例の実態は，前記全国登録報告によれば全切除例のおよそ20%を占めていた.

これらT4，M1lymに対する姑息切除，姑息的放射線治療の代替治療法として，非外科的治療の標準治療となりつつあった化学放射線療法が注目され，臨床試験が精力的に行われた. 1992〜94年にがん集学的治療財団の共同研究として，切除不能・再発食道がんを対象として放射線療法30 Gyにsequential にCisplatin/5-FUを併用し2コース施行する化学放射線療法の第Ⅱ相試験[8]が行われ，その結果CR（Complete response）率11%，PR（Partial response）を含む奏効率は64%であった. JCOG食道がんグループでは，同様なstageを対象に放射線療法60 GyとCisplatin/5-FUを同時併用する根治的化学放射線療法Definitive chemoradiotherapyの第Ⅱ相試験（JCOG9516）[9]を，またOhtsuら[10]は放射線療法60 GyとCisplatin/5-FUを同時併用2 cycle分割投与した化学放射線療法の第Ⅱ相試験を行い，CR率は評価法は異なるもののそれぞれ15%，30%，生存率は31.5%（2生率）と23%（3生率）であった. 治療による毒性も対象の進行度を考慮すれば許容範囲内で，耐容可能と考えられた. 大津らの成績は同一施設内の同様なStage症例に対する過去の外科手術の成績に匹敵するものであった[11].

局所進行食道がんに対する化学放射線療法によりCRには至らなくとも，気管・気管支，大動脈など隣接周囲臓器への直接浸潤部に対する顕著な局所制御効果により，がん遺残を伴う姑息切除を回避でき根治手術が可能となる症例が増え，新しい治療戦略[12]となりつつある. このようなdown staging後の手術療法も含め根治的化学放射線療法Definitive chemoradiotherapyがこのstageに対する標準治療となった. 現在の検討課題は放射線と併用する化学療法の投与方法，投与量などである. 低用量Cisplatin/5-FU・放射線療法はその使いやすさから，有効性と安全性の確たるエビデンスもないまま日常臨床の場で普及しつつあるので，これを検証するためにJCOG食道がんグループでは通常用量Cisplatin/5-FU・放射線併用療法と低用量Cisplatin/5-FU・放射線併用療法とのランダム化第Ⅱ/Ⅲ相試験を現在遂行中である.

自験例を供覧する. 症例は68歳，男性で，腎盂がんの診断で当院泌尿器科入院中に嚥下困難を訴え，上部消化管X線造影では胸部上部から頸部食道にまたがる頸胸境界部に長径5cm，3型の陰影欠損像を認めた. 食道内視鏡検査の結果21cmから全周性の狭搾を認め，

生検の結果中分化扁平上皮癌と診断した. 頸胸部CT検査では気管膜様部への直接浸潤T4が疑われ，左鎖骨上リンパ節が周囲との癒着を伴い大きく腫大していた. 腎盂がんとの同時性重複がんで一期的手術は過大な侵襲になり，主癌巣の局在のために喉頭合併切除の必要性も高いこと，胃切除術の既往歴のために食道再建術による侵襲がさらに高いこと，なによりも局所の完全切除の困難性が高いことなどを考慮し，切除手術は極力回避しなければならず化学放射線療法を選択した. 低用量cisplatin/5-FU・放射線併用療法50 Gy後の内視鏡所見では，軽度狭搾は残存するが潰瘍病変は消失，瘢痕化し，生検により癌細胞は検出されず，主病巣に対する効果はCRと判定した. 左鎖骨上リンパ節腫大は25%の縮小は認められたが，消失には至らなかった. 以上の所見より食道切除は行わずに，左鎖骨上リンパ節のみ摘出した. 病理組織学的検索の結果，リンパ節にはviable cancer cellを認めなかった. 化学放射線療法終了後16カ月の現在，食道，喉頭の臓器犠牲がない状態で無再発生存中である（図1, 2）.

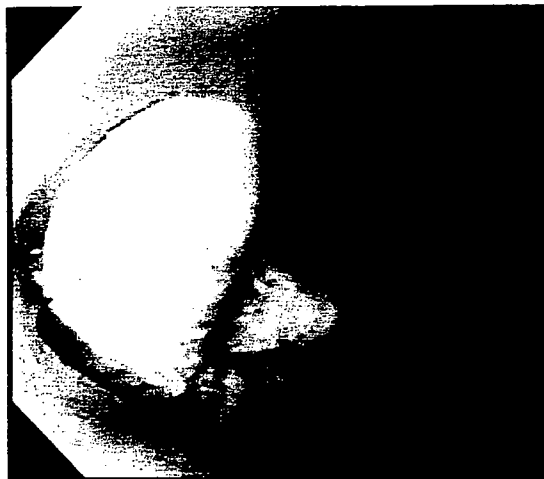**図1　食道X線造影所見**
左：化学放射線療法前，右：後

図2　食道内視鏡所見
上：化学放射線療法前，下：後

b. Stage I（T1N0）食道がんに対する標準治療とその推移

食道表在がん（壁深達度T1）に対する治療は，近年ではT1a（mがん）には，そのリンパ節転移陽性率が極めて低いことより，原発腫瘍のみの切除となる内視鏡的粘膜切除術EMRでも十分根治性があると認知されている，前述したように食道癌治療ガイドラインでは，T1aのうち深達度亜分類のm1，m2（粘膜固有層までに留まるもの）をEMRの絶対的適応としているが，m3（粘膜筋板にまで達するもの）およびT1b（粘膜下層がん）の中のsm1は，患者が外科手術を望まない場合や全身状態から根治手術不能と判断された症例ではEMRの相対的適応としている．しかしT1bでより深部のsmに浸潤した食道がん（sm2，sm3）のリンパ節転率は40〜50%と高率で，しかもその転移部位は，進行がんと同様に頸部を含めた広い範囲に及んでいる．さらに

画像診断を用いたリンパ節転移の陽性予測率は70%，陰性予測率60%と決して精度は高くはなく[13]，画像診断などを用い臨床的にリンパ節転移がないと診断される症例においても，組織学的に転移を有する可能性があるため，標準的な広範囲リンパ節郭清が行われているのが現況である．したがって本邦では，表在がんといえども臨床的にT1bと診断される食道がんの標準的治療は，リンパ節郭清を伴う食道切除術である．

このリンパ節郭清を伴う食道切除術はStage I（T1N0）食道がんに対する標準的治療と認識されてはいるものの，Stage II以上と同様の開胸開腹による手術が過大侵襲ではないかという疑問と，最近の進行食道がんに対する化学放射線療法の良好な成績を勘案して，非外科的治療の化学放射線療法で治療を試行することが計画された．

JCOG食道がんグループでは，比較的早期の進行度でありながらEMRの適応外で，外科手術が根治的治療と考えられている臨床病期I期相食道扁平上皮癌を対象として，放射線とCDDP/5-FU同時併用療法の第II相臨床試験（JCOG9708）[14]を行った．1997年12月〜2000年7月に72例の症例登録を行い，長期成績解析のため現在も症例追跡中である．CRは63例（CR率88%）で，腫瘍遺残例のうち3例には外科的切除術が行われた．登録終了後2年の時点でCR後の再発，新病変出現は30例と比較的多数に認められたが，21例は切除可能病変であった（EMRやアルゴンプラズマ凝固術：13例，外科的切除術Salvage surgery：6例）．対象病変が小さいので放射線照射野も比較的狭く，したがって有害事象は軽微であった．ただし放射線肺臓炎，胸水貯留，心嚢液貯留などの侮りがたい晩期毒性は軽視できない．登録終了後4年の時点での2年生存率は93%，4年生存率は80%で，この生存成績は同じ臨床病期を対象としたこれまでの外科手術成績[15]とほぼ同等である．

以上より，Stage I（T1N0）食道がんに対する化学放射線療法は，CR率が高く，短期的な生存成績では歴史的対照である外科手術とほぼ同等であった．再発・新病変も決して少なくはないが，適切な二次治療により多くの症例は治癒可能であり，このステージに対する化学放射線療法の生存成績や低侵襲性は極めて有望であり，何よりも切除手術に伴う臓器犠牲がなく食道を温存できることは大きな魅力である．しかしこの第II相臨床試験（JCOG9708）の結果により，このステージに対する標準治療がこれまでのリンパ節郭清を伴う食道切除術から化学放射線療法へは変わり得ない．化

学放射線療法が本当に外科的切除術にとって代わることができるか否かは，ランダム化比較試験（RCT）による科学的な検証が必要である．JCOG食道がんグループでは，Stage I（T1N0）食道がんに対する外科手術vs. 化学放射線療法のRCTを現在計画中で，JCOG臨床試験審査委員会におけるプロトコール審査中である．

　自験例を供覧する．症例は77歳，男性で，嚥下時違和感に対する内視鏡検査の結果，門歯より33〜36cmに及ぶ1/2周の0-IIc病変を認めた．超音波内視鏡検査にて深達度は粘膜下層sm深部に及ぶT1b，N0でcStage Iと診断した．患者は60本/日の喫煙歴があり高度閉塞性肺機能障害を併存した高齢者であったために，標準治療である手術ではなく非手術的治療を選択した．低用量Cisplatin/5-FU・放射線併用療法50Gy後に，食道局所にboost照射を追加した．治療終了3カ月後には局所は完全瘢痕化しCRとなり，9カ月後の現在，CRが持続している（図3）．

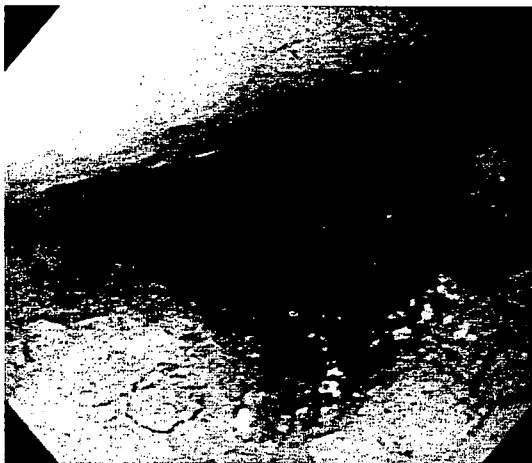

図3　食道内視鏡所見
上：化学放射線療法前，下：治療終了3カ月後

c．Stage II，III食道がんに対する標準治療とその推移

　Stage II，III，すなわち多くはリンパ節転移を有する中期進行がんに対する標準治療は，リンパ節郭清を伴う食道切除術であることに異論はなく，外科手術がもっともその効果を発揮しうる進行度でもある．しかし前述して来たような化学放射線療法により得られる目覚ましい治療効果の体験から，本邦では一部の積極的な腫瘍内科医Medial Oncologistらは，Stage II，III食道がんに対する根治的化学放射線療法を精力的に施行している．JCOG消化器がん内科グループではclinical Stage II，III進行食道がんを対象に，主病巣のみならずリンパ節好発部位をも照射野に含めた化学放射線療法の第II相試験を2000〜2002年に行った．登録例74例中CR例は50例(68%)で，3生率は45%であった．これはStage IIIが対象例の過半数を占めていた背景を考慮すれば，外科手術には決して劣らない成績ではあるが，国立がんセンター中央病院の成績ではCR持続は半数のみで，全体の2/3の症例には遺残・再発が認められた．したがってがんの非外科的治療が標準治療の一つになるためには，非外科的治療によりCRに至らなかった症例およびCR後再発例に対する救済手術Salvage surgeryが必要である．このSalvage surgeryという新しい外科手術の概念が生まれ，最近では食道外科領域の重要な検討課題となり，定義，適応および適切な手術時期などが議論されている．

　自験例を供覧する．症例は72歳，男性，主訴は嚥下困難で食道X線造影にて胸部中部食道Mtに長径7cmのType 1の陰影欠損を認め，内視鏡検査の結果28cmから1/2周を占める腫瘍を認め，生検の結果中分化扁平上皮癌と診断した．胸部CTでは右反回神経リンパ節，気管分岐部リンパ節の腫大を認めT2N1M0 cStage IIbと診断した．僧帽弁閉鎖不全による軽度心不全を併存していたので，標準治療である手術ではなく非手術的治療を選択した．低用量Cisplatin/5-FU・放射線併用療法50Gy後に，食道局所にboost照射を追加した．腫大リンパ節は縮小し，治療終了1カ月後に潰瘍病変が残存したが，4カ月後には局所は完全瘢痕化しCRとなり，12カ月後の現在CRが持続している（図4）．
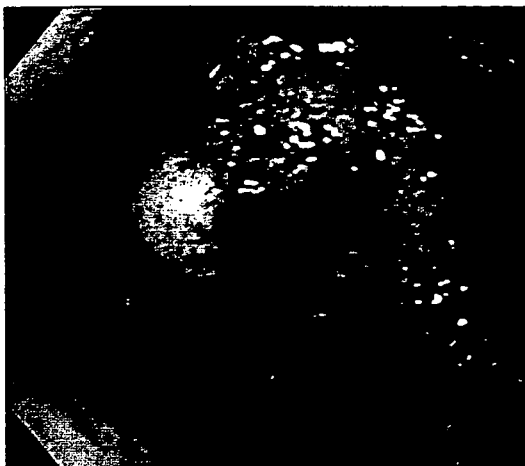
図4 食道内視鏡所見
左：化学放射線療法前，右：治療終了4カ月後

おわりに

　食道がん治療はこれまでの切って治す外科的治療から，化学放射線療法を中心とした非外科的治療への移行が急速に試されつつある．それはまずT4などの高度進行がん例に対して行われ，次にStage Iの早期がん例に対して現在進行中であり，さらにStage II，IIIの中期進行がん例に対しても近未来の展開が予想される．い

ずれが標準治療となるかは整備された臨床試験の結果を待たねばならず，現時点では未だcontrovertialである．一方でがんの非外科的治療が標準治療候補のひとつとして認知されると，それによる非完治例，あるいは再発例に対する救済手術Salvage surgeryという新しい外科手術の概念が生じ，検討課題となりつつある．

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Esophagectomy: Is It Necessary after Chemoradiotherapy for a Locally Advanced T4 Esophageal Cancer? Prospective Nonrandomized Trial Comparing Chemoradiotherapy with Surgery versus without Surgery

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Abstract. The need for surgery after chemoradiotherapy for a T4N0-1M0 squamous cell carcinoma in the thoracic esophagus was evaluated. A series of 53 patients were enrolled in this prospective nonrandomized trial from among 124 patients with an esophageal cancer assessed as T4 in Kurume University Hospital from 1994 to 2002. After the first chemoradiotherapy cycle, which consisted of radiotherapy in a total dosage of 36 Gy and chemotherapy using cisplatin (CDDP) and 5-fluorouracil (5FU), the patients each decided, after being informed of the efficacy of the chemoradiotherapy, whether to undergo surgery. All patients, including those who had undergone surgery and those who had not, later underwent a second chemoradiotherapy cycle consisting of radiotherapy in a total dosage of 24 Gy and chemotherapy using CDDP and 5FU, as far as practicable. Among the responders to the first chemoradiotherapy cycle, there was no significant difference in the long-term (5-year) survival rate between the 18 patients who underwent esophageal surgery and the 13 patients who did not (23% vs. 23%). Among the nonresponders, the 11 patients who underwent surgery showed a tendency toward longer survival than the five patients who had had no surgery. The nonresponders had 1- and 2-year survival rates of 64% and 33%, respectively. The corresponding rates for the 5 nonsurgical patients who completed the two chemoradiotherapy cycle were 20% ands 20%, respectively. For a T4N0-1M0 squamous cell carcinoma in the thoracic esophagus, full-dosage chemoradiotherapy (definitive chemoradiotherapy) is preferred for responders to a half-dose of chemoradiotherapy as much as esophagectomy, whereas esophagectomy may be preferred for nonresponders.

The prognosis after surgery alone for patients who have a locally advanced esophageal cancer, in particular a T4 tumor involving the trachea, bronchus, or aorta, has remained dismal. Combined resection of a neighboring organ(s) together with esophagectomy has offered no benefit to the survival rate for such patients despite the high incidence of mortality and morbidity [1]. Palliative (R1 or R2) esophagectomy followed by radiotherapy with or without

chemotherapy has also essentially offered no survival benefit compared with nonsurgical treatment [2].

Many surgeons have considered that chemoradiotherapy followed by surgery (whenever possible) is standard treatment for patients with a locally advanced esophageal cancer (i.e., T3/T4, N-any, M0 clinical stage tumors), whereas chemoradiotherapy alone should be given for nonresectable esophageal cancer or to patients who are medically unfit for surgery [3-5]. These surgeons have believed that only complete (R0) resection of the tumor following chemoradiotherapy can provide a survival benefit for patients with a locally advanced esophageal cancer, and that the volume of chemoradiation should be the minimum required to decrease the otherwise substantial associated postoperative morbidity and mortality (neoadjuvant chemoradiotherapy).

However, the relatively high rate of clinical and pathologic complete response with combined chemoradiotherapy has raised the question of whether surgical resection is necessary after chemoradiotherapy [6]. Radiologists and oncologists have also thought that chemoradiotherapy can offer a survival benefit even for such a tumor, when a complete response is achieved by high-volume chemoradiation (definitive chemoradiotherapy) [7]. They have thought that esophagectomy was necessary, rather, for persistent or recurrent disease after definitive chemoradiotherapy (salvage surgery) [8].

In the prospective nonrandomized trials reported here, long-term results were compared between definitive chemoradiotherapy with and without surgery to evaluate the need for surgery in the multimodal treatment for a T4 esophageal cancer.

Patients and Methods

Population

Among 482 patients with a cancer in the thoracic esophagus referred to the Kurume University Hospital between 1994 and 2002,

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the tumor in 124 patients was defined as T4 according to the TNM classification of the International Union Against Cancer (UICC) [9] during the preoperative staging. The criteria for inclusion in this prospective trial were as follows: (1) biopsy-confirmed squamous cell carcinoma in the thoracic esophagus; (2) locally advanced stage clinically defined as a T4 tumor [tumors defined according to the latest UICC classification as M1-Lym because of celiac or supraclavicular nodal involvement were also included in this trial (regional disease), excluding any patient with distant metastasis (M1-Org)]; (3) no previous treatment; (4) WHO performance status 0 to 2; (5) adequate hematologic, hepatic, renal, cardiac, and pulmonary function; the patient must also have a general condition adequate to tolerate esophagectomy or definitive chemoradiotherapy; (6) =75 years of age; (7) no active double primary cancer; (8) no contraindication to 5-fluorouracil (5FU), cisplatin (CDDP), or extensive irradiation; and (9) the patient must give a written informed consent.

The pretreatment staging evaluation consisted of: (1) a general physical examination; (2) chest and abdominal radiography; (3) contrast esophagography; (4) esophagoscopy; (5) cervical and upper abdominal ultrasonography (US); (6) computed tomography (CT) of the neck, chest, and upper abdomen; (7) magnetic resonance of imaging of the neck and chest; and (8) bone scintigraphy; with (9) bronchoscopy performed only for a cancer in the upper or middle thoracic esophagus.

Among the 124 patients with a T4 esophageal cancer referred to our department during the study period, only 53 were included in this trial. The excluded patients were as follows: 2 with adenocarcinoma or small-cell carcinoma; 16 with distant organ metastases; 9 with previous chemotherapy, radiotherapy, or both; 17 with a low performance status index or a contraindication to surgery or chemotherapy; 7 were >75 years old; 1 had an active double primary cancer; and 19 did not give informed consent for this trial. Among the last group, 11 patients chose preceding surgery (palliative esophagectomy), and the other 8 patients chose chemoradiotherapy alone from the beginning.

Treatment

This study was a nonrandomized prospective trial based on the informed decision that patients chose whether to undergo surgery between the first and second chemoradiotherapy cycles (Fig. 1). The first cycle consisted of (1) CDDP 24 mg/m^2 on days 1 and 8 and 10 mg/day from days 2 to 5 and from days 9 to 12 as a drip intravenous infusion for 2 hours; (2) 5FU 500 mg/day as a continuous intravenous infusion for 24 hours from days 1 to 5 and from days 8 to 12; and (3) radiotherapy delivered in hyperfractions of 1.2 Gy twice a day from days 1 to 5, days 8 to 12 and days 15 to 19, to a total dose of 36 Gy.

The first chemoradiotherapy cycle was evaluated 2 weeks after the end of radiotherapy and consisted of a physical examination, contrast esophagography, esophagoscopy, and CT scan. Patients them each decided whether to undergo surgery after being fully informed of the efficacy of the chemoradiotherapy (informed decision). When patients elected to have surgery, they were subjected to esophagectomy or a bypass operation. On the other hand, when patients elected not to have surgery, they underwent only the second cycle of chemoradiotherapy, which consisted of the same chemotherapy protocol as the first cycle and radio-

Fig. 1. Our treatment protocol for a locally advanced (T4) esophageal cancer. Arm A: Chemoradiotherapy with surgery. Arm B: Chemoradiotherapy alone. CDDP: cisplatin; 5FU: 5-fluorouracil.

therapy in a total dose of 24 Gy. Patients who did have surgery also underwent a second chemoradiotherapy cycle the same as described above 1 month after surgery.

Radiotherapy was administered using an 10-MV linear accelerator. The visible tumor volume also included 2 cm longitudinal margins and 2 cm lateral margins. In cases of definitive chemoradiotherapy, the radiation fields of the second chemoradiotherapy cycle were the same as those of the first cycle. In the patients with surgery, boost fields, with an oblique field, covered the primary tumor with at least 2 cm margins.

Surgery was scheduled for 1 month after the preoperative treatment. Esophagectomy with systemic lymphadenectomy, including thoracoabdominal two fields or cervicothoracoabdominal three fields, was performed through a right thoracotomy with cervical esophagogastrostomy depending on the tumor location and the macroscopic findings of residual tumor (R classification [9]). For patients who underwent curative (R0) resection of a cancer in the upper or middle thoracic esophagus, three-field dissection was performed, whereas for those who underwent curative (R0) resection of a cancer in the lower thoracic esophagus, two-field dissection (total mediastinal lymphadenectomy) was performed [10]. For patients who underwent macroscopic incomplete (R2) resection of an esophageal cancer in any location, selective lymphadenectomy was performed. When, in the opinion of the surgeon, esophagectomy could not be satisfactorily achieved, a bypass operation was done. In all cases, the stomach was used for the reconstruction.

Criteria for Response and Statistical Analyses

After the first chemoradiotherapy cycle, patients were reevaluated using contrast esophagography, endoscopy, and CT scanning. The response was considered complete (CR) when no radiographic evidence of disease was seen, no residual tumor was found during esophagoscopy, and the biopsy was negative. Otherwise, the response was classified as partial (PR): >50% regression in the tumor size in square measure on the contrast esophagograms or >30% regression in the tumor size in its maximal diameter on the CT scan. The final categories were either stable disease (no change, or NC) or progression (progressive disease, or PD) [11, 12]. After resection, a complete histologic response was defined as the absence of residual tumor in the esophagus and in nodal tissue. Toxicity was graded using

the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) [13].

Follow-up using a general physical examination, tumor markers including SCC antigen and carcinoembryonic antigen (CEA), and chest radiographs were performed every month for the first 2 years, every 2 months for 2 to 3 years after treatment, every 3 months for 3 to 5 years after treatment, and every 6 months thereafter. Endoscopy, US of the neck and abdomen, CT scan, and bone scintigraphy were routinely scheduled every year and repeated when any new clinical symptoms appeared or if any of the tumor markers increased to an abnormal level.

The overall survival was estimated according to the Kaplan-Meier method and compared using the generalized Wilcoxon test. The survival rates were calculated as being from the first day of chemoradiotherapy.

Results

Response to Chemoradiotherapy

Fifty-three patients were enrolled in this trial. All patients received the complete dose of the first chemoradiotherapy cycle planned. After the first cycle, there were 32 (60%) patients with a partial response, 16 (30%) patients with no change or stable disease, and 5 (9%) patients with progressive disease. None of the patients had a complete response. Accordingly, the response rate to the first chemoradiotherapy cycle was 60% (32/53). Among the 23 patients who elected not to surgery, the second chemoradiotherapy cycle was completely administered to 18 patients; among them 7 (39%) patients had a complete response, 7 (39%) had a partial response, and 4 (22%) had no change or progressive disease. The other five patients did not undergo the second chemoradiotherapy cycle due to fistulas, tumor progression, or poor general condition. On the other hand, among the 30 patients who elected to undergo surgery, the second chemoradiotherapy cycle was completely administered to 21 patients but not in the other 9 patients due to postoperative complications or the patient's refusal (Fig. 2).

The pathologic response was assessed according to the Guidelines for Clinical and Pathological Studies on Carcinoma of the Esophagus of the Japanese Society for Esophageal Diseases [11] in the 27 resected specimens: 26 specimens after the first chemoradiotherapy cycle and 1 after the second chemoradiotherapy cycle. A complete pathologic response (pCR)-no cancer was seen in the resected specimen of the esophagus-was found in four (15%) patients. Of these four patients, however, two had metastases in their lymph nodes. Accordingly, only 2 (7%) of 26 patients who underwent esophagectomy after the first chemoradiotherapy cycle in our regimen were cancer-free.

Toxicity

Concurrent chemoradiotherapy was generally well tolerated. The major toxicity was hematologic, with 30% of the patients experiencing grade 3 or 4 leukopenia, 13% with grade 3 or 4 anemia, and 9% with grade 3 or 4 thrombocytopenia during or after the first chemoradiotherapy cycle. Altogether, 2 (6%) of 34 patients experienced grade 3 or 4 leukopenia, and 6% of those experienced grade 3 or 4 anemia during or after the second chemoradiotherapy cycle [13]. There were no death due to hematologic toxicity. Among those with nonhematologic toxicity, fistula formation was
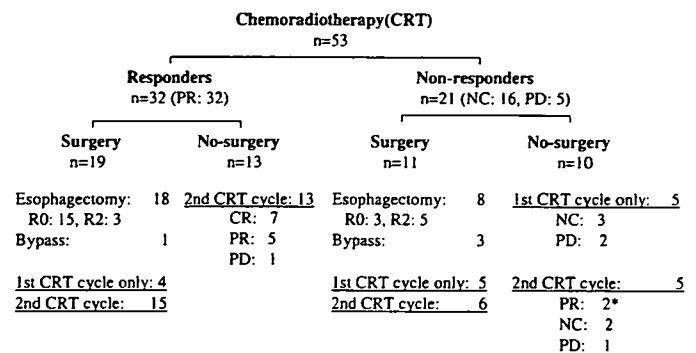

Fig. 2. Response to chemoradiotherapy and treatment modalities. After being informed of the response to the first chemoradiotherapy cycle, each patient decides whether to undergo surgery (informed decision). PR: partial response; NC: no change; PD: progressive disease; R0: no residual tumor (complete resection); R2: macroscopic residual tumor (incomplete resection).

the most common and serious toxic response, with 6% of the patients developing esophagopulmonary fistula, 6% esophagobronchial fistula, and 2% aortoesophageal fistula during or after the first chemoradiotherapy cycle; 3% of the patients developed an aortoesophageal fistula and 3% an aortobronchial fistula during or after the second chemoradiotherapy cycle. Among the nine patients with fistula formation, five (56%) died of the fistula during hospitalization (Table 1). The overall hospital mortality rate due to chemoradiotherapy associated toxicity was 9% (5/53).

Surgical Results

Chemoradiotherapy followed by esophagectomy resulted in two (8%) hospital mortalities: one 3 days after surgery caused by pulmonary infarction and the other 7 months after surgery caused by a brain abscess. The most common postoperative complications in patients who underwent chemoradiotherapy followed by esophagectomy were recurrent nerve paralysis and aspiration pneumonia, which were the same as those in the patients who underwent surgery alone in our hospital [10]. The most common postoperative complications after chemoradiotherapy followed by bypass operation were anastomotic leak and aspiration pneumonia. The morbidity rates after esophagectomy and after the bypass operation were 85% and 100%, respectively (Table 2).

Survival Outcomes

The median follow-up for the surviving population was 51 months. No patient was lost to follow-up. Altogether, 37 patients died of progressive or recurrent disease: 19 after surgery and 18 after no surgery. Other causes of death were a postoperative complication in one patient (pulmonary embolism), pneumonia without recurrence in one, myocardial infarction in one, and another primary cancer in two (cholangiocellular carcinoma, prostate cancer). For one patient, the precise cause of death and the disease status at the time of death were unknown.

The median survival time for the whole population was 29 months, with 1-, 3-, and 5- year overall survival rates of 60%, 21%, and 16%, respectively. The 1-, 3-, and 5-year survival rates for the 30 patients who elected to undergo surgery (esophagectomy in 26, and bypass in 4) were 73%, 28%, and 17%, respectively. The

Table 1. Toxicity of grade 3 or higher according to the NCI-CTC

First CRTx cycle (n = 53)	
Leukopenia	16 (30%)
Anemia	7 (13%)
Thrombocytopenia	5 (9%)
Esophagopulmonary fistula	3[b] (6%)
Esophagobronchial fistula	3[b] (6%)
Sepsis/fever	2 (4%)
Diarrhea	2 (4%)
Pneumonia	2 (4%)
Aortoesophageal fistula	1[b] (2%)
Renal dysfunction	1 (2%)
DIC	1 (2%)
Second CRTx cycle (n = 39)[a]	
Leukopenia	2 (5%)
Anemia	2 (5%)
Aortoesophageal fistula	1[b] (3%)
Aortobronchial fistula	1[b] (3%)
Pneumonitis	1 (3%)

NCI-CTC: National Cancer Institute-Common Toxicity Criteria Version 2.0, January 30, 1998; CRTx: chemoradiotherapy; DIC: disseminated intravascular coagulation:
[a]Surgery group 21, no-surgery group 18.
[b]Hospital death in one cases each.

Table 2. Postoperative complications

Complication	Esophagectomy (n = 26)	Bypass (m = 4)
Recurrent nerve paralysis	13 (50%)	1 (25%)
Aspiration pneumonia	9 (35%)	3 (75%)
Tracheal ischemia (ulcer, erosion)	6 (23%)	0
Pyothorax	6 (23%)	0
Anastomotic leak	5 (19%)	4 (100%)
Ileus	3 (12%)	0
Severe arrhythmia	2 (8%)	0
Pulmonary infarction	1[a] (4%)	0
MRSA enteritis	1 (4%)	0
Brain abscess	1[a] (4%)	0
Morbidity	22 (85%)	4 (100%)
Mortality	2 (8%)	0

MRSA: methicillin-resistant *Staphylococcus aureus*.
[a]Hospital mortality.

Fig. 3. Survival curves for patients who underwent surgery and those who did not. The survival rate for the surgery group was not different from that for the no-surgery group (p = 0.08).

Fig. 4. Survival curves for responders and for nonresponders to chemoradiotherapy. There was a significant difference in the survival rates between the responders and the nonresponders (p = 0.008).

corresponding rates for the 23 patients who elected not to undergo surgery (chemoradiotherapy alone in 16, additional esophageal stent in 6, and emergency salvage surgery in 1) were 44%, 13%, and 13%, respectively. There was no significant difference in the survival rate between the surgical patients and the nonsurgical patients (p = 0.08) (Fig. 3).

The 1-, 3-, and 5-year survival rate for the 32 responders to the first chemoradiotherapy cycle were 75%, 31%, and 23%, respectively, and for the 21 nonresponders the 1- and 3-year survival rates were 38% and 6%, respectively, with no patient surviving more than 4 years. There was a statistically significant difference in the survival rates between the responders and the nonresponders to chemoradiotherapy (p = 0.008) (Fig. 4).

To analyze the outcome fairly, it seems preferable to compare the surgical patients to the nonsurgical patients according to response to chemoradiotherapy. For the 19 surgical patients among the 31 responders, the 1-, 3-, and 5-year-survival rates were 79%, 37%, and 23%, respectively; the corresponding rates for the 13 nonsurgical patients were 69%, 23%, and 23%, respectively. Among the responders to chemoradiotherapy, there was no dif-
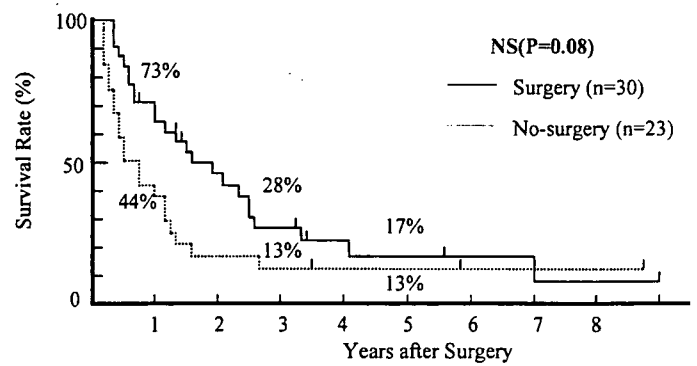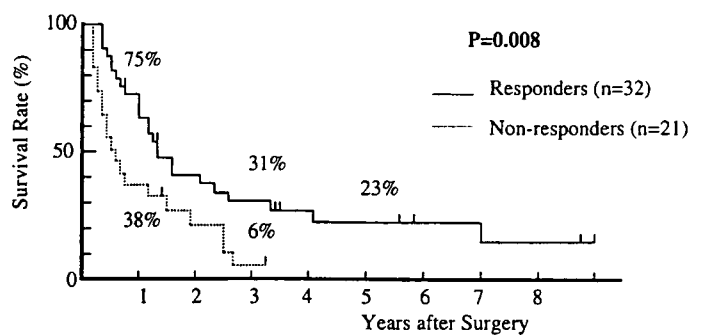
ference in the survival rate between the surgical patients and the nonsurgical patients (Fig. 5).

On the other hand, for the 11 surgical patients among the 21 nonresponders, the 1- and 2-year-survival rates were 64% and 33%, respectively; the corresponding rates for the 5 nonsurgical patients who completed both the first and second chemoradiotherapy cycles-definitive chemoradiotherapy-were 20% and 20%, respectively. For the nonresponders to chemoradiotherapy, the surgical patients had a tendency toward longer survival than the nonsurgical patients, although there was no significantly difference between them (p = 0.168) (Fig. 6). Among five patients classified as nonsurgical patients, one underwent salvage surgery after definitive chemoradiotherapy and survived 32 months, whereas the other four patients died within 1 year. Accordingly, the 1- and 2-year-survival rates of the patients who underwent surgery were 66% and 39%, respectively, whereas the corresponding rates for the patients who did not were 0% and 0%. The difference between them was statistically significant (p = 0.001).

Discussion

We have presented the results of a prospective comparative trial of 53 patients with T4N0-1M0 squamous cell carcinomas in the thoracic esophagus treated with chemoradiotherapy and with or without surgery. This trial was not randomized. It was difficult for us to perform a randomized control trial comparing surgery versus no surgery in Japan. Patients themselves chose a treatment arm-surgery versus no surgery-(informed decision) based on
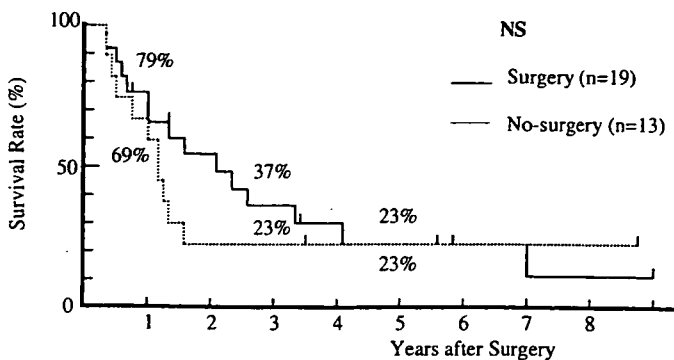
Fig. 5. Survival curves for the responders to chemoradiotherapy. There was no difference in the survival rates between the patients who underwent surgery and those who did not.
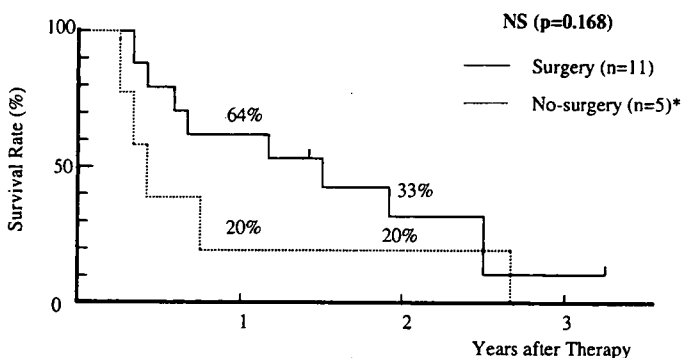

Fig. 6. Survival curves for nonresponders to chemoradiotherapy. *Patients who received both the first and second chemoradiotherapy cycles (i.e., definitive chemoradiotherapy). There was a tendency toward a better survival rate for patients who underwent surgery than for those who did not ($p = 0.168$).

information from both surgeons and radiologists about their response to the first chemoradiotherapy cycle, the method of the next treatment, expected prognosis, and other factors. Because of such a complicated situation, we obtained informed consent using a certain printed form from almost all patients enrolled, whereas for other patients we used hand-written consent forms

A total of 14 patients did not receive the second chemoradiotherapy cycle because of fistulas, postoperative complications, patient's refusal. Moreover, 5 of the 14 patients underwent neither surgery nor the second chemoradiotherapy cycle mainly due to a fistula or poor general condition (or both). When the survival rates were compared in this study, therefore, we included the patients who underwent surgery, regardless of esophagectomy or bypass and regardless of with or without the second chemoradiotherapy cycle; in contrast, we excluded the patients who did not undergo the second chemoradiotherapy cycle from the nonsurgical patient group.

In this trial, chemotherapy using (1) CDDP 24 mg/m² on days 1 and 8, and 10 mg/day on days 2 to 5 and days 9 to 12; (2) 5FU 500 mg/days on days 1 to 5 and days 8 to 12; and (3) hyperfraction radiotherapy of 1.2 Gy twice a day on days 1 to 5, days 8 to 12, and days 15 to 19, to a total dosage of 36 Gy were applied as the first cycle. The clinical effect of the first chemoradiotherapy cycle was evaluated after 2 weeks; then more than 1 to 2 weeks was needed to obtain informed consent. Thus the interval between the first

and second cycles of chemoradiotherapy, even in the nonsurgical cases, was about 4 weeks on average. In one-third of patients who underwent chemoradiotherapy according to this regimen, a nadir of grade 3 or higher bone marrow suppression was observed 2 weeks after chemoradiotherapy (Table 1). It was therefore difficult to start the second chemoradiotherapy cycle within 3 weeks after the first chemoradiotherapy cycle. On the other hand, we thought that the first cycle of chemoradiotherapy in our regimen should achieve an effect equal to that of other regimens of neoadjuvant chemoradiotherapy for T4 esophageal cancers [4, 5]. The biologic effect of twice-daily radiotherapy of 2.4 Gy per day, to a total dosage of 36 Gy for 3 weeks, was considered comparable to that of once-daily radiotherapy of 2 Gy per day to a total dosage of 40 Gy for 4 weeks. The area under the curve (AUC) of the CDDP concentration in the blood after administration of CDDP 24 mg/m² on days 1 and 8 and 10 mg on day 2 to 5 and day 9 to 12; that is approximately 150 mg/2 weeks in total, was considered comparable to that after every-day administration of CDDP 10 mg for 4 weeks, that is, 200 mg/4 weeks in total.

The 5-year survival rate in this trial was 16% for the whole population, 23% for the responders, and 0% for the nonresponders. The 5-year survival rate was 17% for the surgical patients and 13% for the nonsurgical patients. Surgery did not seem to have improved the survival for responders to the first chemoradiotherapy cycle: Those patients had a 5-year survival rate of 23% with surgery versus 23% without surgery. On the other hand, surgery seemed to have improved the survival for nonresponders to the first chemoradiotherapy cycle: Those patients had 1- and 2-year survival rates of 64% and 33%, respectively, with surgery versus 20% and 20%, respectively, without surgery. When the patient undergoing salvage surgery was included in the surgical patient group, the 1- and 2-year survival rates for the surgical patients were 66% and 39%, respectively, whereas the corresponding rates for the nonsurgical patients were 0% each. It was concluded that in patients with a T4N0-1M0 esophageal cancer definitive chemoradiotherapy offered a survival similar to that achieved by surgery for responders but not for nonresponders.

Many studies using neoadjuvant chemoradiotherapy followed by esophagectomy to treat locally advanced esophageal cancers have been reported. Most of them used CDDP-based chemotherapy with a radiation dosage between 40 and 45 Gy. The complete histologic response rate in the resected specimens ranged from 28% to 33%. This rate for all patients who had undergone neoadjuvant chemoradiotherapy has ranged from 18% to 28%. They reported the superiority of neoadjuvant chemoradiotherapy followed by surgery over chemoradiotherapy alone or surgery, alone [3-5]. However, some investigators have doubted the need for surgical resection after chemoradiotherapy for a locally advanced esophageal cancer [6]. Phase III studies to determine any significant benefit from neoadjuvant chemoradiotherapy followed by surgery for a locally advanced esophageal cancer compared with chemoradiotherapy alone are rare.

Recently, a French randomized controlled trial on locally advanced but resectable (T3-4N0-1M0) esophageal cancers including squamous cell carcinoma and adenocarcinoma compared chemoradiotherapy followed by surgery to chemoradiotherapy alone. It demonstrated similar 2-year survival rates (34% vs. 40%) for the two treatment modalities in the responders to two-thirds doses of definitive chemoradiotherapy [14]. A German randomized controlled trial also demonstrated no difference in 3-year

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survival rates (28% vs. 30%) between preoperative chemoradiotherapy followed by surgery versus chemoradiotherapy alone for a T3-4N0-1M0 squamous cell carcinoma [15]. As reported above, some authors have maintained that surgery is not necessary for responders to chemoradiotherapy.

Another approach has been to explore whether surgical resection after chemoradiotherapy can improve the survival results compared to chemoradiotherapy alone. Murakami et al. [16] reported results from a trial comparing chemoradiotherapy alone to chemoradiotherapy followed by esophagectomy for locally advanced (T3 or T4) esophageal cancers. They divided the patients into two groups. In one group, esophagectomy was performed in nonresponders to chemoradiotherapy but was not performed in responders; in the other group, patients underwent esophagectomy alone. The 5-year survival rate was no different between the two groups (31% vs. 30%). They concluded that surgery was not necessary for responders to chemoradiotherapy. Whether esophagectomy is necessary for those who do not respond chemoradiotherapy remains controversial. Murakami et al. suggested, similar to our conclusion, that surgery was necessary only for nonresponders to chemoradiotherapy. There are some reasons to support esophagectomy for nonresponders. First, clinical evaluation of the response to chemoradiotherapy does not always correlate with the pathologic response. Therefore, a complete pathologic response in the resected specimen or complete R0 resection of esophageal cancer can be achieved even in patients who were evaluated as being nonresponders. In this trial, 3 (27%) of the 11 nonresponders to the first chemoradiotherapy cycle underwent R0 resection of esophageal cancer (Fig. 2). Second, esophagectomy for nonresponders to the first cycle of chemoradiotherapy and subsequent chemoradiotherapy (the second cycle of chemoradiotherapy) might be comparable to salvage surgery for partial responders to definitive chemoradiotherapy [17].

A consensus is not always obtained regarding the need for esophagectomy in a multimodol treatment regimen for T4 esophageal cancers. Further evaluation using a large-scale prospective randomized study is needed.

Acknowledgments

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Invited Commentary (DOI: 10.1007/s00268-004-1081-3)

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The authors performed a prospective nonrandomized trial to evaluate the role of surgery secondary to chemoradiotherapy in patients with T4N0-1M0 esophageal cancer. They found significantly better survival in responders to chemoradiotherapy than in nonresponders and a better survival rate in the surgery group than in the nonsurgery group. They analyzed whether responders obtained any additional benefit by undergoing surgical resection compared with responders who did not, probably because per-

formance of surgery after chemoradiotherapy was associated with a high rate of serious postoperative complications. They could not detect any benefit of surgical resection following chemoradiotherapy by comparing the survival curves of these two groups, although the 2- and 3-year survival rates were 55% and 37%, respectively, which were higher than the rates of 23% and 23%, respectively, in the nonsurgery group. The same analysis was done for nonresponders and showed no significant difference in survival between the surgery and nonsurgery groups, but the 1- and 2-year survival rates for the surgery group (64% and 33%, respectively) were considerably better than in the no-surgery group (20% and 20%, respectively).

This is an important study for trying to determine the role of surgery in treating of a T4 stage esophageal cancer, which cannot be cured by surgery alone and might be systemic with micrometastases. From a historical point of view, surgery after radiation therapy has not achieved good results for resectable esophageal cancer because of the difficulty performing anatomically precise resection due to severe postradiation fibrosis and various severe postoperative complications. The survival curves in their Figures 4 and 5 show that the 5-year survival rate for responders was 23%

irrespective of surgery, so surgery might provide little if any benefit for T4N0-1M0 cancer in this protocol.

In the discussion, the authors recommended surgery for nonresponders, and not for responders. This might be reasonable because surgery did not lead to better survival in responders and a tendency for a better survival rate with the surgery group was noted only in nonresponders. The survival curves of nonresponders in their Figure 6 shows higher survival rates within 2 years for the surgery group compared with the nonsurgery group. We might say that surgery can be recommended for the nonresponders who would like to have a higher probability of living 1 to 2 years longer. In Figure 5, we see a 50% two-year survival rate for the surgery group of responders, although it is only 23% for the no-surgery group, so surgery might also be recommended for responders who want a higher probability of living at least 2 years.

In conclusion, this is an interesting study that showed meaningful efficacy of chemoradiotherapy for T4N0-1M0 esophageal cancer independent of surgery. We would like to see another prospective randomized study by these investigators using another protocol.

ORIGINAL ARTICLE

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Salvage surgery after definitive chemoradiotherapy for esophageal cancer

Abstract
Background. Definitive chemoradiotherapy has been performed as a first-line treatment for esophageal cancer, whereas salvage surgery might be the only reliable treatment for patients with recurrence after definitive chemoradiotherapy.
Methods. We reviewed 38 patients with squamous cell carcinoma who underwent esophagectomy and 6 patients who underwent lymphadenectomy after definitive chemoradiotherapy ($\geq$50 Gy).
Results. The median survival time and 5-year survival rate after salvage esophagectomy were 16 months and 27%, respectively. Three of the 7 patients who had cervical esophageal cancer underwent cervical esophagectomy with laryngeal preservation. Two patients (5.2%) who underwent salvage esophagectomy with three-field lymphadenectomy before 1997 died of postoperative complications, but no patient died of complications thereafter. Although the overall survival after salvage esophagectomy was correlated with residual tumor (R) ($P = 0.0097$), the median survival time of 7 patients with residual tumors (R_2) was 7 months. Overall postoperative survival was closely correlated with the response to chemoradiotherapy ($P < 0.0001$) but was not associated with histologic effects on resected specimens. Survival was significantly correlated with the depth of viable tumor invasion (pT) ($P = 0.0013$) and with lymph node metastasis (pN) ($P < 0.0001$). Long-term survival was achieved in 5 of the 6 patients who underwent salvage lymphadenectomy.

Conclusions. Salvage surgery should be considered for patients with recurrence after definitive chemoradiotherapy. Salvage lymphadenectomy may be useful for recurrence confined to the lymph nodes whereas postoperative complications of salvage esophagectomy should be warranted.

Key words Esophageal cancer · Squamous cell carcinoma · Chemoradiotherapy · Salvage surgery · Salvage lymphadenectomy

Introduction

Definitive radiotherapy combined with infusion of cisplatin and 5-fluorouracil (5-FU) improves the survival of esophageal cancer patients compared with radiotherapy alone [1,2]. Medical and radiation oncologists have also reported the improved survival of esophageal cancer patients treated by definitive chemoradiotherapy without surgery [3–7]. However, local failure and lymph node metastasis are frequent problems after definitive chemoradiotherapy [8,9]. Further radiotherapy is not indicated because the dose will exceed that treated by the spinal cord and no effective second-line chemotherapy agents for esophageal cancer have been discovered. Thus, surgery is the only useful treatment for recurrence after definitive chemoradiotherapy. The outcome of salvage esophagectomy after definitive chemoradiotherapy is comparable with that of esophagectomy after neoadjuvant chemoradiotherapy [10,11], but the operative risk of salvage esophagectomy might be higher than that of esophagectomy after neoadjuvant chemoradiotherapy [11]. Lymphadenectomy might also be indicated including as part of salvage surgery after definitive chemoradiotherapy.

In this study, we reviewed the profile and prognosis of esophageal cancer patients who underwent salvage esophagectomy or lymphadenectomy after definitive chemoradiotherapy. To search for prognostic valuables after salvage esophagectomy, we examined various clinical and pathological parameters.

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Patients and methods

We reviewed the records of 725 patients with esophageal cancer who underwent esophagectomy between 1992 and 2003 at the Institute of Gastroenterology of Tokyo Women's Medical University in Japan. Thirty-eight patients with a clinical diagnosis of esophageal cancer who received definitive chemoradiotherapy (≥50Gy) before esophagectomy were included in this study, whereas 3 patients who underwent esophagectomy 10 years or more after definitive radiotherapy were excluded. Lymphadenectomy was performed in 6 patients in whom lymph node metastases were detected after definitive chemoradiotherapy. In all patients, chemotherapy consisted of 5-fluorouracil and/or cisplatin/nedaplatin was given concurrently or sequentially with definitive radiotherapy.

Eight patients who received chemoradiotherapy at another hospital were referred to our institute at the diagnosis of recurrence. The other 30 patients received chemoradiotherapy and were followed in our institute. Data on the general condition and clinical stage before treatment were obtained in all patients. A diagnosis of squamous cell carcinoma was histologically confirmed before treatment by endoscopic biopsy in all of the patients. Clinical staging was based on the results of barium swallow, endoscopy, endoscopic ultrasound (EUS), and computed tomography (CT) scanning, and was performed according to the TNM classification (UICC) [12].

The response was assessed at 1 month after chemoradiotherapy according to the criteria for the response assessment of nonsurgical treatment proposed by the Japanese Society for Esophageal Diseases [13]. The primary tumor was reevaluated by review of the barium swallow, endoscopy, and biopsy findings, whereas the metastatic lesions were assessed by using CT scans of the neck, chest, and abdomen as well as the results of EUS. Diagnosis of response to chemoradiotherapy in the patients was evaluated together in the primary tumor and in the metastatic lesions.

On examination of the resected specimens, the depth of tumor invasion (pT) was defined on the basis of the deepest detected layer of viable cancer cells. Lymph node metastasis (pN) or distant metastasis (pM) was defined by the detection of viable cancer cells in lymph nodes or other organs. The tumor response to treatment was also evaluated by examination of the resected specimens according to the histopathologic criteria for assessing the effects of radiation and/or chemotherapy [13]. If no viable cancer cells were detected (grade 3), this was classified as a pathologic complete response (pCR), whereas viable cancer cells comprising less than one-third of the tumor (grade 2) was classified as a partial response. If viable cancer cells comprised one-third or more of the tumor (grade 1) or there was no discernible effect of treatment (grade 0), this was classified as no response.

Differences of quantitative data were assessed by Student's t test. Differences of percentages were evaluated

Table 1. Characteristics of patients who underwent esophagectomy after definitive chemoradiotherapy

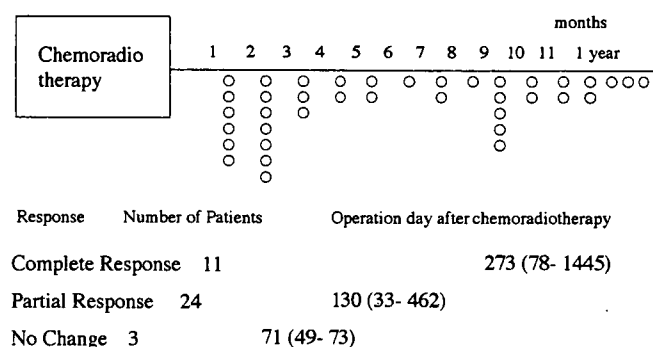| Characteristics	Number of patients ($n = 38$)
Male:female ratio	28:10
Median age, years (range)	63 (36–79)
Tumor location	
Cervical	7 (18%)
Upper	3 (8%)
Middle	21 (55%)
Lower	7 (18%)
Tumor invasion	
T1	6 (16%)
T2	2 (5%)
T3	12 (32%)
T4	18 (47%)
Distant metastasis	
M0	29 (76%)
M1	9 (24%)
Total dosage of irradiation: mean (range)	62.4 (50–78) Gy

Fig. 1. Interval between the final day of chemoradiotherapy and salvage esophagectomy

by the two-sided chi-square test or Fisher's exact test. Survival was calculated from the day of operation until the last known date of follow-up. All survival data were analyzed with Statview, Version 4 (SAS Institute, Cary, NC, USA). Survival curves were constructed according to the Kaplan–Meier method and were compared using the log-rank test.

Results

The tumor locations and pretreatment clinical stages are shown for the 38 patients who underwent salvage esophagectomy in Table 1. The median interval from the final day of chemoradiotherapy until the operation was 156 (33–1445) days (Fig. 1), and its duration was associated with the response to chemoradiotherapy.

Although three of the seven patients who had cervical esophageal cancer underwent cervical esophagectomy with preservation of the larynx, one patient died of tracheal obstruction caused by local recurrence. The other four patients underwent pharyngolaryngoesophagectomy.

Table 2. Approaches and short outcomes of salvage esophagectomy

Approaches	Early period ($n = 15$)	Later period ($n = 16$)	Probability
Right thoracotomy	11	7	
Left thoracotomy	2	6	NS
Transhiatal	2	3	
Lymph node dissection			
Three-field	6	4	
Two-field	5	5	NS
Local and abdominal	4	7	
Outcomes			
Mortality (within 30 days)	1		
Hospital mortality (>30 days)	1		
Leakage (surgery)	6 (3)	3 (2)	
Pneumonia	4	2	
Wound infection	1	1	
Pleural effusion	1	2	
Residual tumors (%)			
R_0	9	10	
$R_{1,2}$	6	6	
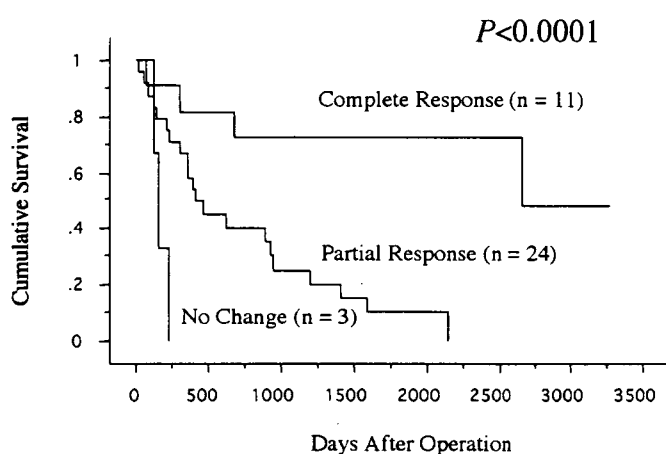
Fig. 2. Survival after salvage esophagectomy was correlated with response to definitive chemoradiotherapy
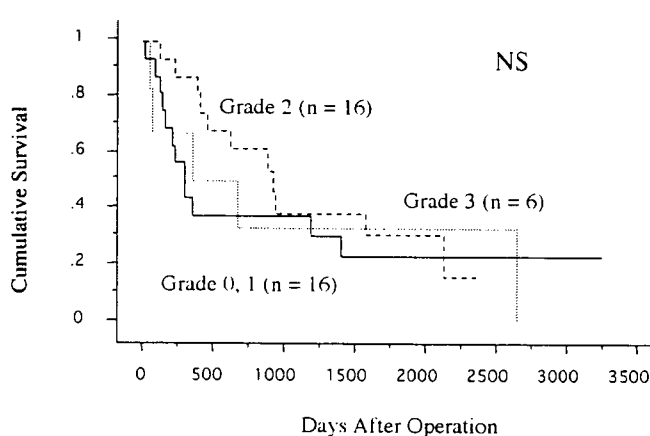
Fig. 3. No differences were shown in overall survival after salvage esophagectomy according to histopathologic effect in the resected specimens

Surgical procedures and postoperative complications of esophagectomy are shown for 31 patients with thoracic esophageal cancer (Table 2). Two patients (5.2%) who underwent extended esophagectomy with three-field lymph node dissection before 1997 died of postoperative complications; less-invasive procedures were adopted thereafter. One patient died of acute respiratory distress syndrome (ARDS) on postoperative day 22, and 1 patient died of anastomotic leakage and pneumonia on postoperative day 62. Both patients underwent extended esophagectomy via right thoracotomy with three-field lymphadectomy during the early period (1992–1996). Then, three-field lymphadenectomy was performed limited to 4 patients with cervical metastasis diagnosed preoperatively. There was no operative mortality and no hospital deaths during the later period (1997–2003). The incidence of postoperative pneumonia also decreased in the later period (from 5 to 2 cases). However, the incidence of anastomotic leakage was high in the both periods (5 versus 4 cases).

With a median follow-up period of 61 months, the median survival time and the 5-year survival rate after salvage esophagecotmy were 16 months and 27%, respectively. There were no significant differences of overall postoperative survival in relation to the pretreatment clinical staging. In contrast, the response to chemoradiotherapy had a significant influence on postoperative survival ($P < 0.0001$) (Fig. 2). Postoperative survival was not influenced by the interval between the final day of chemoradiotherapy and the day of surgery. There was also no difference in survival related to the pathologic effect of therapy on the resected specimens (Fig. 3). Four of six patients with a pathologic complete response (grade 3) died of pneumonia or heart failure. The survival of the patients without residual tumor (R_0) was significantly better than that of the R_1 or R_2 patients ($P = 0.0097$) (Fig. 4). However, the median survival time of 7 patients with residual tumors (R_2) was 231 days (133–410 days). The depth of viable tumor invasion (pT) ($P = 0.0013$) (Fig. 5) and lymph node metastasis
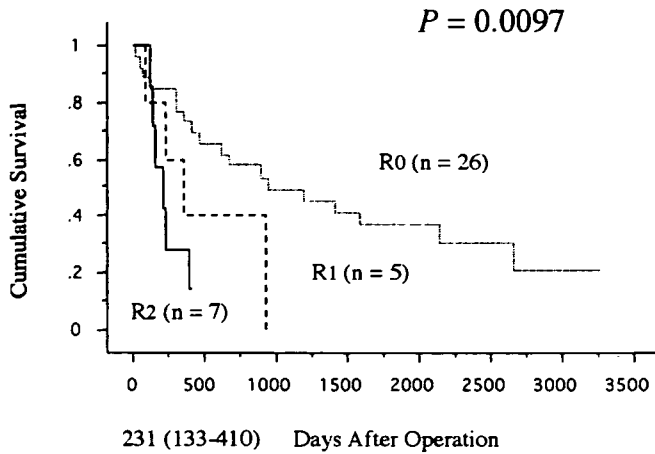
$P = 0.0097$

231 (133-410)   Days After Operation

Fig. 4. Survival of patients after salvage esophagectomy without residual tumors (R_0) was significantly better than that of patients with R_1 or R_2
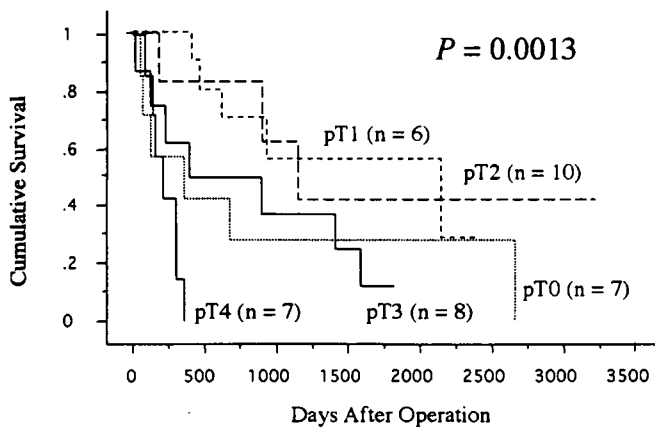
$P<0.0001$

Days After Operation

Fig. 6. Survival after salvage esophagectomy was correlated with viable metastasis in the resected lymph nodes (pN)

$P = 0.0013$

Days After Operation

Fig. 5. Survival after salvage esophagectomy was correlated with depth of viable cancer cells in the resected specimens (pT)

(pN) (Fig. 6) ($P < 0.0001$) both had a significant influence on survival.

Six patients underwent lymphadenectomy alone for lymph node metastasis after chemoradiotherapy (Table 3). The primary tumors showed a complete response in all six patients. Among them, three patients had metastatic nodes within the radiation field (cases 2, 3, and 4), but the other three had nodes located outside the field and were given further radiation after lymphadenectomy (cases 1, 5, and 6). One patient died of multiple metastases to distant lymph nodes, but the other five patients survived without recurrence.

Discussion

Definitive chemoradiotherapy is performed as a first-line treatment for squamous cell cancer of the esophagus, not only for advanced disease but also for operable tumors. The
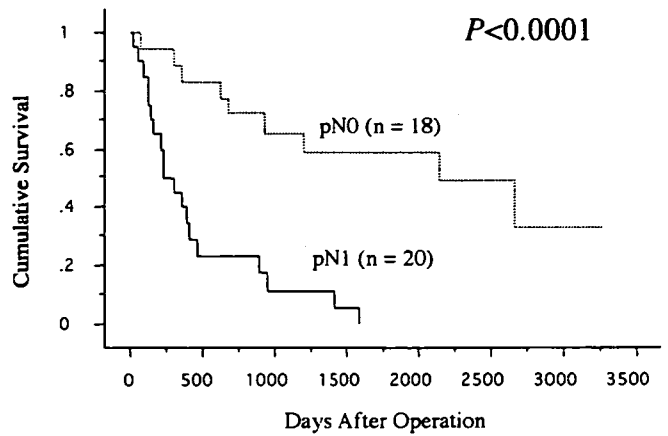
CR rate is reported to be high, ranging from 33% to 61%, but the long-term survival rate is low [5-7]. A considerable number of patients develop local and/or regional recurrence after definitive chemoradiotherapy. Surgeons are forced to treat these patients because only salvage surgery is an effective treatment for recurrence after definitive chemoradiotherapy. Although we could not compare with the outcome of definitive chemoradiotherapy without surgery, the results of this study indicated that salvage surgery might be regarded as an effective second-line treatment after definitive chemoradiotherapy.

Esophagectomy with three-field lymphadenectomy is the most radical surgery, but it is not suitable for all patients treated by definitive chemoradiotherapy because of the high operative risk. Our previous study showed that the risk of salvage esophagectomy was higher than that of planned esophagectomy after neoadjuvant chemoradiotherapy [11]. Although the interval between chemoradiotherapy and esophagectomy was not short, two patients died of postoperative complications. We could not anticipate these complications because both patients had no obvious indicators on physical examination or laboratory tests. A recent study showed that several cancer-free patients died of chronic heart failure, pneumonia, and myocardial infarction after definitive chemoradiotherapy [14]. These events tended to occur in the postoperative period after salvage esophagectomy, suggesting that salvage surgery should be done by a less invasive approach.

At present, definitive chemoradiotherapy is indicated in patients with cervical esophageal cancer to preserve the larynx. Three of our seven patients with cervical cancer underwent cervical esophagectomy with preservation of the larynx, but one patient developed local recurrence. Both the diagnosis of recurrence and detection of the proximal tumor margin might be difficult because of esophageal stricture. Therefore, salvage cervical esophagectomy with preservation of the larynx might only be indicated for a limited number of patients. Recently, we have used positron emission tomography with 2-[^{18}F]-fluoro-2-deoxy-D-glucose

Table 3. Characteristics of patients who underwent lymphadenectomy after definitive chemoradiotherapy

Patients	Stage	Location	Interval[a]	Lymph node[b]	Prognosis after lymphadenectomy
1. 75 Male	T3N1M1	Middle	9 months	Rt-supraclavicular	56 months alive
2. 54 Male	T4N1M0	Upper	11 months	Lt-supraclavicular	46 months alive
3. 43 Male	T2N1M0	Cervical	5 months	Lt-deep cervical	16 months alive
4. 79 Male	T3N1M0	Middle	6 months	Lt-supraclavicular	12 months dead
5. 67 Male	T1N0M0	Middle	13 months	Lt-cardial	38 months alive
6. 67 Male	T4N1M0	Middle	13 months	Rt-supraclavicular	16 months alive

[a] Interval from the final date of radiotherapy to the operation date
[b] Location of recurrent lymph node: Rt, right; Lt, left

(FDG-PET), but it cannot detect small recurrent tumors [15].

The pretreatment clinical stage was not associated with postoperative survival after salvage esophagectomy, but the clinical response to chemoradiotherapy was closely correlated. Histologic response on the resected specimens was not associated with postoperative survival because recurrent tumors might show viability without degeneration long term after achieving complete response. Therefore, histologic response might be useful for patients who underwent esophagectomy after neoadjuvant chemoradiotherapy but not for salvage esophagectomy, with the exception of pathological complete response (grade 3). Although staging of recurrence after definitive chemoradiotherapy might be difficult by imaging, residual tumor (R), pathologic tumor invasion (pT), and lymph node metastasis (pN) were valuable for prognostic factors after salvage esophagectomy. Even though their tumors were deemed unresectable on imaging, six patients with macroscopic residual tumors (R_2) survived for more than 4 months after salvage esophagectomy. Although we could not compare with results of nonsurgical treatment for these patients, palliative esophagectomy might improve the prognosis unless postoperative complications occur.

Salvage lymphadenectomy is another mode of salvage surgery for lymph node metastasis after chemoradiotherapy. When the local tumor maintains a complete response, esophagectomy may be unnecessary and the risk of lymphadenectomy is lower than that of esophagectomy. This study showed that the outcome of salvage lymphadenectomy was favorable, except in one patient who died of multiple metastases. The results of salvage lymphadenectomy were similar to those of lymphadenectomy for recurrence in the cervical nodes after esophagectomy with two-field lymphadenectomy. To improve the outcome of salvage surgery, patients with recurrence after definitive chemoradiotherapy should probably be immediately referred to experienced surgical institutions by their medical and radiation oncologists.

In conclusion, salvage surgery seems to be useful for recurrence of esophageal cancer after definitive chemoradiotherapy, but less invasive approaches should be adopted for salvage esophagectomy because of the high operative risk. Salvage lymphadenectomy is also useful for patients who have distant nodal metastasis without local recurrence.

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進行・再発食道癌に対する second-line としての Docetaxel + Nedaplatin 併用療法の検討

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要旨　食道扁平上皮癌に対する化学療法を含む前治療後の無効，再発例に対する second-line 治療としてのドセタキセル（TXT）／ネダプラチン（CDGP）併用化学療法を2002年から2004年に13例施行，評価可能な10例（男9例，女1例）を対象とした。年齢の中央値は65歳（56〜70歳），前治療は切除手術＋術後補助化学放射線療法が4例，切除手術＋術後補助化学療法1例，切除術後再発に対する化学療法3例で，切除不能例は2例であった。治療回数は1回が8例，2回が1例，3回が1例であった。投与は TXT 60 mg/m^2，CDGP 80 mg/m^2 を静脈内投与とし，3週間以上の休薬期間をおいた。効果は PR 2例，SD 6例，PD 2例であり CR はなかった。PD を除いた8例の本治療開始日からの50%無増悪生存期間は135日（88〜370日）で，50%生存期間は170日（88〜570日）であった。有害事象は白血球減少が主で Grade 2が1例，3が2例，4が5例であった。本併用療法は second-line の化学療法として有用である。
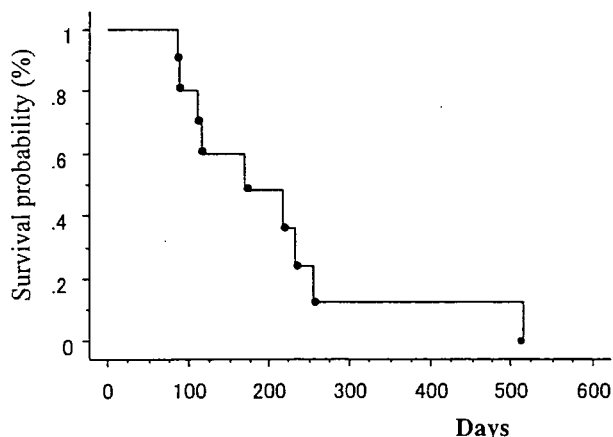
キーワード：ドセタキセル，ネダプラチン，進行・再発食道癌，セカンドライン，
　　　　　　化学療法

I．はじめに

食道扁平上皮癌に対する化学療法としては，シスプラチン（CDDP）・5FU 併用療法（FP 療法）がゴールドスタンダードとして広く行われており，根治または導入治療のみならず術前後の補助化学療法として広く普及している[1,2]。当科でもこの2剤，またはこれにアドリアマイシン（ADR）を加えた FAP 療法を第一選択として行っている[3]。一方，これを上回る有効性を有する化学療法は開発されておらず，またこの一次治療で十分な効果が得られなかっ

た症例に対する second-line の化学療法も確立されていない。そうした中で Nedaplatin（CDGP）と Docetaxel（TXT）の2剤はそれぞれ単剤での食道扁平上皮癌を対象とした第Ⅱ相臨床試験で優れた奏効率を示し[4-6]，また他の薬剤で化学療法が先行した症例にも奏効することが報告され注目されている[4-6]。そこで，当科では2002年より食道原発扁平上皮癌で FP 療法または FAP 療法の無効例あるいはその後の再発例に対して，second-line の薬剤として CDGP と TXT を併用した治療を行ってきた。今回，その有効性や有害事象につき臨床的検討を行った。

II．対象と方法

当科では second-line 化学療法の適応を食道原発の扁平上皮癌で，① FP 療法または FAP 療法が無効あるいはその後再発したことが画像上確認されて

Table 1 Characteristics of Patients

Patient no.	Sex	Age (yr)	TNM classification	Prior operation	Prior chemotherapy regimens	Prior radiation	Target lesion (overlapped)
1	M	65	T4N2M0	+	FAP 1 course	−	Lung mediastinal lymph node
2	M	69	T3N2M0	+	FAP 1 course	−	Mediastinal lymph node
3	F	63	T1N1M0	+	5 FU · Nedaplatin	+	Lung mediastinal lymph node
4	M	66	T3N2M0	+	FAP 1 course	+	Lung mediastinal lymph node
5	M	70	T4N2M0	−	FAP 2 courses	−	Liver bone mediastinal lymph node
6	M	56	T4N2M0	−	FAP 2 courses	+	Lung abdominal lymph node
7	M	67	T4N2M0	+	FP 1 course	+	Lung
8	M	66	T3N1M0	+	FP 1 course	+	Lung pleura mediastinal lymph node
9	M	59	T4N4M0	+	FP 1 course	+	Mediastinal and abdominal lymph nodes
10	M	61	T3N2M0	+	FP 1 course	+	Mediastinal lymph node

いる, ② 治療開始時の年齢が20歳以上70歳以下, ③ 評価可能病変を有する, ④ performance status (PS) が0～2である, ⑤ 重篤な合併症を有しない, ⑥ 本人から文書による Informed Consent が得られている, ⑦ 前治療終了から1カ月以上の間隔がある, としている。また, 前治療として放射線治療の有無を問わなかった。

2002年から2004年までの期間で, 当科で化学療法を行った食道原発扁平上皮癌患者のうち, 上記の適格基準すべてを満たしかつ TXT・CDGP 併用療法を施行しえた13例の中で, 十分かつ詳細な効果判定が行えた10例について臨床的検討を行った。残りの3例は現在化学療法中で, 今後評価を行う予定である。

症例10例の内訳は, 男性9名, 女性1名, 本治療開始時の年齢は中央値65歳 (56～70歳) であった。初治療前の病期は Stage II が1例, III が3例, IV a が6例であった。前治療は切除手術＋術後補助化学放射線療法4例, 切除手術＋術後補助化学療法1例, 切除術後再発に対する化学療法が3例に施行さ

れていた。切除不能は2例で1例は化学放射線療法, 1例に化学療法が行われていた。前化学療法の効果は PR が1名, SD が1名, 8名が PD であった。また, 本治療開始時の評価対象病変は肺転移5例, 肝転移1例, 骨転移1例, 縦隔リンパ節転移8例, 腹部リンパ節転移2例, 胸膜転移1例であった (重複あり) (Table 1)。

用量設定に関して, 1999年犬山らの多施設共同研究の進行・再発頭頸部癌に対する第II相臨床試験の結果に基づき[7], TXT は 60 mg/m^2 とした。また, 1992年田口らの CDGP 100 mg/m^2, 4週ごと点滴静注を用いた第II相臨床試験の結果[4]と1998年室らの CDGP 90 mg/m^2, 5 FU 800 mg/m^2 5日間の併用療法, 第I-II相臨床試験の用量設定, 投与方法[8,9]を参考とし, 2剤を併用した場合の安全性, 実行可能性を試みる意味もあり CDGP は 80 mg/m^2 を使用することとした。その他に, second-line ということで患者の予備力が少ないことなども考慮した。

投与は, TXT 60 mg/m^2 を1時間, CDGP 80 mg