TABLE 2. Postoperative Complications

Complication	Total *n* (%)	2-field ($n = 55$) *n* (%)	3-field ($n = 101$) *n* (%)	*P* value (χ^2 test)
Anastomotic leakage	55 (35)	16 (29)	39 (39)	0.234
Vocal cord palsy	19 (12)	10 (18)	9 (9)	0.091
Pneumonia	14 (9)	6 (11)	8 (8)	0.104
Wound infection	12 (8)	4 (7)	8 (8)	0.885
Empyema	8 (5)	3 (5)	5 (5)	0.892
Renal insufficiency	4 (3)	2 (4)	2 (2)	0.532
Peritonitis	3 (2)	1 (2)	2 (2)	0.944
Ileus	3 (2)	1 (2)	2 (2)	0.944
Cylothorax	3 (2)	1 (2)	2 (2)	0.944
Cardiac insufficiency	1 (1)	1 (2)	0 (0)	0.174
None	50 (32)	16 (29)	34 (34)	

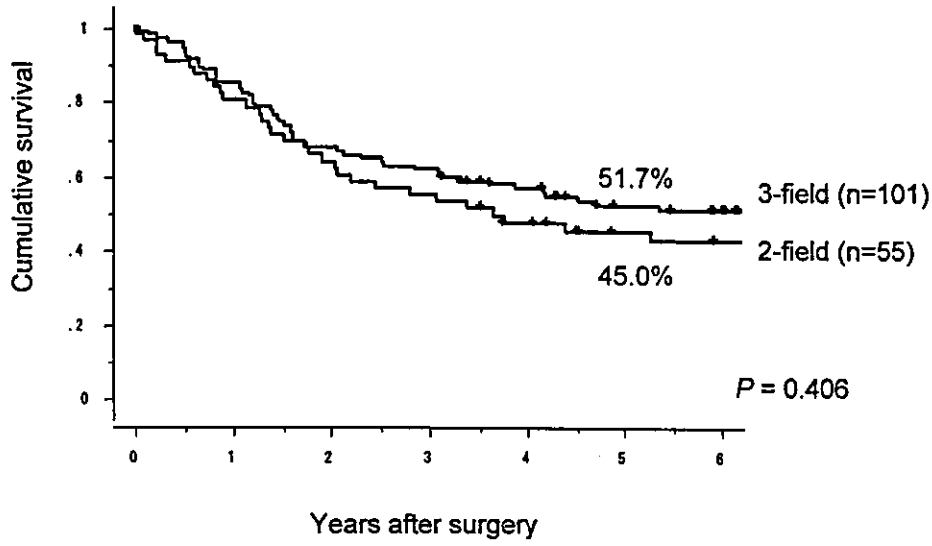

FIGURE 1. Survival curves of patients with squamous cell carcinomas of the lower thoracic esophagus after 2-field or 3-field lymph node dissection.

metastasis, is still alive 4 years after surgery without recurrence of disease.

Pathologic Characteristics

Pathologic characteristics according to lymph node dissection are summarized in Table 4. Of 4 patients with pathologic T4 tumors, 2 were diagnosed as clinical T3 tumors. The primary tumor directly invaded into the aorta, liver, and lung in 1 patient each in the 2-field dissection group. Those with liver and lung involvement were resected completely with co-resection of the invaded organ. A patient treated with 3-field dissection, in whom the primary tumor had directly invaded into the lung, pericardium, and left main bronchus simultaneously, underwent co-resection of both lung and pericardium. However, the tumor was left grossly in the left main bronchus.

Of 3 patients with M1b disease in the 2-field group, 1 had left paratracheal lymph node metastasis that was diagnosed positive preoperatively and resected at the time of anastomosis in the neck; the remaining 2 patients had paraaortic nodal metastases in the abdomen. Of 15 with M1b disease in the 3-field group, 14 had nodal metastases in the neck and 1 of the paraaorta in the abdomen. Three with nodal metastases of the paraaorta died of recurrent disease at 8, 21, and 31 months after surgery.

Complete resection (R0 resection) of the original tumor was accomplished in 95% of patients treated with both 2- or 3-field dissection. Of 2 with microscopically residual tumors (R1 resection) after 2-field dissection, in 1 the vertical margin of the primary tumor positive and in the other the distal margin was positive because of intramural metastasis. Of 4

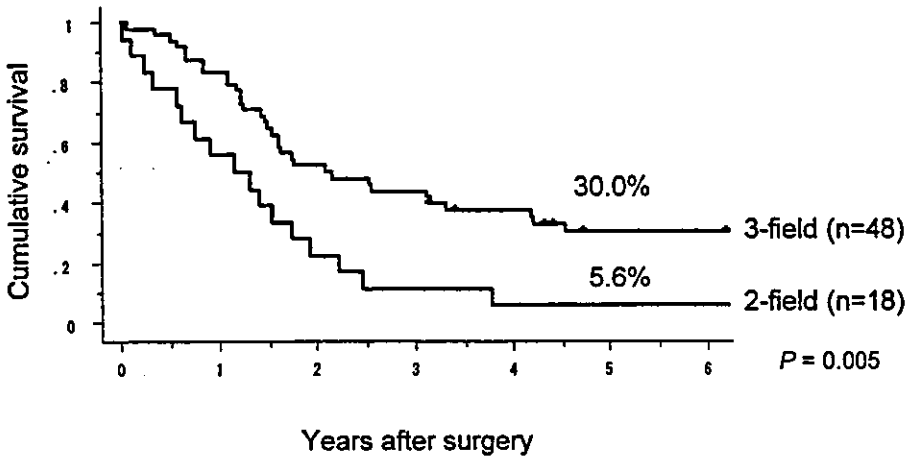

FIGURE 2. Survival curves of patients with lymph node metastases of the upper and/or middle mediastinum treated with 2-field and 3-field lymph node dissection.

with R1 resection in the 3-field group, 3 were positive of the proximal surgical margin of the resected esophagus because of multiple primary lesions and the remaining 1 was distal surgical margin positive because of intramural metastasis.

Pathologic Characteristics and Survival Rates According to Lymph Node Dissection

Pathologic characteristics and survival rates according to lymph node dissection are shown in Table 4. There was a statistically significant difference between patients with upper and/or middle mediastinal lymph node metastases undergoing 2-field and 3-field dissection ($P = 0.005$) (Fig. 2). Thirteen (27%) of 48 patients with upper and/or middle mediastinal lymph node metastases treated with 3-field dissection had simultaneous cervical lymph node metastases and their 5-year survival rate was 23.1%.

The 5-year survival rates for patients with R0 resection after 2-field and 3-field dissection were 47.6% and 52.3%, respectively. Two with microscopically residual tumors (R1 resection) after 2-field dissection died 11 and 38 months after surgery. Of 4 with R1 resection after 3-field dissection, 2 died after 5 and 16 months, and remaining 2 were still alive at 8 and 12 years after surgery. Of 2 with macroscopically residual tumors (R2 resection), the 1 undergoing 2-field died after 8 months, and the other died 11 months after 3-field dissection.

The patients with stage 0 disease treated with 2-field and 3-field dissection are still alive 10 and 11 years after resection, respectively. The 5-year survival rates after 2-field dissection were 70.7% for stage I, 56.3% for stage II, 26.3% for stage III, and 14.3% for stage IV. Those after 3-field dissection were 75.2% for stage I, 71.1% for stage II, 33.4% for stage III, and 27.8% for stage IV.

The distribution of subdivisions of stage IV differed between the 2-field and 3-field groups. Cervical nodal involvement was classified as M1b disease according to the 1997 UICC-TNM staging system. Of 7 patients treated with 2-field dissection, 4 were with stage IVA and 3 were stage IVB (1 M1b-neck and 2 M1b-abdominal paraaorta). Of 21 with stage IV treated with 3-field dissection, 6 were stage IVA and 15 were stage IVB (14 M1b-neck and 1 M1b-abdominal paraaorta).

TABLE 3. Status of Lymph Node Metastases and Survival Rates of Patients With Squamous Cell Carcinoma of the Lower Thoracic Esophagus Treated With Extensive Lymph Node Dissection

Lymph Node Metastases	*n*	5-year Survival (%)
Negative	49	74.5
Abdomen alone	34	55.7
Lower mediastinum + abdomen	6	83.3
Upper and/or middle mediastinum	66	23.3
Neck alone	1	. . .
Total	156	49.3

DISCUSSION

The present study of extensive lymph node dissection for patients with squamous cell carcinoma of the lower thoracic esophagus demonstrated a high frequency of lymph node metastases in the upper and/or middle mediastinum. Furthermore, 3-field dissection provided better survival benefit for patients with upper and/or middle mediastinal lymph node metastases than 2-field dissection.

In Japan, the most common histologic type of carcinoma of the thoracic esophagus is the squamous cell carcinoma, accounting for over 90% of the total cases. The lower thoracic esophagus was the site for 30% of all patients treated with extensive lymph node dissection in the period of this study. In the Western world, a drastic increase in adenocar-

TABLE 4. Pathological Characteristics According to Lymph Node Dissection

Variable	No. of Patients (%) 2-field	3-field	*P* value*
T status			0.168
Tis	1 (2)	1 (1)	
T1	20 (36)	26 (26)	
T2	4 (7)	15 (15)	
T3	27 (49)	58 (57)	
T4	3 (5)	1 (1)	
N status			0.642
N0	20 (36)	33 (33)	
N1	35 (64)	68 (67)	
M status			0.210
M0	48 (87)	80 (79)	
M1	7 (13)	21 (21)	
M1 status			0.172
M1a	4 (7)	6 (6)	
M1b	3 (5)	15 (15)	
M1b status			0.011
M1b-neck	1 (2)	14 (14)	
M1b-abdominal paraaorta	2 (4)	1 (1)	
Lymph node metastases			0.534
Negative	19 (35)	30 (30)	
Positive	36 (65)	71 (70)	
Status of lymph node metastases			0.062
Abdomen alone or abdomen + lower mediastinum	18 (33)	22 (22)	
Upper and/or middle mediastinum	18 (33)	48 (48)	
Multiple primary lesions			0.783
Single	43 (78)	77 (76)	
Multiple	12 (22)	24 (24)	
Lymphatic invasion			0.349
Negative	13 (24)	31 (31)	
Positive	42 (76)	70 (70)	
Vascular invasion			0.958
Negative	34 (62)	62 (61)	
Positive	21 (38)	39 (39)	
Intramural metastasis			0.723
Absent	50 (91)	90 (89)	
Present	5 (9)	11 (11)	
Completeness of resection			0.904
Complete (R0)	52 (95)	96 (95)	
Incomplete (R1)	2 (4)	4 (4)	
Incomplete (R2)	1 (2)	1 (1)	
Stage			0.439
0	1 (2)	1 (1)	
I	12 (22)	13 (13)	
II	16 (29)	35 (35)	
III	19 (35)	31 (31)	
IV	7 (13)	21 (21)	

*χ^2 test

cinoma of the lower thoracic esophagus and esophagogastric junction has been reported during the last 2 decades. Orringer and his associates reported that adenocarcinomas of the lower thoracic esophagus or esophagogastric junction accounted for 73% and 69% of the total tumors seen from 1976 to 1998.[12] Clearly, the tumor location and histologic type of carcinomas of the thoracic esophagus differ between the Western world and Japan.

The lymphatic drainage system of the esophagus, which is well developed in the submucosal layer and forms an intensive longitudinal extension, causes a unique pattern of lymph node metastasis.[13] Lymphoscintigrams of the esophagus reveal uptake in the cervical, upper mediastinal, and perigastric nodes.[14] Akiyama reported that the most frequent sites of lymph node metastases were the perigastric nodes in patients with squamous cell carcinoma of the lower thoracic esophagus, and the upper mediastinal nodes in patients with squamous cell carcinoma of the upper thoracic esophagus.[3] Metastases in both the upper mediastinal and perigastric lymph nodes occurred similarly with high frequencies in patients with squamous cell carcinoma of the middle thoracic esophagus, spread thus being in both upward and downward directions.

Differences in tumor location and sites of lymph node metastases between the Western world and Japan have caused different surgical approaches for tumors of the lower thoracic esophagus. In Japan, transthoracic esophagectomy with extensive lymph node dissection has been carried out as a standard surgical procedure with curative intent. In the Western world, with the recent increase of adenocarcinoma of the lower thoracic esophagus and esophagogastric junction, the surgical approach has changed. The majority of Western surgeons have more favored a transhiatal approach without thoracotomy rather than transthoracic esophagectomy, because it is controversial whether transthoracic esophagectomy with extensive lymph node dissection carries a survival benefit.[12,15] The lack of data on the benefit of extensive lymph node dissection for adenocarcinoma of the lower thoracic esophagus and esophagogastric junction discourages extension of lymph node dissection. In our series of squamous cell carcinoma, lymph node metastases in the upper and/or middle mediastinum from the lower thoracic esophageal lesions were present in 42% of patients after extensive lymph node dissection, and a 23.3% 5-year survival rate obtained. Less extensive surgery without removal of these lymph nodes might leave tumors. While the impact of microscopically residual tumor (R1 resection) on survival is controversial, gross residual tumors in lymph nodes may mean a poor prognosis. Despite the lack of prospective randomized controlled trials comparing the different degrees of lymphadenectomy, the survival rates of our series are substantially superior to those obtained with less extensive lymph node removal.[8,12]

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Lecture

解　説

食道がんに対する術後補助化学療法の有効性*

山名秀明**　安藤暢敏***

Key Words : esophageal carcinoma, surgical treatment, adjuvant chemotherapy, CDDP/5-FU, randomized controlled study

はじめに

胸部食道がんの外科手術成績は，近年の色素内視鏡診断の普及による表在がんの増加や手術手技の進歩によって著しく向上し[1]，根治手術例の5年生存率は50%を超えるまでになってきた．とくに1983年を境に頸・胸・腹の3領域リンパ節郭清術[2]が試みられるようになったことから所属リンパ節の転移形式や転移頻度が総合的かつ詳細に検討[3]されるようになった．その結果，3領域の系統的リンパ節郭清術式の合理性が認知され，多くの施設で3領域郭清を伴う根治切除術が行われるに至ったことが遠隔生存率向上の最大要因である．しかし，外科的切除術はあくまで局所療法であり，進行がん患者における微小転移巣遺残などによる再発防止には集学的治療が不可欠なことは従来から提唱されてきた通りである．

食道がんの補助化学療法としては，1980年代初頭に扁平上皮がんに有効な化学療法剤としてcisplatin(CDDP)が保険適用となり，それを契機として食道がんにおいても術後補助化学療法が試みられるようになった．そこで本項では，筆者らが長年参加してきた日本臨床腫瘍研究グループ(JCOG)の食道がんグループ(JEOG：Japan Esophageal Oncology Group，飯塚紀文班長：1978～1993年，安藤暢敏班長：1994年～)での多施設共同試験として施行された術後化学療法の無作為比較試験の成績を年代ごとに解説し，現時点の胸部進行食道がんに対する標準治療について見解を述べる．

術後補助療法としての放射線療法と化学療法(CDDP/VDS)の第III相試験

1981年から1983年の間に，JEOGの第2次研究[4]として施行した術前後放射線治療と術後放射線治療の無作為比較試験の結果，術後照射群が有意($p=0.0069$)に良好な5年累積生存率を示した．そこで，第3次研究[5](1984～1987年)では，術後放射線療法(A群)と術後化学療法(B群)の無作為比較試験を施行した．対象症例は，術後の病理組織診断でがん遺残がなく根治切除術が施行された術前無治療の胸部食道扁平上皮がん患者とし，術後2か月以内にblock randomizationにより両治療法のいずれかが選択され，ただちに術後治療を開始した．本プロトコールでは，放射線照射野は両側鎖骨上窩と上縦隔を含むT字型とし，照射線量は50Gy/25Fr/5 weeksとした．化学療法のレジメンは，CDDP(50mg/m^2, day 1)とvindesine(VDS；3 mg/m^2, day 1)の併用療法とし，3週間隔で2コースの施行が規定された．本研究にはA群128例，B群130例が登録(適格例：A群127例，B群126例)されたが，両群間の性別，年齢，がん占居部位，UICC-pTNM分類などの背景因子に有意差を認めなかった．A, B両治療による有害反応(adverse reaction；AR)をWHO毒

* Effect of postoperative adjuvant chemotherapy for squamous cell carcinoma of the thoracic esophagus.

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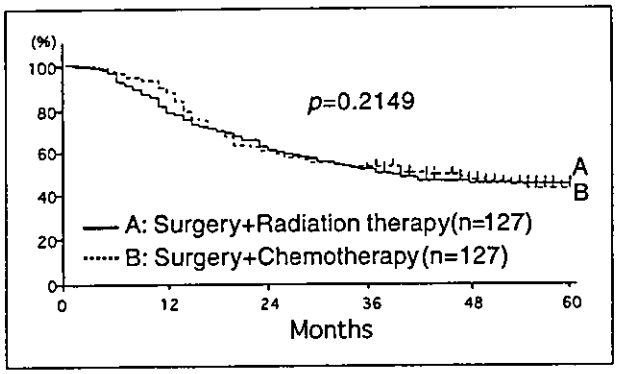

図1 胸部食道がん根治切除術後放射線治療群と化学療法群の全生存曲線による比較(JEOG第3次研究)

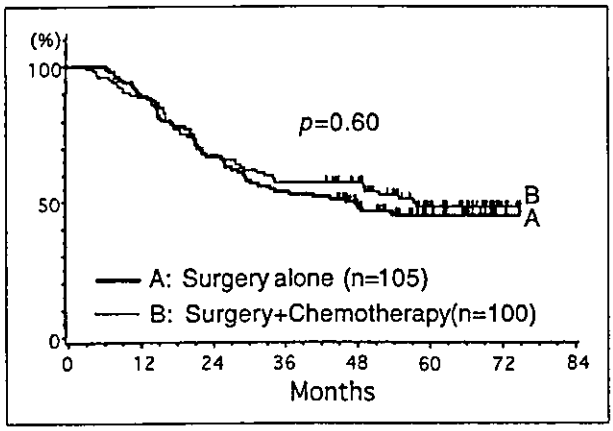

図2 胸部食道がん根治切除術単独群と術後補助化学療法群の全生存曲線の比較(JEOG第4次研究)

性判定規準で比較すると，術後治療開始前では両群間に差を認めなかったが，治療開始後にはB群においてgrade 3-4の白血球数減少が有意($p=0.026$)に多く認められ，また血漿BUN($p=0.018$)と血漿クレアチニン値($p=0.006$)もB群が有意な高値を示した．治療成績をKaplan-Meier法による全生存曲線で解析すると，図1に示すように両群の5年累積生存曲線に差を認めなかった．また，術後のリンパ節再発や血行性再発の頻度でも両群間に有意差を認めず，両補助療法による予後向上効果はほぼ同等であるか，もしくは両治療ともに無効であるかのいずれかであると判定した．

なお，CDDPとVDSの第Ⅱ相試験[6]を高度進行・再発食道がん患者を対象として施行したが，完全奏効(CR)例はなく奏効率は16.1%と低率であった．

術後補助化学療法(CDDP/VDS)と手術単独療法の第III相試験

第3次研究の成績から，術後放射線治療と術後化学療法の遠隔生存率には差がないことが判明したが，手術単独での遠隔生存率に関する成績がいまだ不明なことが重要な問題点としてあげられた．そこで，次期研究としては手術単独群と術後補助療法群との無作為比較試験を行う必要性に迫られた．そこで，第4次研究[7](1988～1991年)では，手術単独群(A群)と術後化学療法群(B群)の2群を設定し，術後補助化学療法の有効性について比較検討することにした．術後化学療法のレジメンは第3次研究と同じであるが，CDDPは70mg/m²に増量した．対象症例の設定も第3次研究と同様に設定したが，リンパ節転移陽性例と陰性例の偏りをなくすため登録時に両者を前層別することを規定した．

当試験には，A群100例，B群105例が登録(適格例：A群100例；B群105例)された．両群の背景因子の比較では，B群に女性が有意($p=0.02$)に多く，遠隔リンパ節転移陽性例(pM1-LYM)もB群に多い傾向($p=0.1$)を認めたが，年齢，がん占居部位，pTNM分類(UICC)などにおいては有意差を認めなかった．なお，B群には化学療法の施行が1回のみの症例が13例あり，化学療法非施行も3例存在した．術後化学療法によるARをJCOGの毒性判定規準でみると，grade 3-4のヘモグロビン減少が2例，白血球減少13例，嘔気・嘔吐13例，血漿クレアチニン上昇8例，下痢2例，感染症が1例に認められた．両群の術後5年累積生存率を術後経過観察期間の中央値が59.2か月の時点で比較した結果，図2に示すようにA群45.1%，B群48.3%と差を認めず($p=0.60$)，また術後のリンパ節再発や血行性再発の頻度でも両群間に差を認めなかった．そこで，リンパ節転移陰性例と陽性例とに層別して同様に予後を比較すると，図3に示すようにリンパ節転移陰性例(pN0)の5年累積生存率はA群72.1%，B群60.3%と有意差はないもののA群が若干高値($p=0.215$)を示し，リンパ節転移陽性例(pN1)では，図4に示すようにA群の35.5%に対し，B群43.7%とB群が良好な傾向($p=0.1337$)を示した．この結果から，胸部食道がんの標準治療

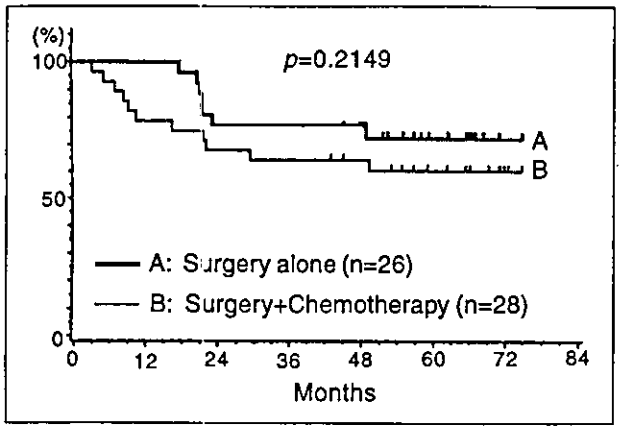

図3 pN0症例における胸部食道がん根治切除術単独群と術後化学療法群の全生存曲線の比較（JEOG第4次研究）

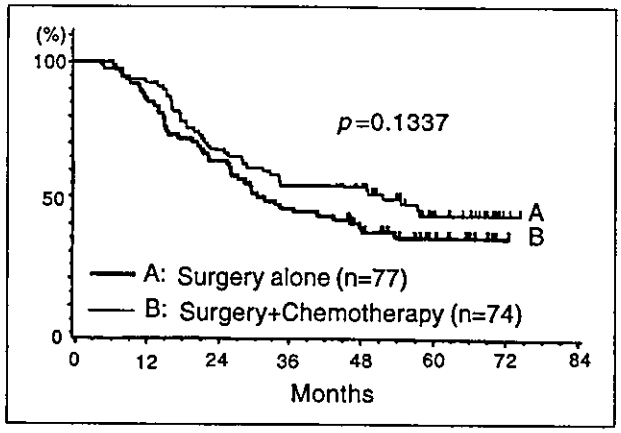

図4 pN1症例における胸部食道がん根治切除術単独群と術後化学療法群の全生存曲線の比較（JEOG第4次研究）

表1 高度進行・再発食道がん39例に対するCDDP＋5-FUの第II相試験の奏効例とその内訳

PR症例	PS	標的臓器	治療回数	効果	奏効期間(日)
1	0	肺	2	PR	360
2	1	肺	4	PR	120
3	0	肺	2	PR	120
4	1	縦隔リンパ節	3	PR	120
5	1	肝，腹部リンパ節	3	PR	63
6	2	肺	4	PR	60
7	0	肺	3	PR	60
8	0	食道	3	PR	55
9	0	食道	4	PR	53
10	1	肺	2	PR	33
11	0	食道，肝	1	PR	31
12	1	食道	4	PR	30
13	0	肺，縦隔リンパ節	2	PR	29
14	0	食道，肝	5	PR	28

奏効率＝35.9%（14/39例）．Regimen：CDDP 700mg/m² day 1，5-FU 700mg/m² days 1-5を3週ごと．

は手術単独療法であることが確認され，pN0症例には術後補助療法は不要と考えられた．また，pN1症例には奏効率の高い抗がん剤を使用すると術後補助化学療法の有効性が証明される可能性が高いことが示唆された．

高度進行・再発食道がんを対象としたCDDP/5-FUの第III相試験

第4次研究の成績から考察すると，より有効性の高い化学療法レジメンを確立することが最重要課題となった．そこで，CDDP(70mg/m², day 1)と5-FU(700mg/m² 24時間持続投与，days 1-5)の第II相試験[6]を高度進行・再発食道がん患者39例を対象に施行した．その結果，表1に示すようにCR例はなかったが，部分奏効(PR)例を35.9%に認め，CDDP/ VDSと比べて良好な成績が得られた．

手術単独療法と術後補助化学療法（CDDP/5-FU）の第III相試験

CDDP/5-FUによる第II相試験の成績から，第5次研究としてはCDDP(80mg/m², day 1)と5-FU(800mg/m² 24時間持続投与，days 1-5)による術後化学療法群と手術単独群の無作為比較試験を1992年7月から開始し，1997年3月に終了した．

表2に，第5次臨床試験に用いたプロトコールの概要を示す．なお，第5次試験が終了近くとなった1996年に，食道扁平上皮がん切除術後

表2　第5次研究(JCOG9204-phase III trial)の研究概要

研究目的
胸部食道扁平上皮がんに対するCDDP+5-FUを使用する術後化学療法を，標準治療としての外科手術単独群と比較する．
対象症例
外科的根治切除術が行われた症例で，以下の条件を満たす．
1)組織診断で扁平上皮がんと診断された胸部食道がん．
2)pStage 0, 1 (pTis-pT1, pN0, pM0)症例を除く．
3)肉眼的所見で腫瘍残存がない．
4)ECOGのPSが0-2.
5)年齢75歳以下．
6)臨床検査成績で臓器機能に異常がない(詳細略)．
7)Informed consentが得られている．
8)術後経過期間が2週以上，2か月以内．
除外条件：重複がん(根治切除後の胃，大腸のmがんを除く)，重篤な心疾患，3か月以内の心筋梗塞，コントロール不能高血圧，インスリン投与中の糖尿病，治療に差し支える合併症．
エンドポイント
Primary endpoint再発までの期間(無再発生存期間)
Secondary endpoint生存期間(術後5年生存率)，有害事象(副作用)の程度．
治療方法
A群：外科手術単独
B群：術後化学療法併用
CDDP+5-FU：3週1コースとして，2コース
CDDP：80mg/m²/day　DIV day 1
5-FU：800mg/m²/day　24時間持続DIV day 1-5
予定症例数，登録期間，追跡期間
登録期間3年，追跡期間5年(改訂により8年)
予定症例数：370例(改訂により290例，最終的に242例で終了)

表3　第5次研究(JCOG9204-phase III trial)登録症例の内訳

背景因子		手術単独群 (n=122)	術後化学療法群 (n=120)
性	男	111	107
	女	11	13
年齢	平均	59	59
	範囲	40～75	40～76
占居部位	上部	5	13
	中部	75	65
	下部	42	42
pT	T1	25	31
	T2	18	18
	T3	77	69
	T4	2	2
pN	N0	21	23
	N1	101	97
pM-LYM	M0	102	97
	M1	20	23
pStage	StageⅡA	21	22
	StageⅡB	34	37
	StageⅢ	47	38
	StageⅣ	20	22

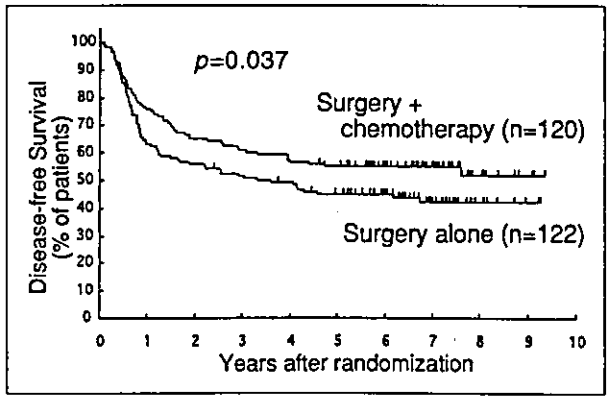

図5　胸部食道がん根治切除術単独群と術後化学療法群の無再発生存曲線の比較(JEOG第5次研究)

化学療法群(CDDP/ 5-FU, n=52)と手術単独群(n=68)の無作為比較試験の成績がフランスから報告[9]された．その成績をみると，術後生存率は本邦と比べて著しく不良ではあるが，生存期間中央値はそれぞれ14か月と13か月で両群間に差はみられず，CDDP/5-FUの有用性は認められなかったと述べている．しかし，本邦の食道がん根治切除術後の5年生存率は手術単独で50%近くを示すことから，フランスの臨床試験成績とは当然異なった成績が得られることが十分に期待された．

当試験には242例が登録され，手術単独群(A群)が122例，術後化学療法群(B群)が120例で，すべて適格例であった．登録症例の内訳を表3に示すが，これらの背景因子として検討した項目においてA, B両群間に有意差は認めなかった[10]．

当試験のprimary endpointである無再発生存率が，2001年12月の予後追跡調査結果を基にJCOGデータセンター(センター長：福田治彦)で解析された．その結果，図5に示すようにB群が有意(p=0.037)に良好な生存曲線を示した．また，組織学的リンパ節転移の有無(pN0 /pN1)で同様に無再発生存曲線を描出すると，図6に示すようにpN0症例では両群間に有意差を認めなかったが，pN1症例ではA群と比べてB群の無再発生存曲線が有意(p=0.041)に良好な結果を示し，所属リンパ節転移陽性の進行胸部食道がん症例に

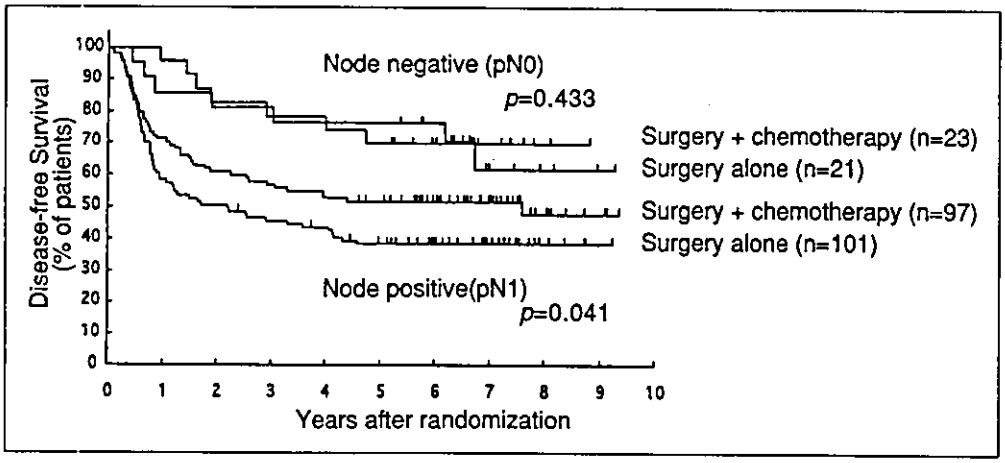

図6　pN0とpN1別にみた胸部食道がん根治切除術単独群と術後化学療法群の無再発生存曲線の比較(JEOG第5次研究)

は根治切除術後早期にCDDP/5-FUによる補助化学療法を行うことによって再発防止効果が得られることが初めて証明された．また，secondary endpointとしての全生存曲線で両群を比較すると，図7に示すようにA群の5年累積生存率が52%，B群が61%と有意差はないものの後者が良好な傾向(p=0.13)を示した．ちなみに，再発頻度を両群間で比較したところ，手術単独群では63例(52%)に再発を認め，このうち54例(86%)に再発に対する治療が，またB群では45例(38%)に再発を認め，36例(80%)に再発に対する治療が施行されていた．リンパ節再発はA群56例(46%)，B群26例(22%)とA群に多く認めたが，血行性再発(A群25例，B群28例)では両群間に差はみられなかった．

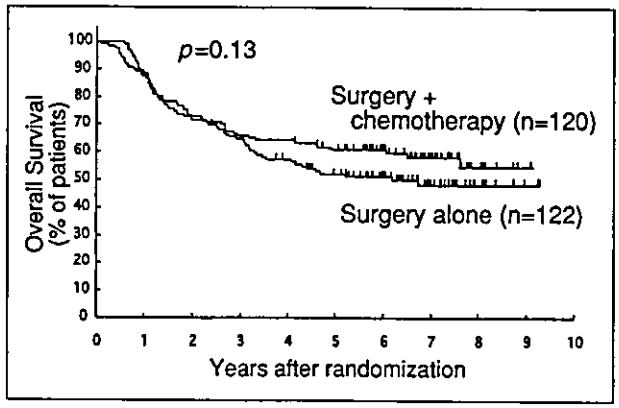

図7　胸部食道がん根治切除術単独群と術後化学療法群の全生存曲線の比較(JEOG第5次研究)

おわりに

1980年以前の食道がんの補助療法としては，有効な化学療法剤がないことから放射線治療が主体に行われ，術前照射療法や術後照射療法として汎用されてきた．その後，CDDPの出現によって化学療法の有効性が報告されるようになり，術後補助化学療法としての期待がもたれるようになった．一方，外科手術においては栄養管理や術前後管理の発達によって手術の安全性が確立され，リンパ節郭清範囲も上縦隔リンパ節のみならず頸部リンパ節にまで拡大されるようになり，これによって術後遠隔成績が著しく向上した[2)3)]．このような背景から，術後補助療法の有効性を検討するため，JEOG studyとして1988年に手術単独療法と術後化学療法の比較試験が初めて施行された．しかし，化学療法のレジメンがCDDP/VDSであったことから十分な再発防止効果を認めることはできず，1992年にはCDDP/5-FUのレジメンで再度比較試験を実施した．当臨床試験の開始から，その結果が米国癌治療学会誌(J Clin Oncol)[10)]に掲載されるまでに約10年の期間を費やしたが，本邦における食道がん術後補助化学療法の有用性が初めて科学的に証明されたことになる．この結果から，リンパ節転移陽性進行胸部食道がんに対する標準治療は，根治切除術単独療法から外科的根治切除術とCDDP/5-FUによる術後補助化学療法に移行したことになる．一方，欧米の食道がんに対する補助療法は，手術成績が不良なことから術前治療

が主体となっており，とくに化学放射線治療が汎用されているが，術前化学療法の報告を検索してみると，2002年5月(Lancet)[11]にCDDP/5-FUによる術前化学療法群(n＝400)が手術単独群(n＝402)に比べて全生存率が有意(p＝0.004)に良好であったと述べている．

JEOGの第6次研究においても，第5次研究の結果を基に術前と術後の補助化学療法による無作為比較試験を計画し，2000年5月より登録を開始した．当研究は，本年5月で終了予定であったが，今日ではインフォームド・コンセントの徹底化とともに医療情勢変化による医療費負担増も重なって，補助療法の選択のみならず治療方法自体においても患者自身の選択権によって決定される上に，各医療施設にも入院期間の短縮化が架せられたことによって，治療期間の延長が余儀なくされる当臨床試験に登録される患者数は減少し，予定症例数の330例に到達するまでにはあと数年を要する見込みである．

以上，これまでJEOGで行った術後化学療法の第Ⅲ相試験の経緯と成績について概説したが，術後補助化学療法の有効性を確立するために20年余りの期間を費やしたことになる．しかし，標準治療を確立するためには適切かつ有用なプロトコールの作成と多大な労力と時間をかけた質の高い臨床試験を行うほかに道はなく，今後も一歩一歩地道に，かつ可能な限り短期間で検証していかなければならないと考えている．

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Excerpta Medica

The American Journal of Surgery

The American Journal of Surgery 188 (2004) 261–266
Scientific paper

Salvage esophagectomy after definitive chemotherapy and radiotherapy for advanced esophageal cancer

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Manuscript received September 16, 2003; revised manuscript December 22, 2003

Abstract

Background: Although local recurrence of advanced esophageal cancer is frequent after definitive chemoradiotherapy (CRT), the clinical benefit of salvage esophagectomy has not been elucidated.
Methods: We reviewed 27 patients with squamous-cell cancer who underwent esophagectomy after definitive CRT (≥50 Gy) (salvage group) and 28 patients who underwent planned esophagectomy after neoadjuvant CRT (30 to 45 Gy) (neoadjuvant group).
Results: The preoperative albumin level and vital capacity were significantly lower in the salvage group than in the neoadjuvant group. Two patients (7.4%) from the salvage group who underwent extended esophagectomy with three-field lymphadenectomy died of postoperative complications, but no deaths occurred after less-invasive surgery. There was no difference of overall postoperative survival between the salvage and neoadjuvant groups.
Conclusions: The outcome of salvage esophagectomy after definitive CRT was similar to that of planned esophagectomy after neoadjuvant CRT. Less-invasive procedures might be better for salvage esophagectomy because of the high operative risk.

Keywords: Definitive chemoradiotherapy; Esophageal cancer; Neoadjuvant chemoradiotherapy; Salvage esophagectomy; Squamous-cell carcinoma

The recent surgical results for advanced esophageal cancer have been improved by extended lymphadenectomy and perioperative management , but patients with residual tumors (R1,2) still do not survive long-term after surgery [1,2]. Neoadjuvant or induction chemoradiotherapy (CRT), consisting of cisplatin, 5-fluorouracil (5-FU), and radiation followed by esophagectomy, became the established treatment for locally advanced esophageal cancer [3–5]. A considerable number of the patients who undergo potentially curative surgery after downstaging by CRT achieve a favorable prognosis [6–8].

In Japan, medical and radiation oncologists have reported on the improved survival of patients with esophageal cancer treated by definitive CRT without surgery [9,10], and this has already been documented in Western countries [11–13]. However, local failure, local recurrence, and regional lymph-node metastasis are frequently detected after definitive CRT [14,15]. Preoperative CRT (30 to 45 Gy) may or may not increase operative mortality [16–18], but our previous study showed that definitive CRT increased the risk [19]. The outcome of salvage esophagectomy was recently reported [20], but the appropriate procedures for salvage esophagectomy after definitive CRT for advanced esophageal cancer are still not established.

In this study, we examined the outcome of patients who underwent salvage esophagectomy (n = 27) after clinical T3 or T4 esophageal squamous cancer had been treated by definitive CRT. The results were compared with those in patients who were treated with planned neoadjuvant CRT followed by esophagectomy (n = 28).

Patients and Methods

We reviewed the records of 660 patients with thoracic esophageal cancer who underwent esophagectomy between

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0002-9610/04/$ – see front matter
doi:10.1016/j.amjsurg.2004.06.003

1992 and 2002 at the Institute of Gastroenterology of Tokyo Women's Medical University in Japan. All 27 patients with a clinical diagnosis of advanced esophageal cancer (T3 or T4) who received definitive CRT (≥50 Gy) before esophagectomy were enrolled in this study (salvage group). For comparison, we reviewed all 28 patients with advanced esophageal cancer who underwent planned esophagectomy at 3 to 6 weeks after neoadjuvant CRT (<50 Gy) (neoadjuvant group). In the salvage group, 6 patients received treatment in other hospitals and then were referred to our institution, and the remaining 21 patients received definitive CRT at the Department of Radiology of Tokyo Women's Medical University. Squamous-cell carcinoma was histologically confirmed by pretreatment endoscopic biopsy in all patients. Clinical staging was based on the results of barium swallow, endoscopy, endoscopic ultrasound, and CT scanning, which was performed according to TNM classification (International Union Against Cancer) [21]. All pretreatment records, including these from outside hospitals, were reviewed to confirm staging (stage III or IV).

The chemotherapy schedules, including those from other hospitals, were collected and reviewed to determine treatment details. Radiotherapy was delivered using equally weighted anterior- and posterior-opposed beams from 10-MV linear accelerator in 15 to 25 fractions of 1.8 to 2.0 Gy (total = 30 to 45 Gy), after which an additional 10 to 30 Gy (total = 50 to 75 Gy) was administered by way of two parallel oblique fields or multiple fields to avoid damage to the spinal cord. The interval between the last day of radiotherapy and the time of esophagectomy was calculated. In the salvage group, 13 patients underwent esophagectomy within 3 months after definitive CRT based on the diagnosis of residual tumor, and 14 patients underwent CRT at a later date because of recurrence.

Data on the general conditions and clinical tumor stage before esophagectomy were obtained from the records of the Department of Surgery at the Institute of Gastroenterology. Data such as total protein and albumin levels as well as white blood cell, lymphocyte, and platelet counts were collected from the hospital records. Results of lung function tests were collected including vital capacity (%VC) and forced expiratory volume in 1 second (FEV1%) as well as arterial oxygen tension (Pao_2) and carbon dioxide tension levels. The primary tumor was re-evaluated by review of the barium swallow, endoscopy, and biopsy findings. The metastatic lesions were assessed from the CT scans of the neck, chest, and abdomen as well as the results of endoscopic ultrasound.

Details of the esophagectomy procedures—including operating time, estimated blood loss, and blood transfusion—were collected from the hospital records. Details of postoperative complications and the duration of postoperative ventilation, treatment in the intensive care unit, and postoperative hospital stay were also collected from the records. When drainage of a pleural effusion was needed after 7 postoperative days, this was classified as a complication.

Table 1
Pretreatment characteristics and radiation dose

Characteristics	Salvage group (n = 27)	Neoadjuvant group (n = 28)	*P* value
Male/female	21/6	25/3	0.2158
Median age (range)	63 (36–79)	62 (50–74)	
Tumor location			
Upper	4	5	
Middle	17	17	0.9549
Lower	6	6	
Clinical stage			
T3N1M0	8	7	
T3N1M1	4	2	0.5623
T4N1M0	11	11	
T4N1M1	4	8	
Radiation dose (Gy)			
Mean (range)	60 (50–76)	39 (30–46)	<0.0001
Treatment interval*			
Median (range)	111 (39–462)	28 (19–45)	<0.0001

* Days from the final date of radiotherapy or chemotherapy to esophagectomy.

The depth of tumor invasion was defined on the basis of the deepest layer of viable cancer cells. Lymph-node metastasis or distant metastasis was defined by the detection of viable cancer cells in lymph nodes or organs. The response to treatment was evaluated on the resected specimens according to the histopathologic criteria for assessing the effects of radiation and/or chemotherapy by the Japanese Society for Esophageal Diseases [22]. When no viable cancer cells were detected (grade 3), this was classified as pathologic complete response. Viable cancer cells accounting for less than one third of the tumor (grade 2) was classified as a partial response. Viable cancer cells accounting for one third or more of the tumor (grade 1) and no discernible therapeutic effect on the tumor (grade 0) were classified as no response.

Differences of quantitative data were assessed by Student *t* test. Differences of percentages were evaluated by 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 JMP software (version 4; SAS, Cary, North Carolina). 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 staging did not differ between the salvage and neoadjuvant groups (Table 1). The average radiation dose administered in the salvage group was significantly higher than that administered in the neoadjuvant group (60 vs. 39 Gy, $P = 0.0001$). Duration from the final day of chemoradiotherapy to surgery was 100 days (range 35 to 365) in the salvage group and 28 days (21 to 40) in the neoadjuvant group. Although the mean total protein level was not different in both groups,

Table 2
Preoperative laboratory data

Data	Salvage group (n = 27)	Neoadjuvant group (n = 28)	*P* value
Total protein (g/dL)	6.5 ± 0.47	6.6 ± 0.58	0.3784
Albumin (g/dL)	3.5 ± 0.42	3.8 ± 0.41	0.0330
White cell count (mm^3)	5853 ± 2001	4864 ± 1512	0.0430
Lymphocyte count (mm^3)	781 ± 309	851 ± 366	0.4484
Hemoglobin (g/dL)	11.4 ± 1.5	11.6 ± 1.3	0.5535
Platelets ($\times 10^4/mm^3$)	27.3 ± 10.8	25.5 ± 11.6	0.5546
Pao_2 (mm Hg)*	88 ± 12	94 ± 12	0.0759
$Paco_2$ (mm Hg)†	38 ± 3.7	38 ± 4.2	0.9323
Vital capacity (%)	93 ± 12	104 ± 21	0.0190
Forced expiratory volume 1.0 (%)	76 ± 1.7	78 ± 1.5	0.4231

Values represent mean ± standard deviation.
Pao_2 = arterial partial pressure of oxygen; $Paco_2$ = arterial partial pressure of carbon dioxide.

the mean albumin level in the salvage group was significantly lower than that in the neoadjuvant group (P = 0.0234) (Table 2). The mean white blood cell count of the neoadjuvant group was significantly lower than that of the salvage group (P = 0.0234), but no differences were found between the two groups regarding the lymphocyte count, hemoglobin level, and platelet count. In lung-function tests, %VC in the salvage group was lower than that in the neoadjuvant group (P = 0.0190), but FEV1% did not differ between the two groups. Pao_2 was lower in the salvage group than in the neoadjuvant group, but not significantly so (P = 0.0759).

Extended esophagectomy through right thoracotomy with three-field lymph node dissection has been the standard procedure for advanced esophageal cancer in our institution. Because 2 of 14 (14%) patients of the salvage group who underwent extended esophagectomy died of postoperative complications before 1997, less-invasive procedures were performed in 13 patients, excluding 2 with upper thoracic esophageal cancer thereafter. Esophagectomy by way of left thoracotomy and transhiatal esophagectomy was performed in 7 (26%) and 4 (15%) patients from the salvage group, respectively (Table 3). Esophagogastric tube anastomosis in the neck by way of the mediastinal or retrosternal route was the standard procedure for 1-stage reconstruction after esophagectomy. In the salvage group, the subcutaneous route was selected in 17 patients, and 2-stage reconstruction was performed in 4 patients. Reconstruction was performed using a gastric tube in 24 patients from both groups and using the colon or jejunum in the remaining 3 patients in the salvage group and 4 patients in the neoadjuvant group who had already undergone gastrectomy. Surgical time was shorter in the salvage group than in the neoadjuvant group, but the difference was without significance. The blood loss and transfusion requirements of the neoadjuvant group were larger than those of the salvage group, but the difference was not significant.

One patient (3.7%) died of adult respiratory distress syndrome on postoperative day 22, and 1 patient (3.7%) died of anastomotic leakage and pneumonia on postoperative day 62 in the salvage group (Table 4). Both patients underwent extended esophagectomy by way of right thoracotomy with 3-field lymphadectomy before 1997, but no operative mortality or hospital deaths were recorded thereafter. There was no 30-day mortality, but 1 patient (3.6%) in the neoadjuvant group died of pneumonia on postoperative day 122. From 1992 to 2002, 11 (1.7%) of all 660 patients who underwent esophagectomy for esophageal cancer died of postoperative complications within 30 days, and 19 patients (2.9%), including these 11, died at our institution. Anastomotic leakage occurred in 6 patients (22%) from the salvage group compared with 3 patients (11%) from the neoadjuvant group. Three patients had pleural effusion in the salvage group versus only 1 patient after surgery. Only 3 patients (11%) from the salvage group and 7 patients

Table 3
Surgical procedures and operative factors

Operative factors	Salvage group (n = 27)	Neoadjuvant group (n = 28)	*P* value
Approaches			
Right thoracotomy	16	24	
Left thoracotomy	7	2	0.0809
Transhiatal	4	2	
Lymph node dissection			
Three-field	9	16	
Two-field	12	11	0.1397
Abdominal	6	2	
Reconstruction route			
Subcutaneous	17	11	
Retrosternal	2	8	0.0851
Mediastinal	8	9	
Other operative factors*			
Operation time* (min)	312 ± 106	356 ± 118	0.1442
Blood loss* (mL)	679 ± 414	975 ± 861	0.1125
Blood transfusion* (mL)	571 ± 499	614 ± 915	0.8284

* Values represent mean ± standard deviation.

Table 4
Short outcomes of esophagectomy

Outcomes	Salvage group (n = 27)	Neoadjuvant group (n = 28)	P value
% Mortality (within 30 days)	1 (3.7)		
% Hospital mortality (> 30 days)	1 (3.7)	1 (3.6)	
Mechanical ventilation (days)	3.1 ± 6.4	2.1 ± 2.8	0.4348
Intensive care unit stay (days)	5.9 ± 5.8	5.1 ± 2.8	0.5066
Postoperative hospital stay (days)	39.9 ± 25.4	31.9 ± 22.8	0.2221
Leakage (surgery)	6 (3)	3 (1)	
Pneumonia	3	3	
Wound infection	2	2	
Pleural effusion	3	1	
Residual tumors (%)			
R_0	18 (67)	17 (61)	
$R_{1,2}$	9 (33)	11 (39)	
Pathologic effect (%)			
Complete response	3 (11)	7 (25)	
Partial response	9 (33)	7 (25)	
No response	15 (56)	14 (50)	

(25%) from the neoadjuvant group achieved pathologic complete response. These 3 patients in the salvage group complained of dysphasia caused by stricture of the esophagus within 3 months after definitive CRT. No difference was found between the 2 groups with respect to residual tumor, depth of tumor invasion, lymph-node metastasis, and distant metastasis.

There were no differences in overall postoperative survival between the salvage and neoadjuvant groups (Fig. 1). In the salvage group, the survival of 13 patients with recurrence (>3 months after CRT) was similar to that of 14 patients with residual tumors (<3 months after CRT) (Fig. 2). The survival of 18 patients without residual tumors (R0) was significantly better than that of 9 patients with R1or R2 tumors ($P = 0.0022$) (Fig. 3). The survival of 18 patients who underwent less-invasive esophagectomy was similar to that of 9 patients who underwent 3-field lymph node dissection (Fig. 4). With regard to postoperative recurrence, only 3 patients had distant-organ metastasis in the salvage group versus 6 patients in the neoadjuvant group. The incidence of local recurrence (n = 4), lymph-node metastasis (n = 4), and pleural dissemination (n = 1) in the salvage group was similar to the incidence of local recurrence (n = 3), lymph-node metastasis (n = 3), and pleural dissemination (n = 2) in the neoadjuvant group.

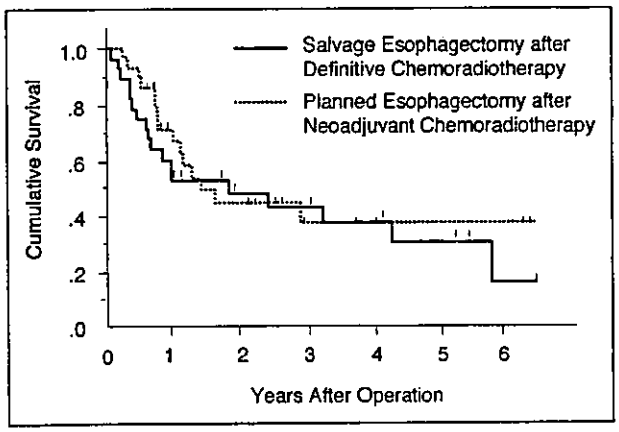

Fig. 1. No difference is shown in cumulative postoperative survival between the salvage and neoadjuvant groups.

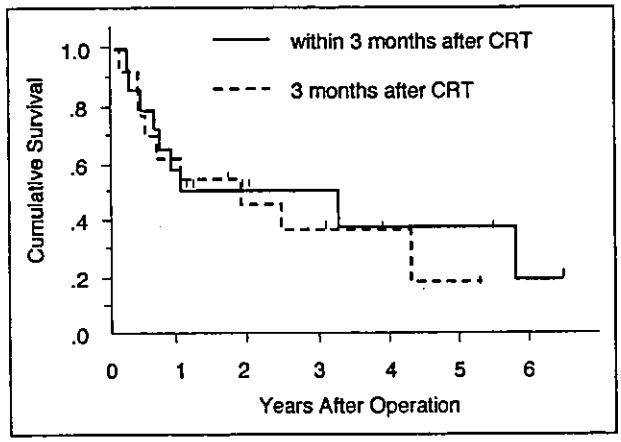

Fig. 2. In the salvage group, no difference was observed in cumulative postoperative survival between patients with recurrence (>3 months after chemoradiotherapy [CRT]) and those with residual tumors (<3 months after CRT).

Comments

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 CRT has proven to be an effective treatment for squamous-cell carcinoma of the esophagus. Although several studies have compared planned neoadjuvant CRT (30 to 45 Gy) plus esophagectomy with definitive CRT (≥50 Gy), the optimum treatment remains unclear [12,13]. Salvage

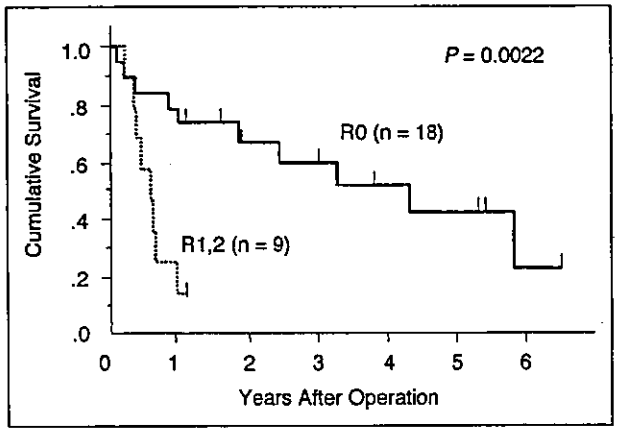

Fig. 3. The survival of patients without residual tumors (R0) was significantly better than that of patients with R1or R2 tumors in the salvage group.

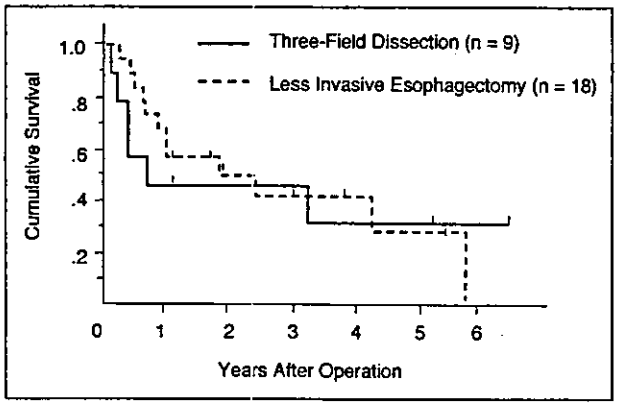

Fig. 4. No difference was observed in cumulative postoperative survival between patients who underwent less-invasive esophagectomy and those who underwent 3-field lymph node-dissection in the salvage group.

esophagectomy could be the best second-line treatment for local and regional recurrence after definitive CRT, but this has not yet been established. The present study showed that the outcome of salvage esophagectomy after definitive CRT was comparable with that of esophagectomy after neoadjuvant CRT.

Although extended esophagectomy with 3-field lymph-node dissection is routinely performed for advanced esophageal cancer, the operative mortality decreased to only 1.7% in this study, the same as that (1.7%) in another Japanese study, because of improved surgical management [1]. However, the 30-day mortality rate of extended esophagectomy with 3-field lymph node dissection was 2.5% (5 of 203), and that of the other less-invasive procedures was 1.3% (6 of 457), during the same periods. Although there was no statistical difference, the mortality rate was twice as high with 3-field lymph node dissection as with the other type. Extended esophagectomy after definitive CRT led to the death of 2 patients who died from postoperative complications before 1997, and we were forced to change the operative procedure to less-invasive methods of esophagectomy. Vogel et al. [6] showed a low mortality rate (5%) and relatively favorable outcome of esophagectomy using less-invasive approaches after neoadjuvant CRT. Neoadjuvant CRT using paclitaxel did not improve outcome of 5-FU–based treatment for locoregionally advanced esophageal cancer [23]. A recent phase III study of definitive CRT showed that outcome of the standard-dose group (50.4 Gy) was relatively superior to that of the high-dose group (64.8 Gy) because of toxicity [24]. These results might suggest that aggressive treatment could guarantee improvement of outcome in patients with advanced esophageal cancer.

Although a previous study of salvage esophagectomy found that preoperative data were similar in both groups [19], %VC and serum albumin level were significantly lower in our salvage group than in our neoadjuvant group. Pretreatment data could not be collected because several patients received definitive CRT at other hospitals, but a lower %VC without change in FEV1% may have been caused by restrictive changes to the lungs as a result of radiation damage [25]. The lungs are usually not affected by neoadjuvant CRT (≤45 Gy) for esophageal cancer using anterior- and posterior-opposed beams, and clinical data have shown no difference in %VC after neoadjuvant CRT [26]. However, more irradiation (>45 Gy) was given obliquely to avoid spinal cord damage, and this may have led to damage to the lung. The low serum albumin level in the salvage group of the present study was possibly related to the long duration of disease. Both %VC and albumin level are important preoperative risk factors for complications after transthoracic esophagectomy [27,28]. Thus, the preoperative risk of salvage surgery could be higher than that of esophagectomy after neoadjuvant CRT.

Anastomotic leakage was frequent (22%) in the salvage group as well as in a previous study (38%) [19]. Irradiation to the cervical esophagus and trachea can influence blood supply, and 1 patient died of tracheal bleeding caused by anastomotic leakage after reconstruction using the mediastinal route. The other 5 patients who had leakage after reconstruction by way of the subcutaneous route did not die, but they needed longer hospital stays. Although we routinely perform 1-stage esophagectomy and reconstruction, 4 patients in the salvage group underwent 2-stage reconstruction to prevent aspiration pneumonia. From 1997 onward, preoperative corticosteroid therapy was routinely given before surgery to prevent pulmonary failure [29]. Enteric nutrition by way of gastrostomy was also used routinely for prolonged pleural effusion in the salvage group.

When compared with patients having residual tumors (<3 months after CRT) or recurrent tumors (>3 months after CRT), no differences were found in the surgical outcome between these groups. Esophagectomy may be unnecessary after complete response, but its diagnosis by imaging is difficult and possible only by esophageal resection [30]. Recently, positron-emission tomography using 2-[18F]-fluoro-2-deoxy-D-glucose has been developed as a tool to assess tumor response to CRT, but it cannot distinguish a complete response from small foci of residual tumors [31]. In this study, cancer cells were detected by endoscopic biopsy specimens in the all patients with locoregional recurrence >3 months after CRT. No difference between the 2 groups was obtained partly because micrometastasis to lymph nodes may have been controlled by CRT, whereas patients with obvious metastasis in distant lymph nodes could not undergo salvage esophagectomy. In either case, to improve the outcome of salvage esophagectomy, patients with residual or recurrent tumors after definitive CRT should be referred immediately to experienced surgical institutions by medical and radiation oncologists.

In conclusion, the outcome of salvage esophagectomy after definitive chemotherapy and radiotherapy was comparable with that of planned neoadjuvant CRT plus esophagectomy. Preoperative risk factors were greater in the salvage esophagectomy group than in the neoadjuvant CRT plus esophagectomy group. Less-invasive surgery and me-

ticulous postoperative care may improve the outcome of patients undergoing salvage esophagectomy.

Acknowledgments

This work was supported in part by a Grant for Cancer Research (11S-4) by the Japanese Clinical Oncology Group from the Ministry of Health, Labor, and welfare of Japan (Tokyo, Japan).

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Diseases of the Esophagus (2004) 17, 315–321
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DISEASES OF THE ESOPHAGUS

Original article

Expression of $p21^{Waf1/Cip1}$ predicts response and survival of esophageal cancer patients treated by chemoradiotherapy

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SUMMARY. **Chemoradiotherapy is a multimodal therapy routinely used as a primary treatment for advanced esophageal cancer. However, it is beneficial only to patients who respond. To identify pretreatment markers predicting response and survival, we examined the expression of cell cycle regulatory molecules, p53, $p21^{Waf1/Cip1}$ cyclin D1, and CDC25B, in biopsy specimens from 76 patients with stage III and stage IV squamous cell carcinoma. Overexpression of p53, p21, cyclin D1 and CDC25B was observed in 58%, 30%, 28%, and 32% of patients, respectively. The expression of p21 correlated significantly with response to chemoradiotherapy ($P = 0.0001$). Survival of patients with p21-expressing tumors was better than that of patients with p21-negative tumors ($P = 0.013$). Expression of other genes was not significantly correlated with treatment response and survival. In patients with p53-negative tumors, survival of those patients with p21-positive tumors was significantly higher than that of those with p21-negative tumors ($P = 0.0452$), but no significant difference was found in patients with p53-positive tumors. Multivariate analysis revealed that p21 expression was an independent variable among pretreatment parameters in predicting survival. These results suggest that p21 expression is potentially useful for predicting the response to chemoradiotherapy and survival of patients with advanced esophageal squamous cell cancer.**

KEY WORDS: **CDC25B, chemoradiotherapy, cyclin D1, p21, p53, squamous cell carcinoma.**

INTRODUCTION

Combined modality therapy, including chemotherapy, is necessary to treat advanced esophageal cancer, which can be widely disseminated at the time of diagnosis.[1] Chemoradiotherapy (CRT) is widely used as an effective therapy for patients with esophageal squamous cell cancer.[2] Combined modality therapy, consisting of CRT and surgery, has been shown to improve the outcome for esophageal cancer.[3,4] In contrast, randomized comparative studies showed no difference in survival between operable patients who received neoadjuvant CRT and those treated with surgery alone.[5,6] The toxicity of CRT is considerable and the operative risk after CRT is increased compared to that without any therapy. If reliable ways to predict the response to CRT could be found, non-responders could be spared the toxicity and the postoperative risk associated with the treatment.[2,4]

Lack of response to CRT can be attributed to the resistance of the carcinoma cells. The presence of functional wild-type p53 is an important determinant of tumor response to chemotherapy and radiotherapy.[7] Although numerous studies have analyzed the association between p53 mutation or expression and anticancer treatment, the results were not consistent in a variety of cancers, including esophageal cancer.[8–11] Cyclin-dependent kinase inhibitor $p21^{Waf1/Cip1}$, which is transcriptionally activated by p53, is necessary for p53-mediated G1 arrest following irradiation.[12] In rectal and pancreatic cancer,[13,14] p21 expression in relation to p53 can predict the response to CRT or radiotherapy. The other cell cycle-related molecules associated with the response of esophageal cancer to CRT or radiotherapy are cyclin D1 and CDC25B.[15,16] Although these studies reported a correlation with treatment response, the predictive value of these molecules in terms of the response to CRT and patient survival was unclear because of small sample sizes.

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In this study, we examined p53, p21, cyclin D1, and CDC25B expression using immunohistochemistry in pretreatment endoscopic biopsy specimens before CRT and compared these with the response to CRT. To evaluate the prognostic value of expression of these genes among the pretreatment parameters, we used a Cox proportional hazards model in 76 patients with advanced esophageal cancer.

MATERIALS AND METHODS

Patients

Between 1993 and 2001, 108 consecutive patients with advanced esophageal cancer received CRT as their initial treatment. Of these, 11 patients who did not complete the planned CRT and 21 patients whose biopsy specimens could not be examined were excluded from this study. The remaining 76 patients who completed the planned CRT were included. Clinical pretreatment features of the patients are shown in Table 1. The Eastern Cooperative Oncology Group performance status was 0 in 28 patients, and 1 in 48 patients. The patients were staged clinically based on barium swallow X-rays, endoscopy, CT and endoscopic ultrasonography findings according to the TNM classification (UICC).[17] Informed consent for examination was obtained from all patients before enrollment in this study.

Treatment schedule

Patients received CRT according to different chemotherapy regimens; however, the external beam irradiation was over 30 Gy in every case. Standard CRT, consisting of cisplatin (70 mg/m^2, day 1) and 5-fluorouracil (FU) (700 mg/m^2/day, days 1–4) and irradiation given as a continuous i.v. infusion, was given to 38 patients. A low-dose CRT regimen, consisting of cisplatin (3–5 mg/m^2/day), 5-FU (200–300 mg/m^2/day) and irradiation, was given to 14 patients. A different CRT regimen, consisting of nedaplatin, an analog of cisplatin (20 mg/m^2/day for 4 days)[18] and 5-FU (700 mg/m^2/day for 4 days) and irradiation, was given to 24 patients. Radiotherapy (40 Gy) was administered in 23 patients using anterior and posterior opposed equally weighted beams from a 10-MV linear accelerator in 20 fractions of 2 Gy. In the other 53 patients, an additional course of chemotherapy and irradiation of 20–30 Gy (a total of 60–70 Gy) were administered via two parallel oblique fields (definitive CRT).

Table 1 Patient and tumor characteristics

Characteristic	*n* (total 76)
Male : female	65:11
Performance status	
0	28
1	48
Location	
Cervical	7
Upper thoracic	12
Middle thoracic	45
Lower thoracic	12
Depth of invasion	
T3	27
T4	49
Distant lymph node metastasis	
M0	44
M1	32
Differentiation	
Well	8
Moderate	55
Poor	13
Gross type	
Localized type	19
Infiltrative type	57

The mean age of the patients was 63 years (range, 47–79)

Evaluation of response

The clinical response of the tumor was determined in accordance with the criteria for assessment of response to non-surgical treatment of the Japanese Society for Esophageal Diseases.[19] For the primary esophageal lesion, the response was assessed on the basis of the two-dimensional reduction rate and the morphologic changes on barium swallow X-rays and endoscopy. For metastatic lesions, the response was assessed on neck, chest and abdominal CT scans.

Clinical evaluation was carried out by re-evaluation of the images at one month after the initial evaluation of response. In the 32 patients who underwent esophagectomy after CRT, response was evaluated on the basis of histologic examination of the resected specimens according to the histopathologic criteria for assessing the effects of radiation and/or chemotherapy.[19] When no viable cancer cells were evident this was classified as a complete response (CR). When viable cancer cells accounted for less than one-third of the tumor, this was classified as a partial response (PR). Viable cancer cells accounting for one-third or more of the tumor tissue with no discernible therapeutic effect on the tumor led to classification as stable disease (SD). If a new lesion was detected, this was classified as progressive disease (PD).

Immunohistochemistry

Specimens of invasive squamous cell carcinoma were obtained from all 74 patients by endoscopic biopsy before starting CRT. Carcinomas present in the resected specimens were also evaluated in 22 patients who underwent esophagectomy, excluding 10 patients who had a pathological CR.

Written informed consent to examination was obtained from all patients before enrollment in this study.

Specimens were fixed in 10% buffered formalin and embedded in paraffin. Serial sections (3 μm thick) were dewaxed in xylene and rehydrated with graded ethanol solutions. After rinsing with 0.01 M phosphate-buffered saline (PBS), the sections were placed in a plastic container filled with 10 mmol/L citrate buffer (pH 6.0), heated in a microwave oven (500 W) for 15 min, and then left at room temperature for 20 min. Endogenous peroxidase activity was blocked by incubating the sections in 0.3% hydrogen peroxide (H_2O_2) in absolute methanol for 15 min. Immunostaining was performed using the labeled streptavidin-biotin-peroxidase technique (DAKO-LSAB2 system, DAKO, Carpenteria, CA). The primary antibodies were a monoclonal mouse antip53 protein antibody (DO7, DAKO), an anti-Waf1 (p21) protein antibody (Clone EA10, Oncogene Research Products, Cambridge, MA), an anticyclin D1/PRAD1 antibody (5D4, Medical & Biological Laboratories, Nagoya, Japan) and an anti-CDC25B antibody (sc-326, Santa Cruz Biotechnology, Santa Cruz, CA). Normal rabbit serum diluted to 1 : 400 was used in place of the primary antibody as a negative control.

After washing with PBS, the sections were incubated with a biotinylated antimouse IgG (DAKO), followed by incubation with peroxidase-conjugated streptavidin (DAKO). The peroxidase reaction was visualized using 0.5 mg/mL diaminobenzidine tetrahydrochloride (DAKO) in 0.03% hydrogen peroxide. The sections were counterstained with hematoxylin, dehydrated and covered with a cover slip. Positive reactivity for p53, p21, cyclin D1 and CDC25B was defined by staining in more than 10% of the cancer cells.

Data analysis

Differences in percentage data were evaluated by the two-sided χ^2 test or Fisher's exact test. Survival was calculated from the first day of the CRT schedule. Survival curves were constructed according to the Kaplan–Meier method and were compared using the log-rank test. Independent prognostic factors for survival were determined by the Cox proportional hazards model. All data were analyzed using JMP version 4 software (SAS Institute, Cary, NC). *P*-values of less than 0.05 were considered to be statistically significant.

RESULTS

Gene expression in biopsy specimens

Expression of p53, p21, cyclin D1 and CDC25B was observed in 44 (58%), 23 (30%), 21 (28%), and 24 (32%) of the pretreatment biopsy specimens, respectively (Fig. 1). No association was found between patients with and without p53, cyclin D1 and CDC25B expression in any pretreatment characteristics. Expression of p21 was inversely correlated with distant metastasis (M0), but without significance ($P = 0.0792$). Four of eight (50%) well-differentiated carcinomas and seven of 19 (37%) localized tumors expressed p21. In the biopsy specimens, p53 expression was inversely correlated with response to CRT, but not to a significant extent ($P = 0.082$) and p21 expression was closely correlated with response to CRT ($P = 0.0001$)

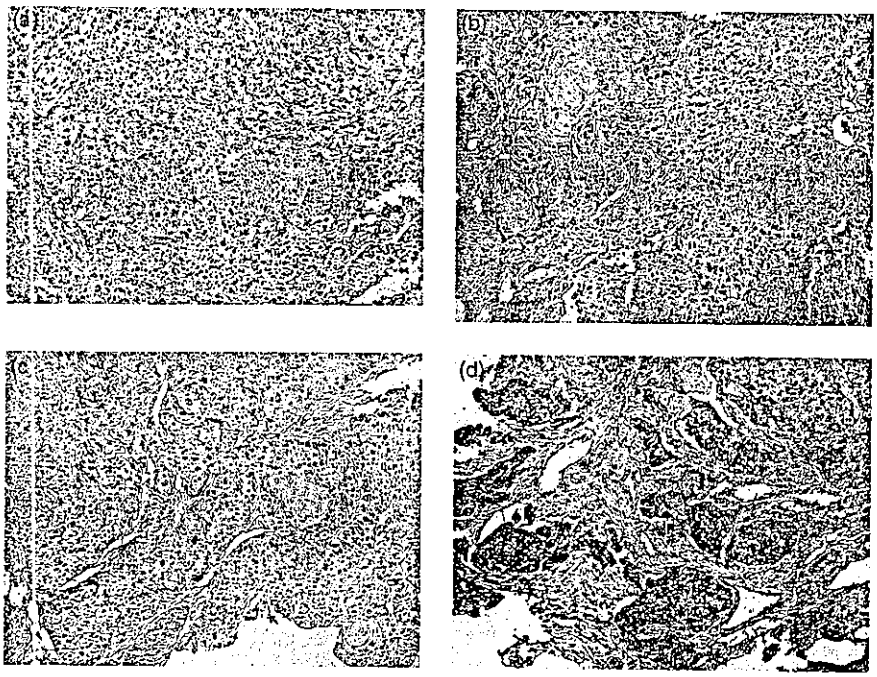

Fig. 1 Results of immunohistochemistry on pretreatment biopsy specimens: (a) p53; (b) $p21^{Waf1/Cip1}$; (c) cyclin D1; and (d) CDC25B. (Original magnification ×100.)

(Table 2). Cyclin D1 expression was not associated with response to CRT. CDC25B expression tended to be correlated with response, but without reaching a significant level.

Gene expression in resected specimens

Tumor specimens were obtained at two time-points during treatment: a biopsy was taken before starting CRT, and tumor specimens were obtained during esophagectomy after CRT in 22 patients (Table 3). No change in p53 expression was shown between the biopsy and resected specimens in 19 of 22 cases (86%). Specimens from 17 of 22 patients (77%) were shown to be p21-negative, both before and after CRT, because only ineffective residual tumors survived and could be investigated in resected specimens. Expression of p21 was found to be induced in three resected tumors, which had been negative at the pre-CRT biopsy. The coincidence rate of cyclin D1 and CDC25B expression was not high.

Survival

Response to CRT was closely correlated with patient survival ($P < 0.0001$). Patients with p53-positive tumors tended to survive for shorter periods of time than those with p53-negative tumors, but the difference was not significant ($P = 0.2323$) (Fig. 2a). The survival of 23 patients with p21-positive tumors was significantly longer than that of 53 patients with p21-negative tumors ($P = 0.013$) (Fig. 2b). No significant difference in survival was observed for cyclin D1 (Fig. 2c) or CDC25B (Fig. 2d) expression. Survival curves divided by the combination of p53 and p21 expression are shown in Fig. 3. In patients with p53-negative tumors, survival of those patients with p21-positive tumors was significantly higher than that of those with p21-negative tumors ($P = 0.0452$), but no significant difference was found in patients with p53-positive tumors ($P = 0.1085$). Pretreatment characteristics were examined by univariate analysis for their value as predictors of survival. M factor and performance

Table 2 Expressions in pretreatment biopsy specimens and response to chemoradiotherapy

	n	p53	$p21^{Waf1/Cip1}$	cyclin D1	CDC25B
Positive cases	76	44 (58%)	23 (30%)	21 (28%)	24 (32%)
Complete response	16	6 (38%)	12 (75%)	4 (25%)	7 (44%)
Partial response	39	24 (62%)	9 (23%)	10 (26%)	12 (31%)
Stable disease	18	13 (72%)	2 (11%)	7 (39%)	4 (22%)
Progressive disease	3	1 (33%)	0	0	1 (33%)

Tumor response to chemoradiotherapy was significantly correlated with $p21^{Waf1/Cip1}$ expression ($P < 0.0001$), but not associated with p53, cyclin D1 or CDC25B expression.

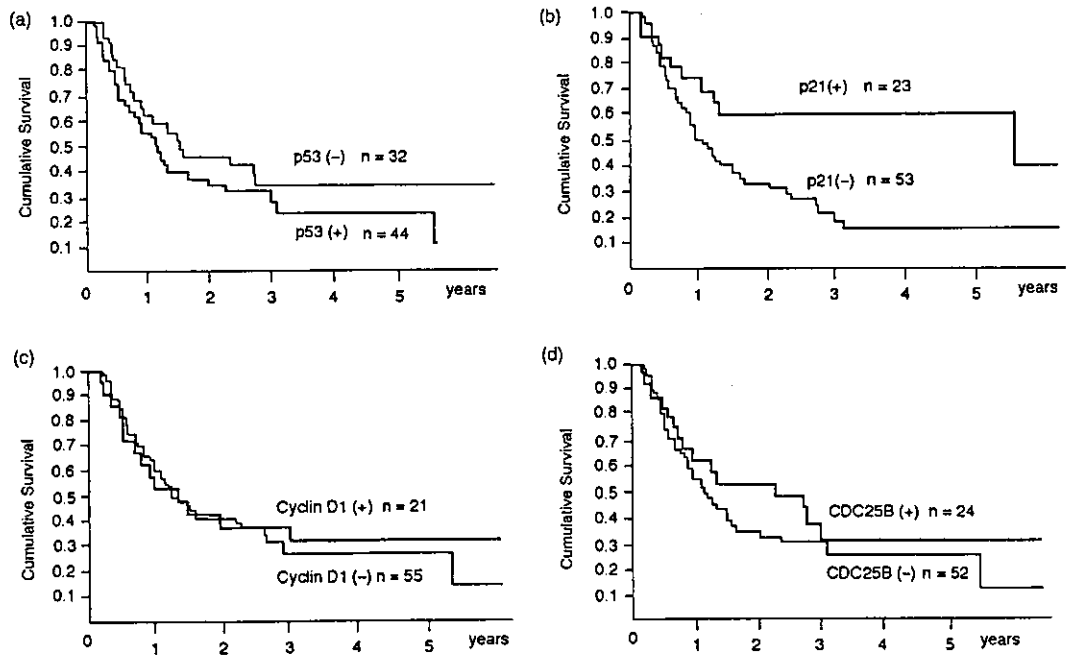

Fig. 2 The probability of survival for the patients was not different by (a) p53; (c) cyclin D1; or (d) CDC25B expression. (b) The probability of survival for patients with $p21^{Waf1/Cip1}$-positive tumors was significantly higher than patients with p21-negative tumors ($P = 0.013$).