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(SAIKAWA Yoshiro, et al 慶應義塾大学医学部外科 :
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Improved Survival for Patients With Upper and/or Middle Mediastinal Lymph Node Metastasis of Squamous Cell Carcinoma of the Lower Thoracic Esophagus Treated With 3-Field Dissection

Hiroyasu Igaki, MD, Yuji Tachimori, MD, and Hoichi Kato, MD

Objective: To evaluate the outcomes with 2 and 3 lymph node dissection for patients with squamous cell carcinoma of the lower thoracic esophagus at a single institution.

Background: Extensive lymph node dissection, including the upper mediastinum, for carcinoma of the lower thoracic esophagus is advocated as a standard surgical procedure with curative intent in Japan. However, its efficacy remains controversial.

Methods: From January 1988 to December 1997, 532 patients with carcinomas of the thoracic esophagus underwent transthoracic esophagectomy and extensive lymph node dissection with curative intent at the National Cancer Center Hospital, Tokyo. Of these, 495 (93%) had squamous cell carcinomas. A total of 156 (29%) with tumors of the lower thoracic esophagus were retrospectively analyzed.

Results: Of the 156 patients, 55 (35%) underwent 2-field and 101 (65%) underwent 3-field lymph node dissection. The operative morbidity and 30-day and in-hospital mortality rates were 68.0%, 1.3%, and 2.6%, respectively. The overall 5-year survival rate for the entire series was 49.3%. One hundred and seven (69%) had lymph node metastases. Upper and/or middle mediastinal lymph node metastases occurred in 42% of the series. The 5-year survival rate for patients with lymph node metastases in the upper and/or middle mediastinum was 23.3%. Among them, the values after 2- and 3-field lymph node dissection were 5.6% and 30.0%, respectively ($P = 0.005$). 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%.

Conclusion: The 3-field approach for extensive lymph node dissection provides better survival benefit for patients with squamous cell carcinoma of the lower thoracic esophagus compared to 2-field

lymph node dissection when lymph node metastases are present in the upper and/or middle mediastinum.

(*Ann Surg* 2004;239: 483–490)

Carcinomas of the thoracic esophagus throughout the world have remained in dismal prognosis despite improvements of surgical technique, perioperative care, and multi-modality treatment approach. During the past 2 decades, prevalence of carcinomas, especially adenocarcinoma, of the lower thoracic esophagus has increased drastically in the Western countries.^{1,2} Many are associated with gastroesophageal reflux and Barrett esophagus. In the East, the most frequent location of esophageal carcinomas is the middle thoracic esophagus and histologic type is mainly squamous cell carcinoma that originates from esophageal squamous epithelium; most are associated with alcohol and tobacco abuse.^{3–5}

Differences of the tumor characteristics between the Western and Eastern countries cause various attitudes in the surgical approach to esophageal carcinomas. The majority of Western surgeons have advocated limited surgical resections such as transhiatal esophagectomy.⁶ Because they consider esophageal carcinomas to have poor prognosis or being already systemic when lymph node metastases exist, the primary goal of surgical intervention is palliative, with low operative morbidity and mortality rates. Furthermore, controversy has persisted about the extent of resection. Transhiatal resection only performs sampling the lower mediastinal or celiac axis nodes.⁷ Esophagectomy with extensive lymphadenectomy such as en bloc resection does not remove the upper mediastinal lymph nodes as a standard practice.⁸

In the East, especially in Japan, extensive lymph node dissection, including not only the abdominal and lower mediastinal but also the upper, middle mediastinal and occasionally cervical lymph nodes, has been advocated as a standard surgical procedure with curative intent, because systematic

From the Esophageal Surgery Division, Department of Surgery, National Cancer Center Hospital, Tokyo, Japan.

Reprints: Hiroyasu Igaki, MD, Esophageal Surgery Division, Department of Surgery, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: hiigaki@ncc.go.jp.

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dissection of metastatic nodes may improve survival and lead to potential cure.⁹ We perform a right transthoracic esophagectomy with extensive lymph node dissection for all surgical candidates with carcinomas of the thoracic esophagus regardless of tumor location.

The aim of the present study was to evaluate our results with 2-field and 3-field lymph node dissection for patients with squamous cell carcinoma of the lower thoracic esophagus.

MATERIALS AND METHODS

Patients

From January 1988 to December 1997, 532 patients with carcinomas of the thoracic esophagus underwent esophagectomy with extensive lymph node dissection via right thoracotomy as a standard surgical procedure at the National Cancer Center Hospital, Tokyo, Japan. The year 1988 was chosen as the beginning of this study because the UICC-TNM staging system revised the T category from length to depth of the primary tumor in 1987.

Four hundred ninety-five patients (93%) had squamous cell carcinomas, and 156 (29% of entire series) had tumors of the lower thoracic esophagus. The records of all of these cases (138 male and 18 female) were analyzed. Ages ranged from 42 to 86 years, with a mean of 62.1 and a median of 62 years. Preoperative evaluation was performed for all patients with a barium swallow examination, endoscopy with biopsy, computed tomography scans from the neck to the abdomen, ultrasonography of the neck and the upper abdominal compartment, and endoscopic ultrasonography. Distant organ metastasis, except in the cervical or celiac nodes, was not evident in any of the patients on preoperative evaluation. Preoperative and postoperative staging was based on the 1997 UICC-TNM classification.¹⁰ Metastasis in the cervical or celiac nodes was classified into M1 disease according to the TNM classification. Among the 156 patients, 4 received preoperative chemotherapy in a clinical trial because of presence of intramural metastases.¹¹

In our institute, 3-field lymph node dissection has been carried out for patients with carcinomas of the thoracic esophagus as a standard surgical procedure by a group of surgeons; another group performed 2-field approach as a standard resection except carcinomas of the upper thoracic esophagus until March 2000. Patients who visited our outpatient service on Monday or Thursday were treated by the group of proponents of the 2-field approach while those who presented on Tuesday, Wednesday, or Friday underwent the 3-field dissection. However, surgeons of the 2-field group performed cervical lymphadenectomy when patients were diagnosed or clinically positive for cervical nodal metastasis.

Thirteen patients received postoperative adjuvant chemotherapy in another clinical trial, and postoperative radia-

tion therapy was performed for 8 patients because of residual tumors.

Surgical Procedure

All patients underwent right transthoracic esophagectomy with extensive lymphadenectomy,⁹ with either the 2-field or 3-field approach. Our 2-field lymph node dissection included total mediastinal, perigastric, and celiac lymphadenectomy. Three-field lymph node dissection adds removal of lymph node in the supraclavicular and cervical paratracheal regions to 2-field approach. Gastrointestinal continuity was restored with a stomach in 145 patients: 127 through a retrosternal route, 10 through a posterior mediastinal route, and 8 through a subcutaneous route. Colon interposition was performed for the remaining 11 patients because of previous gastric surgery for peptic ulcers in 7 and gastric cancer in 1, and simultaneous total gastrectomy for gastric cancers in 3 patients, 5 through a retrosternal, 1 through a posterior mediastinal, and 5 through a subcutaneous route. Anastomoses of 153 patients were performed at the neck, and 3 patients underwent anastomosis in the right thoracic cavity.

All patients were extubated in the operating room after surgery, and returned to the intensive care unit for 4 days on average. Analgesia with morphine was provided through an epidural catheter for the first 5 postoperative days, and postoperative bronchoscopic lavage was also performed for a few days.

Pathologic Assessment of the Resected Specimens

Pathologic evaluation was performed to identify the depth of invasion of primary lesions and to assess additional lesions in the resected specimens. The entire resected esophagus was examined, with 5- μ m sections stained with hematoxylin and eosin for microscopic examination. All removed lymph nodes, identified according to the anatomic location, were formalin fixed and processed to provide 2.5- μ m sections for staining with hematoxylin and eosin.

Follow-up

All data were entered prospectively into a database, and all surviving patients were followed for at least 3 years after surgery. The median follow-up period of all patients was 45 months (range, 0.4–151), that for the 66 survivors being 83 months (range, 37–151). Survival time was measured as the period from the date of surgery until death or until the most recent follow-up investigation, with none lost to follow-up. Information about the cause of death was available for all patients.

Statistical Analysis

Survival curves were calculated according to the Kaplan-Meier method, including all causes of death, and log-rank statistics were used for comparisons. The χ^2 test was

employed for comparisons of proportions. All probabilities were 2-tailed, with a *P* value less than 0.05 regarded as statistically significant. The statistical calculations were conducted with SPSS 10.0J (SPSS Inc, Chicago, IL) and Stat View 5.0J (Abacus Concepts Inc, Berkeley, CA).

RESULTS

Preoperative Characteristics According to Lymph Node Dissection

Of the 156 patients, 55 (35% of this series) underwent 2-field and 101 (65%) 3-field lymph node dissection. Relationships between preoperative characteristics and lymph node dissection are listed in Table 1. Six patients were diagnosed as having T4 tumors. One patient of the 2-field group demonstrated direct invasion of the primary tumor to the liver. Among 5 patients with T4 tumors in the 3-field group, direct invasion to the lung was diagnosed in 4 and to the aorta in 1.

Operative Outcomes

The mean \pm SD for duration of surgery was 456 ± 87 minutes in the 2-field group and 487 ± 84 minutes in the 3-field group. Operative blood loss was 530 ± 247 mL in the 2-field group and 540 ± 356 mL in the 3-field group.

Postoperative complications are listed in Table 2. Fifty patients of this series had an uncomplicated postoperative course. Thus, the operative morbidity was 68.0%, with a 2.6% (4 patients) in-hospital mortality rate. Two patients (1.3%) died of postoperative complications within 30 days of surgery. The incidences of postoperative complications did not differ between the groups undergoing 2-field and 3-field lymph node dissection.

The overall 5-year survival rate for the entire series was 49.3%. Survival curves of patients after 2-field and 3-field lymph node dissection are shown in Figure 1, the 5-year survival rates being 45.0% and 51.7%, respectively (*P* = 0.406).

Status of Lymph Node Metastases and Survival Rates

Survival rates according to the status of lymph node metastases are summarized in Table 3. All patients with lower mediastinal lymph node metastases had simultaneous perigastric nodal involvement. There were 66 patients with lymph node metastases in the upper and/or middle mediastinum, including 3 patients with simultaneous abdominal paraaortic nodal involvement. The 5-year survival rate for these 16 patients, who had lymph node metastases in the upper and/or middle mediastinum but not the other regions, was 30.0%. The value for the remaining 50 patients, who had simultaneous lymph node metastases in the abdomen, was 21.1%. One patient among this series, who had cervical nodal involvement alone without having any other lymph node

TABLE 1. Preoperative Characteristics According to Lymph Node Dissection Approach

Variables	No. of patients		<i>P</i> value*
	2-field (%)	3-field (%)	
Total	55 (100)	101 (100)	
Gender			0.164
Male	46 (84)	92 (91)	
Female	9 (16)	9 (9)	
Alcohol abuse			0.343
No	2 (4)	10 (10)	
Yes	37 (64)	87 (86)	
Tobacco abuse			0.560
No	4 (7)	13 (13)	
Yes	38 (69)	87 (86)	
T status			0.586
Tis	2 (4)	0 (0)	
T1	17 (31)	24 (24)	
T2	9 (16)	15 (56)	
T3	26 (47)	57 (56)	
T4	1 (2)	5 (5)	
N status			0.961
N0	27 (49)	50 (50)	
N1	28 (51)	51 (50)	
M status			0.439
M0	52 (95)	92 (91)	
M1	3 (5)	9 (9)	
M1 status			0.418
M1a-celiac	0 (0)	3 (3)	
M1b-neck	1 (2)	5 (5)	
M1b-abdominal paraaorta	2 (4)	1 (1)	
Lymph node metastasis			0.945
Negative	27 (49)	49 (49)	
Positive	28 (51)	52 (51)	
Differentiation			0.073
Well, moderate	39 (71)	84 (83)	
Poor	16 (29)	17 (17)	
Multiple primary lesions			0.214
Single	46 (84)	75 (74)	
Multiple	9 (16)	17 (17)	
Intramural metastasis			0.337
Absent	52 (95)	91 (90)	
Present	3 (5)	10 (10)	
Stage			0.149
0	2 (4)	0 (0)	
I	13 (24)	23 (23)	
II	21 (38)	28 (28)	
III	16 (29)	41 (41)	
IV	3 (5)	9 (9)	

* χ^2 test.

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)	

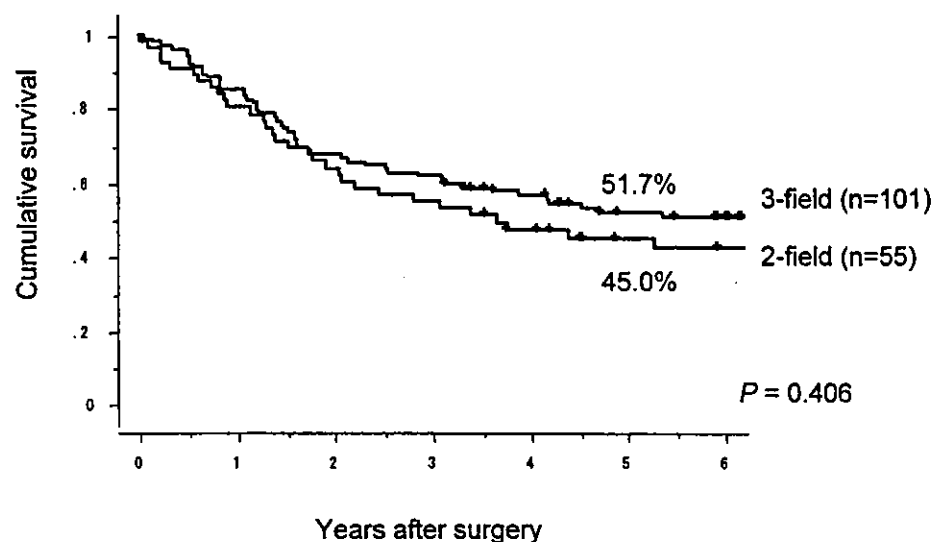


FIGURE 1. Survival curves of patients with squamous cell carcinomas of the lower thoracic esophagus after 2-field or 3-field lymph node dissection.

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

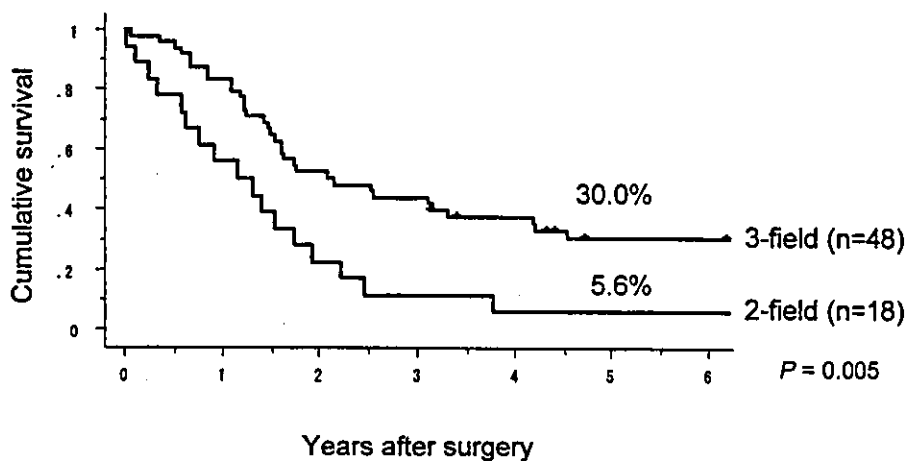


FIGURE 2. Survival curves of patients with lymph node metastases of the upper and/or middle mediastinum treated with 2-field and 3-field lymph node dissection.

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 (%)		P value*
	2-field	3-field	
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)	

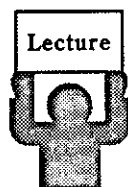
* χ^2 test

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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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、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も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/m², day 1)とvindesine (VDS; 3 mg/m², 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.

** Hideaki YAMANA, M.D., Ph.D.: 久留米大学病院集学治療センター〔〒830-0011 久留米市旭町67〕; Multidisciplinary Treatment Center, University of Kurume Hospital, Kurume 830-0011, JAPAN

*** Nobutoshi ANDO, M.D.: 東京歯科大学市川総合病院外科

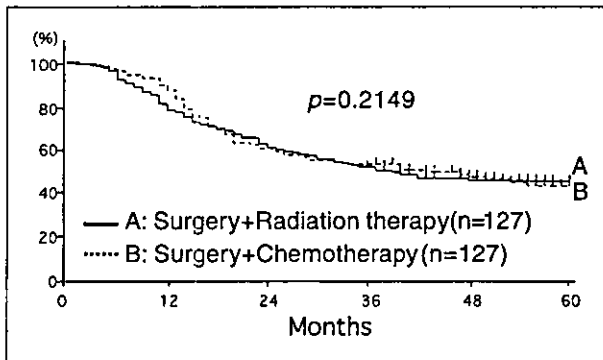


図1 胸部食道がん根治切除術後放射線治療群と化学療法群の全生存曲線による比較(JEOG第3次研究)

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

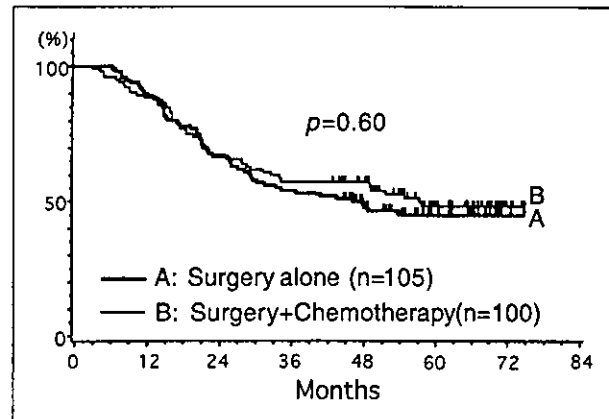


図2 胸部食道がん根治切除術単独群と術後補助化学療法群の全生存曲線の比較(JEOG第4次研究)

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るため登録時に両者を前層別することを規定した。

当該試験には、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と比較すると、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

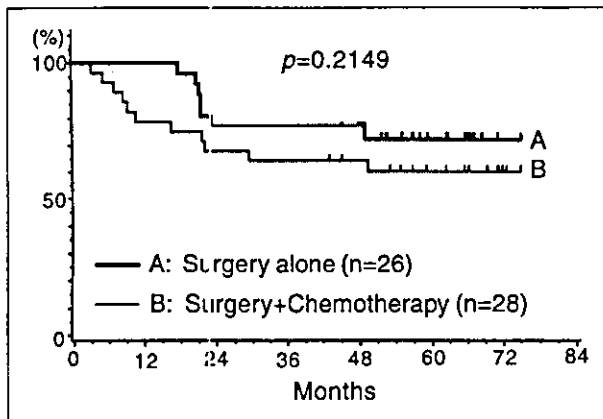


図3 pN0症例における胸部食道がん根治切除術単独群と術後化学療法群の全生存曲線の比較 (JEOG第4次研究)

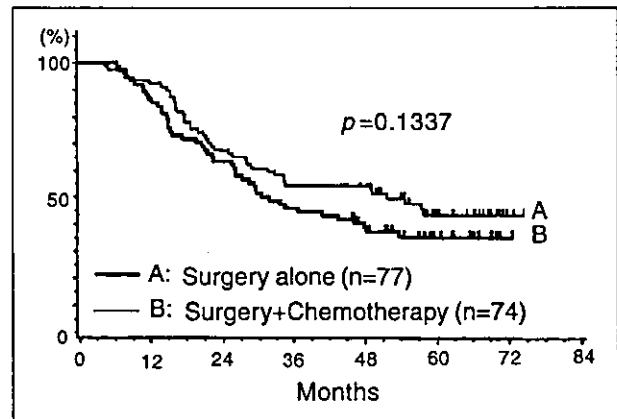


図4 pN1症例における胸部食道がん根治切除術単独群と術後化学療法群の全生存曲線の比較 (JEOG第4次研究)

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⁸⁾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/m ² /day DIV day 1 5-FU:800mg/m ² /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)

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

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		
Stage II A	21	22
Stage II B	34	37
Stage III	47	38
Stage IV	20	22

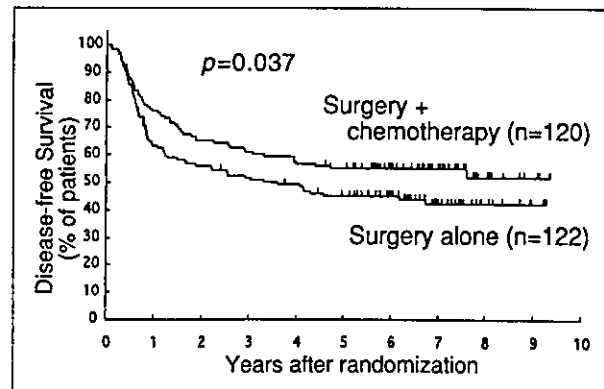


図5 胸部食道がん根治切除術単独群と術後化学療法群の無再発生存曲線の比較(JCOG第5次研究)

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

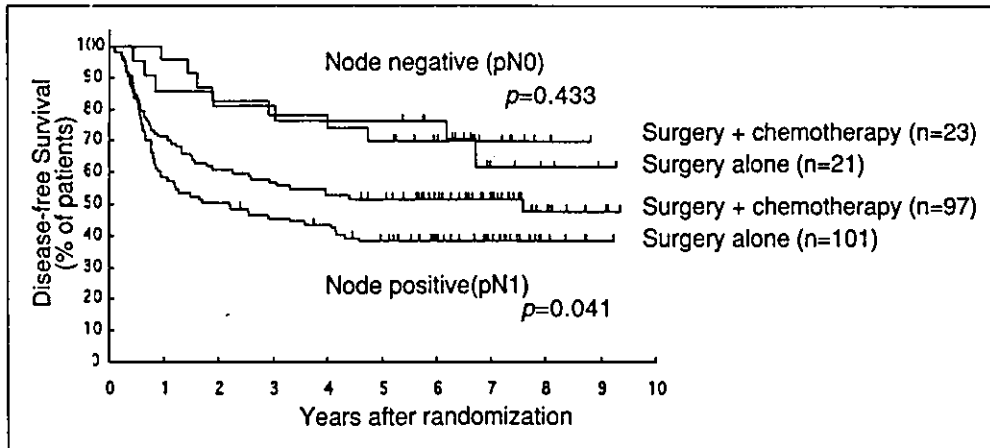


図6 pN0とpN1別にみた胸部食道がん根治切除術単独群と術後化学療法群の無再発生存曲線の比較(JEOG第5次研究)

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群に多く認められたが, 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。

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

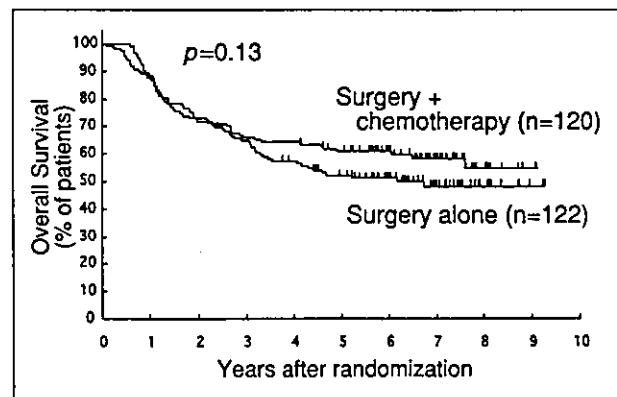


図7 胸部食道がん根治切除術単独群と術後化学療法群の全生存曲線の比較(JEOG第5次研究)

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、術前化学療法を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余年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、今後も一步一步地道に、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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別刷

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抗癌剤・放射線併用免疫細胞療法の効果と 患者リンパ球サイトカイン産生に関する検討

唐 宇 飛*¹ 藤井 輝彦*^{1,3} 田山 光介*¹ 弥 永 浩*¹ 横山 吾郎*¹ 山口 美樹*^{1,3}
堀内 彦之*¹ 笹富 輝男*¹ 高森 信三*¹ 白水 和雄*¹ 関 直子*² 山名 秀明*²

(*Jpn J Cancer Chemother* 31(11):1649-1651, October, 2004)

The Repetitive Immune Cell Transfer Therapy Combining Non-Myelosuppressive Chemotherapy for Patients with Advanced and Refractory Cancer: Uhi Toh*¹, Teruhiko Fujii*^{1,3}, Kousuke Tayama*¹, Hiroshi Yanaga*¹, Goro Yokoyama*¹, Miki Yamaguchi*^{1,3}, Hiroyuki Horiuchi*¹, Teruo Sasatomi*¹, Shinzo Takamori*¹, Kazuo Shirouzu*¹, Naoko Seki*² and Hideaki Yamana*² (*¹Dept. of Surgery, *²Multidisciplinary Treatment Center and *³Research Center for Innovative Center Therapy, Kurume University School of Medicine)

Summary

Autologous tumor cells stimulated with T lymphocytes (AuTL) were generated *ex vivo* from peripheral blood lymphocytes over a two-week co-culturing process with autologous tumor cells. These AuTLs were capable of lysing established tumor cell lines and may have a potential for efficacy as an adoptive immunotherapy (IT) in advanced and metastatic refractory cancer patients (pts). We investigated the feasibility of a combination of AuTL transfer and chemotherapy (ChT) based on the conventional conditioning regimen in order to take advantage by both the anticancer effects and reconstruction of antitumor immunity. Nineteen patients were enrolled in a pilot clinical trial. The two administrations of AuTL were given prior to chemotherapy (ChT) for one treatment cycle. The treatment was repeated at least for three cycles over a one-week interval. The conventional ChT regimen was based on the standard dosage. The pts consisted of 3 of gastric cancer, colon cancer, lung adenocarcinoma, respectively, 6 of esophageal cancer, and 2 of breast and pancreas carcinoma, respectively. AuTLs were administered 1×/2weeks using direct injection or intraarterial infusion. The median duration of the treatment was over 11.5 months, and the median survival time was 14.8 months. Adverse events related to both the ChT and AuTL transfers at all dosages were minimal. Four of the 13 pts achieved major tumor responses (2 CR: complete regression and 2 PR: partial regression) in this study. Three pts showed progressive disease, and 6 pts had stable disease for over 90 days. PBMC were evaluated for cytokine production prior to the treatment and after 3 treatments.

Two and one of 4 CR/PR pts had increased IFN- γ and TNF- α production with no TGF- β 1 responses by their PBMC after 3 treatments, respectively. Two out of 6 pts who experienced stable disease after the treatment had high IFN- γ and TNF- α responses and no TGF- β 1 or IL-4 response. TGF- β 1 and IL-4 secretion increased in parallel in 3 out of 3 pts that experienced progressive disease after the treatment. These data show that combination therapy of AuTL transfer and non-myeloablative ChT is a feasible option for patients with refractory advanced cancers without serious adverse events and without reducing Th1 cytokine responses in peripheral blood for most of the pts that responded to the treatment. According to each mechanism of IT and ChT, a more stringent evaluation of AuTL transfer combined with non-myeloablative ChT for various kinds of cancers should be performed to manage the immunodeficiency in the pts with advanced cancer and to improve the effect of antitumor AuTLs. **Key words:** Cancer immunotherapy, Adoptive cell transfer, Non-myelosuppressive chemotherapy

要旨 高度進行再発癌に対するペプチドワクチンや自己活性化リンパ球による腫瘍免疫療法の臨床試験から担癌生体においては免疫惹起反応が認められ、若干の臨床有効性もみられたが、新しい癌集学的治療として確立するためには腫瘍免疫拒絶反応を強力で持続的に発揮させることが重要である。われわれは抗癌剤および腫瘍細胞免疫療法の異なる機序を利用した非骨髄抑制性で治療耐性を生じにくい癌集学的治療を開発するため、進行癌に対して癌細胞免疫療法を先行し抗癌剤を反復併用する治療を試験的に行った。本法の副作用発生は従来の標準的化学療法よりも低く、長期的治療が可能であった。有効例の一部では治療後血清中IFN- γ とTNF- α が増加し、無効例ではTGF- β 1とIL-4が同時に増加傾向にあった。本臨床試験の結果により免疫細胞療法と化学療法との相互的な補助効果が示唆された。

*² 久留米大学医学部・集学治療センター

*³ 同 先端癌治療研究センター分子・外科

はじめに

これまでわれわれは第 I/II 相臨床試験に続き、手術不能高度進行癌症例や化学放射線療法が無効な難治性癌に対し、自己活性化混合免疫細胞 (LAK, NK, CTL) による免疫細胞療法の第 II 相試験を 46 例 (評価可能例 31 例) に対し施行した。その臨床治療成績は CR 0 例; PR 3 例 (9.7%); SD 8 例 (35.5%); PD 20 例 (54.8%) であった。この結果から難治性進行再発癌症例に対して免疫細胞療法の単独効果が限定的であることが示唆された。その原因の一つはリンパ球細胞の腫瘍への集積数や寿命とその機能に問題があるといわれている。われわれの研究でも治療後長期間にわたって T 細胞クローンは確認できる症例が非常に少なかった。これは大量の活性化リンパ球を繰り返し癌患者体内に投与しても移入したリンパ球は生体内で長期増殖し、生存できないことが考えられる。つまり高度進行癌患者では、制御性 T 細胞 (regulatory T cell) やサイトカイン (TGF-β など) などによって強い免疫抑制が働き、腫瘍に対する免疫寛容が成立している状態にあると説明される。最近、米国 NCI の Rosenberg ら²⁾ は、骨髄破壊のない (non-myeloablative) 抗癌剤投与後の免疫細胞療法は良好な臨床成績が得られ、その動向が注目されている。われわれは化学療法および癌細胞免疫療法の異なる機序を利用した非骨髄抑制性で、治療耐性を生じにくい癌集学的治療の開発をめざすため、難治性進行癌に対して自己活性化リンパ球による局所的免疫細胞療法を先行した後、抗癌剤投与による化学療法あるいは放射線療法を行い、その反復治療を実施した。本法の臨床成績および副作用発生頻度を解析し、新たな癌集学的治療として非骨髄抑制性抗癌剤併用免疫細胞療法 (non-myelosuppressive chemo-immunocellular therapy) の可能性について検討した。

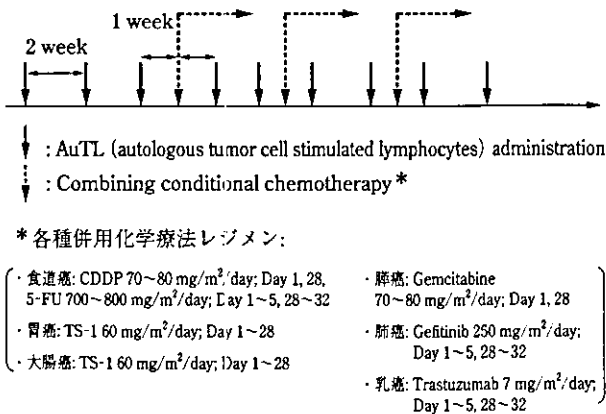


図 1 腫瘍細胞免疫療法の治療計画と各種併用化学療法の内容

I. 方法と症例

これまで報告してきた方法により患者末梢血リンパ球を用いて、自己癌細胞との 2 週間リンパ球腫瘍混合培養 (MLTC) により自己活性化リンパ球を誘導し、生体内投与を行った^{3,4)}。免疫細胞療法は癌局所か経静脈的に 2 週間隔 3 回投与で 1 クールを施行後に、標準的化学療法あるいは放射線療法を平行に施行した (図 1)。対象総症例数は 19 例 (食道 6; 胃 3; 大腸 3; 膵 2; 乳癌 2; 肺 3) であった。患者末梢血中活性化リンパ球の性状や細胞傷害性を flow cytometry や ⁵¹Cr release assay などにて評価し、臨床効果および副作用は JCOG-CTC 基準にて判定した。治療前と治療 3 回目後の患者血清中のサイトカイン産生は ELISA 法で解析した。

II. 培養結果

2 週間混合培養により誘導リンパ球の各分画 (%) は LAK, CTL precursor (CD3⁺CD8⁺): 41.4±28.9, CD3⁺CD4⁺ T 細胞: 65.8±19.3; NK (CD56⁺CD16⁺): 16.6±15.5, DC (CD86⁺CD83⁺): 36.4±24.3 であった。

III. 治療成績および有害事象

本臨床試験において全部で 19 例に (前治療化学療法を受けた症例 13 例) に対して治療を行った。平均治療期間は 11.5 か月であり、そのうち著効例は 8 症例 (CR 2; PR 6); 不変例 (SD) は 7 例; 無効例 (PD) は 4 例であった (表 1)。Kaplan-Meier 法による累積生存率では中間生存期間 (MST) が 14.8 か月で前治療無効例に対する免疫細胞療法群 (phase II) に比べ、有意に延長した (図 2)。治療期間中に発生した有害事象は発熱 (37~38°C 台) 15 例 (81%); 倦怠感 12 例 (63%); 消化器症状 4~5 例 (19~25%); 白血球減少 3 例 (16%); 関節痛 2 例 (8%) であった。そのなかで 9 症例が 1 年以上休薬せずに治療継続し、grade 3 以上の骨髄抑制例による治療中断例は 3 例で、いずれも自力または投薬 (G-CSF など) により 2~3 週間内に回復し治療が継続可能であった。消化器などの有害反応による治療中止例は認めなかった。

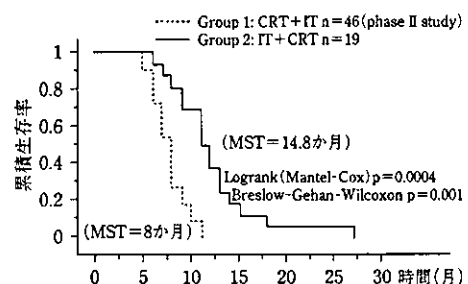


図 2 累積生存率曲線 (Kaplan-Meier 法)

表 1 非骨髄抑制性抗癌剤併用免疫細胞療法の症例とその臨床効果

	総症例数 (前治療 (+) 例)	有効例 (CR/PR)	不変例<SD>	無効例<PD>	平均細胞免疫 療法期間(月)
高度進行・再発食道癌・下咽頭	6(4)	0/4	0	2	13.8~
高度進行・再発肺癌	3(3)	1/1	1	0	12.4~
高度進行・再発胃癌	3(1)	1/1	1	0	12~
高度進行・再発大腸癌	3(3)	0	2	1	13.6~
再発乳癌	2(2)	0	2	0	9.9
高度進行膀胱癌	2(0)	0	1	1	7~
合計	19(13)	8	7	4	11.5~
		42.1%	36.8%	21.1%	
		78.9%			

表 2 治療後患者血清中各種サイトカインの産生量

Cases	Origin of cancer	Gender	Clinical state of cancer	Clinical response	Surum cytokine production							
					IFN- γ (IU/ml)		TNF- α (pg/ml)		TGF- β (ng/ml)		IL-4 (pg/ml)	
					Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-
1	Esophagus	M	Ad. ca. (stage IV)	SD	—	—	—	—	—	—	9.6	20
2		M	Liver metastases	PR	<0.1	5.4	—	—	—	—	—	—
3		M	Liver metastases	PR	—	—	<5	10	—	—	—	—
4		M	Lymph node bone metastases	PD	—	—	—	—	35.3	65.1	3.5	13.1
5	Stomach	M	Liver metastases	CR	0.1	9.7	—	—	—	—	—	—
6		M	Ad. ca. (stage IV)	SD*	—	—	—	—	—	—	—	—
7		M	Lung and lymph node metastases	PD	—	—	—	—	36.4	49.3	51.8	757
8		M	Ad. ca. (stage IV)	SD	<0.1	3	<5	12	—	—	—	—
9	Lung	F	Ad. ca. (stage IV)	SD*	0.1	12.9	—	—	28.2	13.3	103	69.2
10		M	Ad. ca. (stage IV)	CR	—	—	—	—	—	—	—	—
11	Colon	M	Liver metastases	PD	—	—	—	—	34.2	55.2	12.3	37
12	& Rectum	F	Liver metastases	SD*	—	—	—	—	—	—	—	—
13		F	Liver metastases	SD	—	—	—	—	—	—	—	—

Pre-: Pretreatment, Post-: Posttreatment, —: no significant difference

*: pts. had a significant decreasing in serum proteins of the clinical tumor marker

IV. 治療後患者血清中サイトカインの産生量

抗癌剤併用免疫細胞療法の反復投与による治療後の血清中サイトカイン産生量と本治療法との相関性有無を調べるため、治療前および免疫細胞療法6回目、化学療法3回目終了後の計13例癌患者血清中を用いて、IFN- γ 、TNF- α 、TGF- β 1とIL-4の産生量を測定した。著効例中2例でIFN- γ 、1例でTNF- α が増加した。TGF- β 1、IL-4は著変がなかった。SDの6症例中2例ではIFN- γ 、1例ではTNF- α が増加し、1例ではTGF- β 1、IL-4の同時減少を認めた。PDの4例中3例ではTGF- β 1とIL-4同時に分泌増加であった(表2)。

V. 考 察

抗癌剤併用免疫細胞療法では骨髄抑制など発生率が低く、長期的治療が可能であった。有効例中では患者血清中IFN- γ とTNF- α が分泌増加し、無効例ではTGF- β 1とIL-4分泌が同時に増加傾向がみられた。難治性癌

患者に対し特異的免疫細胞療法と化学療法との相互補助効果が得られ、治療成績向上に寄与することが示唆されたが新しい癌の集学的治療法として確立するため、各癌腫別の臨床試験が必要と思われる。

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Salvage esophagectomy after definitive chemotherapy and radiotherapy for advanced esophageal cancer

Tsutomu Nakamura, M.D.^{a,*}, Kazuhiko Hayashi, M.D.^a, Masaho Ota, M.D.^a,
Reiki Eguchi, M.D.^a, Hiroko Ide, M.D.^a, Ken Takasaki, M.D.^a, Norio Mitsuhashi, M.D.^b

^aDepartment of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, Japan

^bDepartment of Radiology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, Japan

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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. © 2004 Excerpta Medica, Inc. All rights reserved.

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 re-

gional 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

* Corresponding author. Tel.: +81-3-3353-8111; fax: +81-3-5269-7507.

E-mail address: tsutomu@ige.twmu.ac.jp

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 (P_{aO_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	0.9549
Middle	17	17	
Lower	6	6	
Clinical stage			
T3N1M0	8	7	0.5623
T3N1M1	4	2	
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,