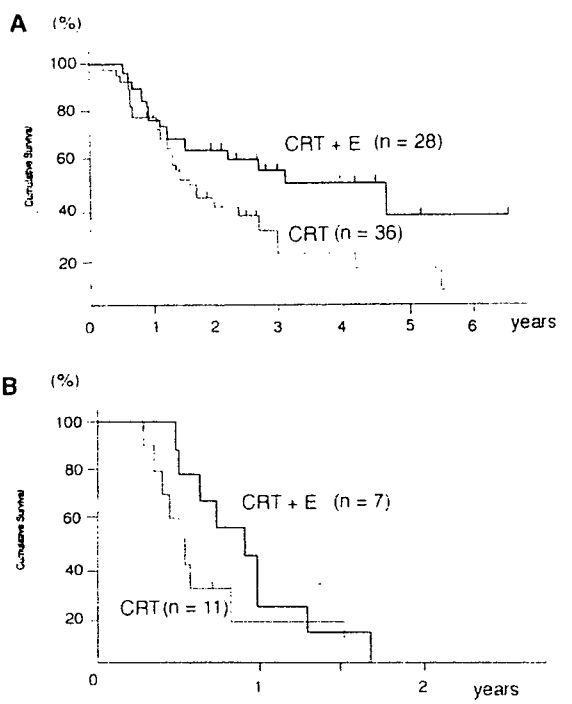

FIGURE 3 Cumulative overall survival of the responders **(A)** and non-responders **(B)** to chemoradiotherapy. **(A)** The probability of survival in responders who received chemoradiotherapy followed by esophagectomy (CRT+E) (solid line) was significantly higher than in patients who received definitive chemoradiotherapy (CRT) (broken line) ($P=0.0448$). **(B)** The probability of survival for non-responders did not differ between the CRT+E group (solid line) and the CRT group (broken line)

Table 2. Univariate and Multivariate Analysis to Identify Factors Predictive for Survival of the 82 Patients who Completed Planned Chemoradiotherapy

Categories (Variables)	Univariate *P*	Multivariate Relative Risk (CI)	*P*
Performance Status (0 *vs.* 1-2)	0.0176	0.766 (0.567-1.020)	0.0687
T (T3 *vs.* T4)	0.4358	0.942 (0.696-1.259)	0.690
M (Lymph) (M0 *vs.* M1)	0.0152	0.749 (0.567-0.998)	0.0487
Response (CR/PR *vs.* NC/PD)	<0.0001	2.379 (1.700-3.313)	<0.0001
Esophagectomy (With *vs.* Without)	0.0985	1.382 (1.049-1.838)	0.0212

Table 3. Clinical Recurrent Sites Following Chemoradiotherapy

Recurrence	With esophagectomy N=14	Without esophagectomy N=30	
Local-regional	2 (14%)	13 (43%)	*P*=0.0014
Lymph nodes	5 (36%)	10 (33%)	NS
Organ	2 (14%)	5 (17%)	NS
Dead of other causes	5 (36%)	2 (7%)	NS

NS: not significant.

T3N0 disease or in the patients with T4 and/or M1 disease. In univariate analysis, the response to chemoradiotherapy, performance status, and M factor were significant prognostic indicators, but the T factor and esophagectomy were not **(Table 2)**. However, Cox proportional hazards analysis of the 82 patients showed that response, M factor, and esophagectomy were significant independent prognostic indicators, while performance status was not. The rate of locoregional recurrence was significantly higher in the CRT group than in the CRT+E group (*P*=0.0014) and the rate of lymph node or organ metastasis was not different **(Table 3)**.

DISCUSSION

The treatment of patients with advanced esophageal cancer remains a challenge for surgeons, medical oncologists, and radiation oncologists. Cisplatin plus 5-FU in combination with radiation therapy has evidently proven to be an effective treatment for squamous cell carcinoma of the esophagus. Therefore, chemoradiotherapy has become the standard primary treatment for advanced esophageal cancer in Japan as well as in the west. The median survival time of the patients with stage III and IV diseases in this study from surgical department was slightly better or similar when compared with the results of previous studies (6-11,15).

Chemoradiotherapy is a powerful treatment, which is able to independently cure patients with advanced esophageal cancer. The studies have shown that the survival of patients receiving surgery was significantly better than that of those without surgery when surgery was performed on almost all responders (9,10). In contrast, no difference was reported in several studies performed by medical and radiation oncologists (7,8). Although this study was retrospective and non-randomized, esophagectomy after chemoradiotherapy seemed to improve the survival of our patients. A recent study (16) by radiation oncologists showed similar results to this study. The five-year survival rate of patients who underwent surgery was higher than that of those without surgery among patients achieving a partial response. Therefore, a randomized trial might answer this question definitively, but it may be difficult to perform because patients select their own treatment, especially esophagectomy.

Surgery may be unnecessary for patients who show CR after chemoradiotherapy, but diagnosis of CR by imaging is occasionally difficult in patients with advanced esophageal cancer and persistent stenosis. Therefore, we did not separate the CR patients from the patients in survival analysis between the CRT+E and CRT groups in this study. Various clinical CR rates have been reported based on various criteria in the previous studies of chemoradiotherapy for esophageal cancer (7,8,15,16). Several studies have showed a discrepancy in evaluation of the response to chemoradiotherapy between clinical and pathological assessment (12,17). Furthermore, clinical CR patients frequently have locoregional recurrence, but this is rare after pathological CR (18). Recently, positron emission tomography (PET) using 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) has been developed to be a promising tool for assessment of tumor response after chemoradiotherapy (19). If reliable imaging diagnosis of CR can be achieved, esophagectomy may be indicated only for PR patients.

Theoretically, the patients who had viable carcinoma cells in their esophagectomy specimens and survived a long time after esophagectomy should have less locoregional recurrence. Indeed, the locoregional recurrence rate of the CRT+E group was low, while the patients of the CRT group suffered locoregional recurrence for a long time (up to 4 years) after treatment in this study. However, difference on survival appeared to be limited between the CRT+E and CRT groups because a considerable number of patients developed distant lymph node or organ metastasis in the both groups. Therefore, the control of distant metastasis might be more important than local control for survival. Recently, regimens consisting of chemotherapy before concurrent chemoradiotherapy have been developed (20). Effective regimens for distant metastasis that include new drugs may be expected to improve survival.

Another reason why no significant difference was found on survival between patients with and without esophagectomy after chemoradiotherapy might be the high mortality rates, which were previously reported as 0-18% (5,6,10,17). Neoadjuvant chemoradiotherapy may increase the postoperative risk, but a low mortality rate is necessary to improve survival by esophagectomy. In this study, there were no early deaths mortality and only one hospital death in the CRT+E group. The risk of esophagectomy for non-responders with advanced cancer is higher than that of responders with downstaged cancer. The outcome after chemoradiotherapy in non-responders with cancer

infiltrating the respiratory tract is extremely poor (21). In contrast, three responders who underwent transhiatal esophagectomy for lower thoracic cancer achieved long survival without recurrence in this study. Therefore, esophagectomy after chemoradiotherapy should only be offered to the responders.

In conclusion, the overall survival of the patients with advanced esophageal cancer treated with chemoradiotherapy in our series was comparable to that in previous studies. Although this study was non-randomized and retrospective, it suggested that esophagectomy might improve the survival of responders to chemoradiotherapy. Clearly, the survival benefit of esophagectomy after chemoradiotherapy also needs to be assessed in larger multicenter phase III trials. At present, however, esophagectomy remains the most reliable treatment for locoregional control in patients receiving multimodal therapy for advanced esophageal cancer.

ACKNOWLEDGEMENT

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

REFERENCES

1 **Ilson DH, Kelsen DP:** Combined modality therapy in the treatment of esophageal cancer. Semin Oncol 1994; 21:493-507.

2 **Ide H, Nakamura T, Hayashi K, Endo T, Kobayashi A, Eguchi R, et al:** Esophageal squamous cell carcinoma: Pathology and prognosis. World J Surg 1994; 18:321-330.

3 **Franklin R, Steiger Z, Vaishampayan G, Asfaw I, Rosen berg J, Loh J, et al:** Combined modality therapy for esophageal squamous cell carcinoma. Cancer 1983; 51:1062-1071.

4 **Wolfe WG, Burton GV, Seigler HF, Crocker IR, Vaughn AL:** Early results with combined modality therapy for carcinoma of the esophagus. Ann Surg 1987; 205:563-571.

5 **Vogel SB, Mendenhall W, Sombeck MD, Marsh R, Woodward ER:** Downstaging of esophageal cancer after preoperative radiation and chemotherapy. Ann Surg 1995; 221:685-695.

6 **Ganem G, Dubray B, Raoul Y, Colin P, Bardet E, Douillard JY, et al:** Concomitant chemoradiotherapy followed, where feasible, by surgery for cancer of the esophagus. J Clin Oncol 1997; 15:701-711.

7 **Burmeister BH, Denham JW, O'Brien M, Jamieson GG, Gill PG, Devitt P, et al:** Combined modality therapy for esophageal carcinoma: Preliminary results from a large Australasian multicenter study. Int J Radiat Oncol Biol Phys 1995; 32:997-1006.

8 **De Pree C, Aapro MS, Spiliopoulos A, Popowski Y, Mermillod B, Mirimanoff RO, et al:** Combined chemotherapy and radiotherapy, followed or not by surgery, in squamous cell carcinoma of the esophagus. Ann Oncol 1995; 6:551-557.

9 **Coia LR, Minsky BD, Berkey BA, John MJ, Haller D, Landry J, et al:** Outcome of patients receiving radiation for cancer of the esophagus: Results of the 1992-1994 patterns of care study. J Clin Oncol 2000; 18:455-462.

10 **Yano M, Tsujinaka T, Shiozaki H, Inoue M, Doki Y, Yamamoto 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.

11 **Ishida K, Iizuka T, Ando N, Ide H:** Phase II study of chemoradiotherapy for advanced squamous cell carcinoma of the thoracic esophagus: Nine Japanese institution trial. Jpn J Clin Oncol 1996; 26:310-315.

12 **Yamanaka H, Motohiro T, Michiura T, Asai A, Mori T, Hioki K:** Nedaplatin and 5-FU combined with radiation in the treatment for esophageal cancer. Jpn J Thorac Cardiovasc Surg 1998; 46:943-948.

13 **Japanese Society for Esophageal Diseases:** Guidelines for clinical and pathologic studies on carcinoma of the esophagus. Ninth English Edition. Kanehara & Co Ltd; 2001.

14 **Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al:** New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000; 92:205-216.

15 **Ohtsu A, Boku N, Muro K, Muto M, Yoshida S, Satake M, et al:** Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. J Clin Oncol 1999; 17:2915-2921.

16 **Hennequin C, Gayet B, Sauvanet A, Blazy A, Perniceni T, Panis Y, et al:** Impact of survival of surgery after concomitant chemoradiotherapy for locally advanced cancer of the esophagus. Int J Radiat Oncol Biol Phys 2001; 49:657-664.

17 **Adelstein DJ, Rice TW, Becker M, Larto MA, Kirby TJ, Koka A, et al:** Use of concurrent chemotherapy, accelerated fractionation radiation, and surgery for patients with esophageal carcinoma. Cancer 1997; 80:1011-1020.

18 **Aoyama N, Koizumi H, Minamide J, Yoneyama K, Isono K:** Prognosis of patients with advanced carcinoma of the esophagus with complete response to chemotherapy and/or radiation therapy: a questionnaire in Japan. Int J Clin Oncol 2001; 6:132-137.

19 **Brücher BLDM, Weber W, Bauer M, Fink U, Avril N, Stein HJ:** Neoadjuvant therapy of esophageal squamous cell carcinoma: response evaluation by positron emission tomography. Ann Surg 2001; 233:300-309.

20 **Minsky BD, Neuberg D, Kelsen DP, Pisansky TM, Ginsberg RJ, Pajak T, et al:** Final report of intergroup trial 0122 (ECOG PE-289, RTOG 90-12): Phase II trial of neoadjuvant chemotherapy and high-dose radiation for squamous cell carcinoma of the esophagus. Int Radiat Oncol Biol Phys 1999; 43:517-523.

21 **Yano M, Shiozaki H, Tsujinaka T, Inoue M, Doki Y, Fujiwara Y, et al:** Squamous cell carcinoma of the esophagus infiltrating the respiratory tract is less sensitive to preoperative radiation and chemotherapy. J Am Coll Surg 2000; 191:626-634.

CASE REPORT

Factors Affecting the Prognosis of Patients With Esophageal Cancer Undergoing Salvage Surgery After Definitive Chemoradiotherapy

YOSHITO TOMIMARU, MD,[1] MASAHIKO YANO, MD,[1]* KO TAKACHI, MD,[1]
ISAO MIYASHIRO, MD,[1] RYU ISHIHARA, MD,[2] KINJI NISHIYAMA, MD,[3] YO SASAKI, MD,[1]
OSAMU ISHIKAWA, MD,[1] YUICHIRO DOKI, MD,[4] AND SHINGI IMAOKA, MD[1]

[1]*Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan*
[2]*Department of Gastrointestinal Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan*
[3]*Department of Radiation Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan*
[4]*Department of Surgery and Clinical Oncology, Graduate School of Medicine, Osaka University, Osaka, Japan*

Background and Objectives: Although salvage surgery after definitive chemoradiotherapy (CRT) is common, the safety and indication has not yet been established.
Methods: We retrospectively compared the mortality and morbidity of 24 patients who underwent salvage surgery with those of historical controls treated with neoadjuvant CRT followed by planned esophagectomy during the same period, and analyzed the prognostic factor of salvage surgery.
Results: Preoperative serum albumin (3.7 vs. 4.1 g/dl, $P = 0.0157$) and lymphocyte count (763 vs. 964/mm^3, $P = 0.0111$) in the salvage group were significantly lower than those in the neoadjuvant group. A significant difference was also observed in operation time (567 vs. 474 min, $P = 0.0381$), C-reactive protein (CRP) on postoperative day 1 (11.2 vs. 8.7 mg/dl, $P = 0.0021$), and postoperative systemic inflammatory response syndrome (SIRS) duration (3.5 vs. 2.9 days, $P = 0.0486$). There were three hospital deaths in the salvage group, whereas no patient died in the neoadjuvant group. Multivariate analysis showed curability (R0 vs. R1 + R2) to be the strongest prognostic factor of salvage surgery ($P = 0.0064$). R1 + R2 operation was more frequently performed in the salvage group (33% vs. 13%), and the reason for all cases was unresectable T4, which had been underestimated preoperatively.
Conclusions: Salvage surgery is a highly invasive and morbid operation, which is performed on immunocompromized hosts. The indication must be carefully considered, with care taken to avoid non-curative surgery.
J. Surg. Oncol. 2006;93:422–428. © 2006 Wiley-Liss, Inc.

KEY WORDS: **esophageal cancer; salvage surgery; operative indication; prognosis**

INTRODUCTION

Esophagectomy with extended lymphadenectomy has been the standard treatment for esophageal cancer in Japan. However, its operative mortality and morbidity still remain high and the postoperative quality of life (QOL) is very poor. Recently, definitive chemoradiotherapy (CRT) without surgery has been proposed as an

*Correspondence to: Masahiko Yano, MD, Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan. Fax: +81-6-6981-8055.
E-mail: yano-ma@mc.pref.osaka.jp

Received 12 February 2005; Accepted 17 November 2005
DOI 10.1002/jso.20475
Published online in Wiley InterScience (www.interscience.wiley.com).

alternative treatment strategy for locally advanced esophageal cancer [1–5]. This non-surgical treatment modality is now being widely accepted because of its low morbidity and high posttreatment QOL of patients. Definitive CRT has a relatively favorable prognosis of 26–46% survival at 5 years, and thus has recently been selected more often as a first-line therapy for locally advanced and resectable esophageal cancer [5,6].

However, not all tumors treated by definitive CRT give a complete response (CR). In addition, even if CR has been once attained, some tumors later recur [4,5]. For such patients, salvage esophagectomy is often necessary. As the number of patients treated with definitive CRT increases, the number of cases of salvage esophagectomy can be expected to increase. Some recent papers have associated salvage esophagectomy with high mortality and morbidity as compared with the planned surgery [7–9]. The safety of salvage surgery has not yet been established.

In this study, we conducted a retrospective review of 24 patients who underwent salvage esophagectomy after definitive CRT, and compared their mortality and morbidity with those of historical controls who were treated with planned CRT followed by esophagectomy during the same period.

MATERIALS AND METHODS

Patients

Between August 1985 and August 2004, 762 patients with esophageal cancer underwent esophageal resection in the Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases. Among the 762 patients, 24 patients underwent salvage esophageal resection after definitive CRT (salvage group).

For comparison, we reviewed 26 patients with advanced esophageal cancer who received planned esophageal resection 4–8 weeks after neoadjuvant CRT (neoadjuvant group) during the same period. Three in the salvage group and four in the neoadjuvant group had received CRT in other hospitals.

In this study, salvage esophagectomy was defined as follows: surgery performed for patients showing local recurrence after a CR or for those showing residual tumor (non-CR) after definitive CRT.

CRT

Patients in the neoadjuvant group were given a total of 40 Gy (2 Gy daily) of external-beam radiation followed by surgery. On the other hand, patients in the salvage group received a total of 60 Gy or more radiation. A daily dose of 2 Gy external-beam radiation was delivered by a 10-MV linear accelerator with parallel opposing fields using anterior and posterior portal arrangements, which was changed to an oblique portal arrangement after 40 Gy. Six patients in the salvage group had received intraluminal brachytherapy ranging from 8 to 15 Gy. Concurrent chemotherapy along with radiotherapy was performed using various protocols including cisplatin (CDDP), adriamycin (ADR), and 5-fluorouracil (5-FU). Eight patients in the salvage group were treated with radiotherapy alone.

Operations

In our hospital, esophagectomy through right thoracotomy with three-field lymph node dissection is the standard procedure for thoracic esophageal cancer except for lower thoracic esophageal cancer without recurrent laryngeal nerve chain node metastasis. For such patients, two-field lymph node dissection was performed. Esophagogastric anastomosis in the neck by way of the retrosternal or mediastinal route was performed for the most of the patients. For patients at poor risk, the subcutaneous route was selected for the reconstruction. Basically, one-stage reconstruction was performed, but for patients at poor risk, two-stage reconstruction was selected. For several patients who had already undergone gastrectomy, the colon or jejunum was used for the reconstruction.

Clinical Data

The stage was assigned according to the criteria of the American Joint Committee on Cancer [10]. Hospital records were reviewed for gender, age, preoperative laboratory data including albumin, total protein, white blood cell (WBC), lymphocyte, hemoglobin, platelet, arterial partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$), and pulmonary function test including vital capacity (%VC) and forced expiratory volume in 1.0 second ($FEV_{1.0}$). Details of the surgical procedures and postoperative outcome including mortality and morbidity were also collected from the records. According to the systemic inflammatory response syndrome (SIRS) criteria, the postoperative duration of SIRS was calculated [11].

Statistical Analysis

Data were expressed as mean ± standard deviation. The significance of differences among the groups was assessed by the Chi-square, Fisher exact test, or the Mann–Whitney U test. Survival rates were calculated according to the Kaplan and Meier method and compared using the log-rank test. The Cox proportional hazards model was used for multivariate analysis. Statistical analysis was performed using Statview (Version 5.0, SAS Institute, Inc., Cary, NC). A P value of <0.05 was considered statistically significant.

TABLE I. Comparison of Preoperative Clinical Features of Patients in the Salvage and Neoadjuvant Groups

	Salvage group (n = 24)	Neoadjuvant group (n = 26)	*P*-value
Gender			
Male	22	22	0.6688
Female	2	4	
Age (years)	63 ± 10	65 ± 9	0.2142
Histological type (SCC/Ad)	24/0	26/0	>0.9999
Tumor location			
Cervical	0	1	
Upper thoracic	5	8	0.6189
Middle thoracic	13	11	
Lower thoracic	6	6	
Clinical stage			
T (1/2/3/4)	5/0/8/11	1/3/8/14	0.1138
N (0/1)	14/10	4/22	0.0028
M (0/1a/1b)	22/2/0	20/6/0	0.2503
Stage (I/IIA/IIB/III/IVA/IVB)	4/6/1/11/2/0	0/3/2/15/6/0	0.0960
Radiation dose (Gy)	62 ± 6	40 ± 0	<0.0001*
Treatment interval (months)	6.1 ± 5.2	1.3 ± 0.7	0.0006*
Clinical effect			
Complete response	11	6	
Partial response	9	17	0.1352
No response	4	3	
Preoperative laboratory data			
Albumin (g/dl)	3.7 ± 0.4	4.1 ± 0.4	0.0157*
Total protein (g/dl)	6.5 ± 0.6	6.8 ± 0.5	0.1084*
White blood cell (mm^3)	4,640 ± 1,168	4,800 ± 1,781	0.7269*
Lymphocyte (mm^3)	763 ± 198	964 ± 319	0.0111*
Hemoglobin (ng/ml)	12.2 ± 1.7	11.3 ± 1.8	0.1097*
Platelet ($\times 10^4/mm^3$)	24.3 ± 8.0	25.5 ± 11.0	0.6794*
PaO_2 (mm Hg)	90.7 ± 6.1	87.5 ± 7.4	0.1247*
$PaCO_2$ (mm Hg)	38.9 ± 3.4	39.6 ± 2.7	0.4359*
%VC (%)	84.2 ± 11.2	88.9 ± 15.0	0.2591*
$FEV_{1.0}$ (%)	79.7 ± 11.0	76.3 ± 13.5	0.3624*

Data were expressed as mean ± standard deviation.

*These results were expressed as the mean and compared by the Mann–Whitney U test. The others were compared by the Chi-square or Fisher exact test.

SCC, squamous cell carcinoma; Ad, adenocarcinoma; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; %VC, vital capacity; $FEV_{1.0}$, forced expiratory volume in 1.0 second.

RESULTS

The clinical characteristics of patients in the salvage group and the neoadjuvant group are summarized in Table I. Gender, age, tumor location, and pretreatment clinical stages did not differ between the two groups. Histological type of all the patients was squamous cell carcinoma, and adenocarcinoma was not seen in patients in this study. The average dose of radiation delivered to the patients was significantly higher in the salvage group than that in the neoadjuvant group (62 ± 6 Gy vs. 40 ± 0 Gy, $P < 0.0001$). Eleven patients out of 24 in the salvage group had been assessed to be complete responders after CRT, but later showed relapse. The remaining 13 patients in the salvage group were non-CR patients, and they underwent salvage surgery for the residual tumor. The interval from the end of CRT to surgery was significantly longer for the salvage group than the neoadjuvant group [6.1 months (range 1.0–25.0) vs. 1.3 months (range 1.0–4.0), $P = 0.0006$]. Additionally, in the salvage group, the interval was less than 3 months in 7 patients, and more than 3 months in the remaining 17 patients. All the seven patients with less than 3-month interval were non-CR patients.

The preoperative laboratory data are also shown in Table I. The serum albumin and lymphocyte count in the salvage group were significantly lower than those in the neoadjuvant group, but no significant differences were

TABLE II. Comparison of Surgical Procedures and Operative Factors of Patients in the Salvage and Neoadjuvant Groups

	Salvage group (n = 24)	Neoadjuvant group (n = 26)	*P*-value
Surgical procedures			
One-stage operation	22	24	>0.9999
Two-stage operation	2	2	
Surgical curability			
Curative (R0)	16	23	0.0631
Non-curative [R1 + R2 (R1/R2)]	8 (3/5)	3 (0/3)	
Lymph node dissection			
Three-field	5	13	
Two-field	12	10	0.0719
Others	7	3	
Reconstruction route			
Subcutaneous	6	3	
Retrosternal	11	8	0.1159
Mediastinal	7	15	
Operation time (min)	567 ± 136	474 ± 153	0.0381
Intraoperative blood loss (ml)	1,109 ± 614	967 ± 618	0.0801*
Blood transfusion (ml)	693 ± 657	393 ± 429	0.0600*

Data were expressed as mean ± standard deviation.
*These results were expressed as the mean and compared by the Mann–Whitney U test. The others were compared by the Chi-square or Fisher exact test.

noted between the two groups for other factors such as total protein, WBC, hemoglobin, platelet, PaO_2, $PaCO_2$, and respiratory function.

As shown in Table II, the operative procedures and results were compared between the two groups. There were no significant differences in surgical procedures such as reconstruction and the extent of lymphadenectomy. Non-curative surgery (R1 + R2) was more frequently performed in the salvage group (33.3% vs. 13.0%), though the difference was not statistically significant. The operation time of the salvage group was significantly longer than that of the neoadjuvant group (567 ± 136 vs. 474 ± 153 min, $P = 0.0381$). Intraoperative blood loss and transfusion of the salvage group showed a tendency to be larger than those of the neoadjuvant group.

Next, we compared short-term outcome and its related parameters between the two groups (Table III). There was no significant difference in the durations of the mechanical ventilator, intensive care unit stay, WBC, and the ratio of the arterial partial pressure of oxygen to the fraction of inspired oxygen (PaO_2/FiO_2 ratio). C-reactive protein (CRP) on postoperative day 1 in the salvage group was significantly higher than that in the neoadjuvant group ($P = 0.0021$). The period of time during which the patients in the salvage group fulfilled the SIRS criteria was significantly longer than that for the neoadjuvant group ($P = 0.0486$). The morbidity rate did not differ statistically. There were three hospital deaths including one operative death in the salvage group, whereas no patient died in the neoadjuvant group. One patient died of hepatic failure after acute peritonitis on postoperative day 17, one died of massive hemoptysis due to brachiocephalic arterio-tracheal fistula on postoperative day 40, and one died of hemoptysis of unknown origin on postoperative day 56.

In order to examine which factors(s) determine prognosis after salvage surgery, univariate analysis was performed for age (<60/60<), clinical T (T1-2/T3-4),

TABLE III. Comparison of Postoperative Factors of Patients in the Salvage and Neoadjuvant Groups

	Salvage group (n = 24)	Neoadjuvant group (n = 26)	*P*-value
Mechanical ventilation (days)	1.0 ± 0.9	0.8 ± 0.4	0.4115*
Intensive care unit stay (days)	1.8 ± 1.0	2.1 ± 1.2	0.3807*
WBC on POD1 (mm^3)	9,780 ± 3,450	11,130 ± 5,360	0.3229
CRP on POD1 (mg/dl)	11.2 ± 2.4	8.7 ± 2.4	0.0021
PaO_2/FiO_2 ratio on POD1 (mm Hg)	311 ± 64	336 ± 73	0.2923*
SIRS (days)	3.5 ± 1.1	2.9 ± 0.9	0.0486
Morbidity			
Anastomotic leakage	5	2	0.2387
Pneumonia	5	3	0.4561
Wound infection	2	1	0.5955
Mortality			
Operation mortality (within 30 days)	1	0	>0.9999
Hospital mortality	3	0	0.1033

Data were expressed as mean ± standard deviation.
These results were expressed as the mean and compared by the Mann–Whitney U test. The others were compared by the Chi-square or Fisher exact test.
POD, postoperative day; WBC, white blood cell count; CRP, C-reactive protein; PaO_2/FiO_2 ratio, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen; SIRS, systemic inflammatory response syndrome.

TABLE IV. Multivariable Analysis of Overall Survival After Salvage Esophagectomy

Factors	OR	95% CI	*P*-value
Clinical T (T1-2/T3-4)	0.151	0.017–1.368	0.0927
Clinical response (CR/non-CR)	0.564	0.111–2.857	0.4886
Curability [Curative (R0)/Non-curative (R1 + R2)]	0.0430	2.420–219.685	0.0064

OR, odds ratio; 95% CI, 95% confidence interval; CR, complete response.

reason for salvage surgery (recurrence after CR/non-CR), curability (curative operation/non-curative operation), preoperative serum albumin (<4.0 g/dl/4.0 g/dl<), lymphocyte (<780/mm^3/780/mm^3<). Among these factors, clinical T (T1-2 vs. T3-4, $P = 0.0106$), reason for surgery (CR vs. non-CR, $P = 0.0142$), and curability [curative operation (R0) vs. non-curative operation (R1 + R2), $P < 0.0001$] were found to be significant prognostic factors. Next, to identify independent prognostic factors, the above three factors detected by univariate analysis were subjected to multivariate analysis. As shown in Table IV, curability [curative operation (R0) vs. non-curative operation (R1 + R2)] was found to be the only independent prognostic factor with an odds ratio of 0.0430 and 95% confidence interval of 2.420–219.685, whereas the other two factors were not statistically significant.

We compared the survival of the patients in the salvage group according to the curability. The overall survival of the 8 patients who underwent non-curative operation was significantly poorer than that of the remaining 16 patients who underwent curative operation ($P < 0.0001$) (Fig. 1). The reasons for the performance of non-curative surgery on these eight patients are summarized in Table V. They had been assessed by conventional examinations to have resectable tumors before salvage surgery, but the tumors could not be resected curatively because they had invaded mediastinal structures: the trachea in five patients, bronchus in two, and both aorta and bronchus in one. Bronchoscopy was not performed for all the preoperative patients in a routine manner. Only patients, who were suspected to have airway involvement by computed tomography (CT) scan or magnetic resonance imaging (MRI), were assessed by bronchoscopy. Among the eight non-curative patients listed in Table V, six patients (No. 2–7) were assessed by bronchoscopy and were diagnosed to have no airway involvement before salvage surgery.

This tumor invasion could not be diagnosed preoperatively. Number 7 patient in Table V, who was diagnosed as T4 (aorta) preoperatively but was expected to undergo curative resection by combined resection of the aorta, resulted in non-curative resection because the tumor also infiltrated to the left bronchus. Number 8 patient in Table V, who was also diagnosed as T4 (aorta and left lung) preoperatively, underwent two-stage operation. At the first operation, combined resection of the thoracic esophagus, aorta, and left lung was performed. However, at the second operation, the mediastinal trachea was found to be involved by the cervical lymph node metastasis. Of the eight patients, two died in our hospital postoperatively.

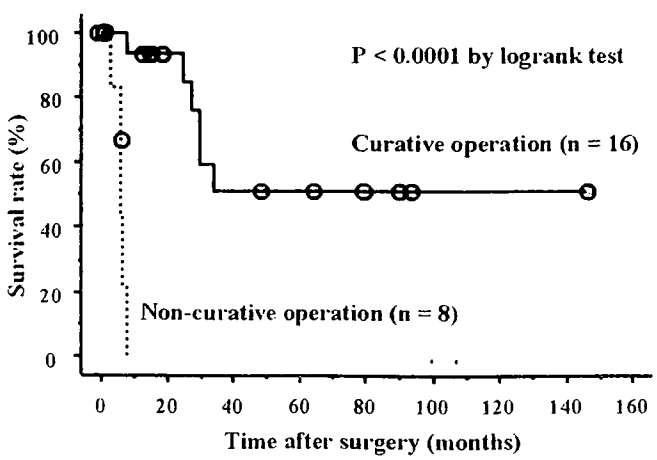

Fig. 1. Survival curves of patients who underwent salvage surgery were compared based on surgical curability. The thick line indicates curative operation and the dotted line non-curative operation. Statistical analysis was done by log-rank test.

DISCUSSION

Recently, as the number of patients treated by definitive CRT increases, the number of patients who require salvage esophagectomy is also increasing [4,5]. What is of concern is whether or not salvage surgery is associated with high operative mortality and morbidity, because these patients have received a high dose of radiation. To date, the details of the risk related to the salvage surgery are not yet fully understood, and the indication for salvage surgery has not been established. In order to clarify the above issues, we retrospectively examined the outcome and prognostic factors of salvage surgery after definitive CRT in comparison with those of planned esophagectomy after neoadjuvant CRT.

The longer operation time and greater blood loss of the salvage esophagectomy suggest that this is a more difficult surgery than planned esophagectomy after neoadjuvant CRT. In addition, a significantly higher postoperative serum CRP level and longer SIRS duration

TABLE V. Clinical Features of the Eight Patients Who Could Not Undergo Curative Salvage Operation After Definitive Chemoradiotherapy (CRT)

No.	Age/gender	Location	Clinical T (before CRT)	Clinical T (after CRT)	Surgical procedure	Combined resection	Pathological T	Reason for non-curative surgery
1	75/M	Lt	T1b	T1b	Esophagectomy, esophagocolostomy	—	T4 (rt-Br)	Unresectable T4 (rt-Br) of LN metastasis
2	66/M	Ut	T4 (Tr)	T3	Esophagectomy, esophagocolostomy	—	T4 (Tr)	Unresectable T4 (Tr)
3	77/M	Ut	T4 (Tr)	T3	Esophagectomy, esophagogastrostomy	—	T4 (Tr)	Unresectable T4 (Tr)
4	65/M	Mt	T4 (Tr)	T3	Esophagectomy, esophagocolostomy	—	T4 (Tr)	Unresectable T4 (Tr) of LN metastasis
5	56/M	Lt	T4 (Tr, lt-Lg)	T3	Esophagectomy, esophagogastrostomy	lt-Lg	T4 (Tr, lt-Lg)	Unresectable T4 (Tr)
6	50/M	Mt	T4 (Ao, lt-Br)	T3	Esophagectomy, esophagogastrostomy	—	T4 (Ao, lt-Br)	Unresectable T4 (Ao, lt-Br)
7	51/F	Mt	T4 (Ao, lt-Br)	T4 (Ao)	Esophagectomy, esophagogastrostomy	—	T4 (Ao, lt-Br)	Unresectable T4 (Ao, lt-Br)
8	50/M	Mt	T4 (Ao, lt-Lg)	T4 (Ao, lt-Lg)	Esophagectomy, esophagocolostomy	Ao, lt-Lg	T4 (Ao, lt-Lg, Tr)	Unresectable T4 (Tr)

Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; Ao, aorta; Tr, trachea; Br, bronchus; Lg, lung; LN, lymph node.

in the salvage group also suggest that salvage surgery is more invasive and more morbid. There were three hospital deaths including one operative death in the salvage group, two of which may have been associated with the high dose of radiation. On the other hand, no patient died in the neoadjuvant group, although the difference was not statistically significant. Accordingly, salvage surgery should be viewed as high-risk surgery with much surgical stress as has been reported by several investigators [7–9].

In addition, since preoperative serum albumin and lymphocyte in the salvage group was significantly lower than those in the neoadjuvant group, patients in the salvage group were speculated to be in a more malnourished and immunosuppressed condition than those in the neoadjuvant group. It remains unknown whether or not such a poor immuno-nutritional status is due to the difference in the radiation dose. However, it is possible that malnutrition and immunosuppression may lead to postoperative complications and poor prognosis. Thus, nutritional support, which alleviates such preoperative malnutrition and immunosuppresion, should be taken into consideration.

We concluded that salvage surgery is a highly invasive and morbid operation, which is performed on immunocompromized hosts. Therefore, care is required when deciding on the indication for salvage surgery. The question then arises of what kind of patients can benefit from such a risky operation. To answer, we tried to identify prognostic factors which determine patient survival. Multivariate analysis revealed that curability (curative operation vs. non-curative operation) was the most significant prognostic factor. The prognosis of patients with non-curative operation was extremely poor. No one survived for more than 10 months. Thus, non-curative surgery should definitely be avoided.

Indeed, all patients in the salvage group had been preoperatively estimated as being "curatively resectable" by conventional examinations, but the surgery was non-curative for eight patients, which is a substantially high non-curative rate and corresponds to almost one-third of the patients, when compared with planned surgery. The reason for non-curative surgery was underestimation of the T4 factor by conventional examinations using CT or MRI. Fibrosis is usually promoted in radiation fields, and cancer cells are likely to be left behind in the deep layer of the esophageal wall after radiotherapy [12,13]. Therefore, it may be difficult to accurately evaluate the T factor of irradiated patients by diagnostic criteria, which were originally prepared for preoperative estimation of non-irradiated patients.

Salvage esophagectomy is an operation with high morbidity and mortality, even if it is performed for well-selected patients as shown in this study. Therefore, it