Long-Term Toxicity After Definitive Chemoradiotherapy for Squamous Cell Carcinoma of the Thoracic Esophagus

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Purpose: To assess the long-term toxicity after definitive chemoradiotherapy (CRT) for squamous cell carcinoma (SCC) of the esophagus.

Patients and Methods: Patients newly diagnosed with SCC of the esophagus and treated with definitive CRT between 1992 and 1999 in our institution were recruited from our database on the basis of the following criteria: age ≤ 75 years, performance status (PS; based on the Eastern Cooperative Oncology Group scale) 0 to 2, and clinical tumor-node-metastasis system stage I to IVA. The CRT consisted of two cycles of cisplatin 40 mg/m^2 on days 1 and 8, and continuous infusion of fluorouracil 400 mg/m^2/d on days 1 to 5 and 8 to 12, repeated every 5 weeks with concurrent radiotherapy of 60 Gy in 30 fractions. For the assessment of toxicity, the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme was adopted.

Results: A total of 139 patients were recruited, and their characteristics were as follows: median age, 62 years (range, 38 to 75 years); 121 males and 18 females; 96 patients PS 0, 42 patients PS 1, and one patient PS 2; 15 patients T1, 11 patients T2, 60 patients T3, and 53 patients T4; and 101 patients M0, 38 patients M1a. With a median follow-up of 53 months, the median survival time and 5-year survival rate were 21 months and 29%, respectively. Of 78 patients with complete remission, two patients died as a result of acute myocardial infarction. Grade 2, 3, and 4 late toxicities occurred with the following incidences: pericarditis in eight patients, seven patients, and one patient, respectively; heart failure in zero, zero, and two patients; pleural effusion in seven, eight, and zero patients; and radiation pneumonitis in one patient, three patients, and zero patients, respectively.

Conclusion: Definitive CRT for SCC of the esophagus is effective with substantial toxicities. Additional investigation to minimize the normal tissue toxicities is warranted.

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CARCINOMA OF the esophagus has been a challenging disease. In contrast to Western countries, where the number of patients with adenocarcinoma has been increasing, most patients in Japan still have squamous cell carcinoma (SCC), and the mortality rate for Japanese patients with esophageal cancer was 8.0 per 100,000 (13.8 per 100,000 males, 2.4 per 100,000 females), representing 3.4% (4.8% males, 1.3% females) of all deaths by malignant neoplasms in 1999.[1] In recent years, the number of patients with stage I disease has been increasing, although most patients are still diagnosed with advanced disease and have a dismal prognosis. The standard therapy in Japan for patients with resectable disease has been surgery. According to the comprehensive registry of esophageal cancer in Japan,[2] 10,455 of 12,794 registered patients (81.7%) underwent surgery during 1988 and 1994. The 5-year survival rates for T1, T2, and T3 diseases were 44.8% to 51.8%, 37.3%, and 28.1%, respectively. Radiotherapy alone had been indicated in unresectable or medically inoperable patients as a definitive or palliative treatment, with a 5-year survival benefit of 8.3% to 12%.[3-5]

During the last decade, chemoradiotherapy (CRT) for esophageal cancer has revealed promising results.[6,7] After the report of a intergroup randomized controlled trial (Radiation Therapy Oncology Group 85–01), which compared CRT with radiotherapy alone, the combined-modality treatment became a standard for patients who received nonsurgical treatment for esophageal cancer.[8,9]

Esophageal cancer deaths often occur before the general time period when one would expect to detect the manifestation of treatment-related late toxicity. However, recent data indicate that the risk of early death from esophageal cancer is not quite as daunting for patients who achieve complete response (CR) after CRT. Therefore, a significant proportion of CR patients may have a sufficiently long survival time to allow for adequate assessment of treatment-related late toxicity. We have already reported a phase II study of cisplatin (CDDP) and fluorouracil (FU) with concurrent radiotherapy for patients with unresectable, T4, M1 lymph node (according to the International Union Against Cancer tumor-node-metastasis system, 1987) esophageal cancer, which resulted in promising survival rates.[10,11] During and after the study, this regimen was adopted as a clinical practice for patients with the same stage and with potentially resectable stages but who refused surgery.

We report on the long-term toxicity after definitive CRT for SCC of the thoracic esophagus.

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PATIENTS AND METHODS

Patient Population

Patients newly diagnosed with SCC of the thoracic esophagus and treated with definitive CRT between August 1992 and April 1999 in our institution were recruited from our database on the basis of the following criteria: age ≤ 75 years, performance status (Eastern Cooperative Oncology Group) 0 to 2, clinical stage I to IVA (International Union Against Cancer tumor-node-metastasis system, 1997), adequate organ functions, and no other site of carcinoma except for early stage. Informed consent was obtained from all patients. Of the patients in the previous study,[11] those who were treated in our institution and met the recruitment criteria were also included in this analysis.

Pretreatment Evaluation

Pretreatment evaluation included barium swallow, endoscopy of the esophagus, and computed tomography (CT) of the neck, chest, and abdomen. Endoscopic ultrasound of the esophagus and ultrasound of the neck were optional. Bronchoscopy was performed if tracheobronchial involvement was suspected and surgical resection was under consideration. The tracheobronchial tree was judged to be involved if the tumors extended into the lumen or caused deformity of the lumen. The descending aorta was judged to be involved if the contact angle of the tumor was 90 degrees or greater on the CT scan. The T-factor in patients with less than T4 was determined by endoscopic ultrasound or endoscopy (or both). Metastatic lymph nodes were defined if they were ≥ 1 cm in their greatest diameter on any imaging technique.

Treatment Details

The treatment consisted of two cycles of CDDP 40 mg/m^2 on days 1 and 8 and continuous infusion of FU 400 mg/m^2/d on days 1 to 5 and 8 to 12, repeated every 5 weeks, with concurrent radiotherapy of 60 Gy in 30 fractions over 8 weeks, including a 2-week break. An additional two cycles of CDDP 80 mg/m^2 on day 1 and continuous infusion of FU 800 mg/m^2/d on days 1 to 5 every 4 weeks were administered for responders.

Radiation therapy was delivered with megavoltage equipment using anterior-posterior opposed fields up to 40 Gy, including the primary tumor, the metastatic lymph nodes, and the regional nodes. A booster dose of 20 Gy was given to the primary tumor and the metastatic lymph nodes for a total dose of 60 Gy, using bilateral oblique or multiple fields. The clinical target volume for the primary tumor was defined as the gross tumor volume plus 3 cm craniocaudally. The planning target volumes for the primary tumor and the metastatic lymph nodes were determined with 1- to 1.5-cm margins to compensate for setup variations and internal organ motion. Lung heterogeneity corrections were not used.

Toxicity Assessment

Acute toxicity, including complete blood cell count and serum chemistry profile, was assessed weekly during the CRT segment and every 2 weeks during the additional chemotherapy. Toxicity assessments for all patients were performed using the criteria defined by the Japan Clinical Oncology Group.[12] These criteria were based on the National Cancer Institute common toxicity criteria (version 1.0). Late toxicity assessments for CR patients were performed using Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme. Late toxicity was defined as that occurring more than 90 days after the treatment initiation.

Follow-Up Evaluation

The following evaluations were performed until disease progression every 3 months for the first year and every 6 months thereafter: physical examination, toxicity assessment, complete blood cell count, serum chemistry profile, endoscopy of the esophagus, and CT scan of the neck, chest, and abdomen. Biopsy of the primary tumor site was routinely performed at each follow-up examination. Pulmonary function testing, ECG, and cardiac ultrasound were performed when indicated.

Response Assessment

CR for the primary tumor was defined by endoscopy when all visible tumors, including ulcerations, disappeared with negative biopsy and lasted for ≥ 4 weeks.

Responses of the metastatic lymph nodes were assessed using the World Health Organization response criteria for measurable diseases. In brief, CR was defined as the complete disappearance of all measurable and assessable disease for ≥ 4 weeks. Uncertain CR was defined as the persistence of small nodes (≤ 1 cm) with no evidence of progression for ≥ 3 months after completion of treatment, and patients with uncertain CR were included in the analysis of those with CR.

Pattern of Treatment Failure

Patterns of treatment failure were defined as the first site of failure. Locoregional failure included the primary tumor and regional lymph nodes. Distant failure included any site beyond the primary tumor and regional lymph nodes.

Statistics

Survival analysis was performed using the Kaplan-Meier method,[13] and differences between the curves were analyzed using the log-rank test.[14] The time to event was calculated from the start of the treatment.

RESULTS

Patient Characteristics

There were 217 patients who received definitive or palliative CRT during the period: 139 patients matched the recruitment criteria, and 78 patients were excluded from the analysis. The reasons for exclusion were stage IVB (16 patients), double cancer (16 patients), recurrence after surgery (13 patients), inadequate organ function (seven patients), age more than 75 years (five patients), fistula (five patients), prior endoscopic mucosal resection (three patients), poor performance status (three patients), small-cell carcinoma (three patients), prior chemotherapy (three patients), comorbidity (two patients), and carcinoma of the cervical esophagus (two patients). The characteristics of the remaining 139 patients are listed in Table 1. The median age was 62 years (range, 38 to 75 years). One hundred thirty-three patients (96%) completed at least the CRT segment with a total radiation dose of 60 Gy. Sixty-six patients (47%) received two or more additional cycles of chemotherapy.

Response

Of 139 patients, 78 achieved CR (56%; 95% confidence interval [CI], 47% to 65%). Patients with T4 disease showed CR of 36% (95% CI, 23% to 50%), which was worse than 69% (95% CI, 58% to 78%) in patients with non-T4 disease.

Survival and Pattern of Treatment Failure

With a median follow-up period of 53 months (range, 14 to 86 months) for surviving patients, the median survival time of the 139 patients was 21 months. Three- and 5-year overall survival rates were 38% and 29%, respectively. In a subgroup analysis, 3- and 5-year overall survival rates for patients with potentially resectable T1-3 M0 disease, and patients with unresectable T4 or

Table 1. Patient Characteristics

Characteristic	No. of Patients (N = 139)
Male	121
Female	18
Age, years	
Range	38-75
Median	62
PS	
0	96
1	42
2	1
Tumor length, cm	
Range	1-20
Median	5
Weight loss, kg	
Range	0-15
Median	2
Site	
Upper thoracic portion	23
Mid-thoracic portion	81
Lower thoracic portioni	35
Tumor*	
1	15
2	11
3	60
4	53
Node*	
0	55
1	84
Metastasis*	
0	101
1a	38
Stage	
I	13
IIA	22
IIB	8
III	58
IVA	38
Involved sites in T4	
Aorta only	22
Bronchial tree only	21
Aorta and bronchial tree	8
Others	2

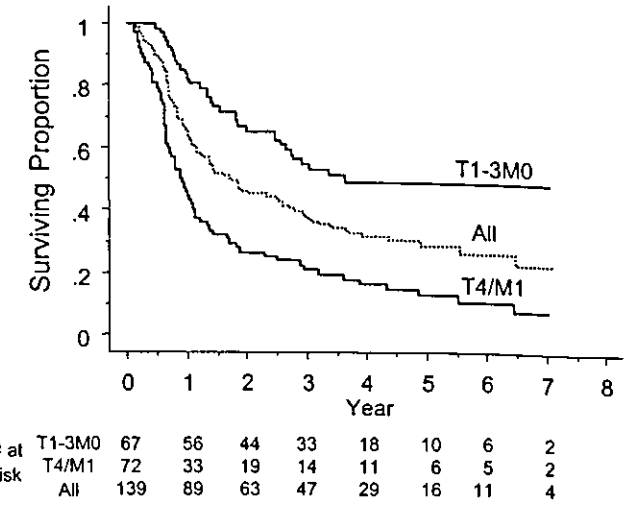
Abbreviation: PS, performance status.

*Numbers correspond to the tumor-node-metastasis system of classification.

M1 lymph node disease (or both T4 and M1 lymph disease) were 44 months, 55%, and 49%; and 11 months, 22%, and 13%, respectively (Fig 1). There was significant difference in survival benefit between the two groups ($P < .0001$). For 78 CR patients, 3- and 5-year survivals were 63% and 51%, whereas 3- and 5-year survivals were 6% and 2% for 61 non-CR patients (Fig 2), respectively. The patterns of first treatment failure were local only (15 patients), local and distant (two patients), and distant only (13 patients). Thirteen patients died without progression, and 35 patients are still alive with no evidence of disease.

Acute Toxicity

The worst toxicities throughout the treatment period are listed in Table 2. Major treatment toxicities included myelosuppression and esophagitis. Grade ≥ 3 toxicities of leukopenia, anemia, thrombocytopenia, and esophagitis occurred in 43%, 23%, 18%, and 10% of patients, respectively. There were three (2%) treatment-related deaths, including sepsis in one patient, pneumonitis in one patient, and renal failure in one patient. All of the three patients had unresectable disease at baseline, and no treatment-related deaths occurred in the 67 patients with potentially resectable disease.



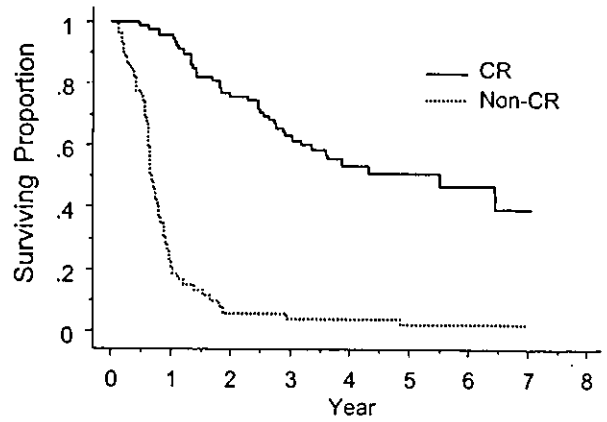
# at risk									
	T1-3M0	67	56	44	33	18	10	6	2
	T4/M1	72	33	19	14	11	6	5	2
	All	139	89	63	47	29	16	11	4

Fig 1. Overall survival data for all patients; T1-3 M0 patients; and T4 and/or M1 lymph node patients.

Late Toxicity

Four patients suffered benign esophageal strictures and required esophageal dilatation one to three times.

Grade ≥ 2 late cardiopulmonary toxicities are summarized in Table 3. Two patients died as a result of acute myocardial infarction at 30 and 40 months, respectively, after the initiation of treatment. The median time to the onset of pericarditis from the initiation of treatment was 17 months (range, 3 to 42 months) for grade ≥ 2 pericarditis and 15 months (range, 10 to 36



# at risk									
	CR	78	75	60	45	27	15	10	3
	Non-CR	61	14	3	2	2	1	1	1

Fig 2. Overall survival data for patients who achieved complete remission (CR) and patients who did not achieve complete remission.

Table 2. Acute Toxicities (N = 139)*

	Grade					≥Grade 3	
	1	2	3	4	5	No. of Patients	%
Leukopenia	10	62	54	5	1	60	43
Anemia	23	63	32	0	0	32	23
Thrombocytopenia	30	19	20	5	0	25	18
Nausea or vomiting	65	34	3	0	0	3	2
Diarrhea	13	4	0	0	0	0	0
Mucositis	12	15	4	1	0	5	4
Esophagitis	46	32	7	7	0	14	10
Renal dysfunction	9	1	3	0	1	4	3
Pneumonitis	0	0	2	3	1	6	4

*Japan Clinical Oncology Group toxicity criteria.

months) for grade ≥ 3 pericarditis. Of eight patients with grade ≥ 3 pericarditis, one patient suffered grade 4 heart failure, required pericardial window placement 23 months after the initiation of treatment, and died as a result of heart failure without cancer recurrence 15 months later. Another patient also suffered grade 4 heart failure at 35 months and died without cancer recurrence. The other six patients required pericardiocentesis once and needed no further treatment. Of eight patients with grade 2 pericarditis, one patient died as a result of an unknown cause 1 month later, and the other seven patients with pericarditis were manageable with diuretics only for various periods (2 to 75+ months).

The median time to the onset of pleural effusion from the initiation of treatment was 19 months (range, 3 to 42 months) for grade ≥ 2 pleural effusion and 18 months (range, 5 to 39 months) for grade 3 pleural effusion. Of eight patients who required pleurocentesis, two patients suffered grade 3 pericarditis, and two patients suffered grade 3 radiation pneumonitis simultaneously. One patient without cancer recurrence died as a result of pneumonia 4 months later. One patient required frequent repeated pleurocentesis and two patients required pleurocentesis three to five times. Of seven patients with grade 2 pleural effusion, one patient suffered grade 4 heart failure and five patients suffered grade 2 pericarditis simultaneously. Six

Table 3. Patients With ≥Grade 2 Late Cardiopulmonary Toxicities (RTOG/EORTC late radiation morbidity scoring scheme)

	Pericardial Effusion		Heart Failure		Myocardial Infarction		Pleural Effusion		Radiation Pneumonitis				
Case No.	Grade	Onset (months)	Grade	Onset (months)	Grade	Onset (months)	Grade	Onset (months)	Grade	Onset (months)	Outcome or Survival	Months	Cause of Death
1	4	23	4	19	—		2	19	—		Died w/o cancer	38	Chronic heart failure
2	3	36	4	35	—		3	35	—		Died w/o cancer	37	Chronic heart failure
3	3	19	—		—		3	19	—		Died w/o cancer	33	Pneumonia
4	3	10	—		—		3	39	—		Died w/o cancer	43	Pneumonia
5	3	11	—		—		—		—		Died of cancer	47	
6	3	15	—		—		—		—		Died of cancer	30	
7	3	10	—		—		—		—		Alive/NED	58	
8	3	14	—		—		—		—		Alive/NED	35	
9	2	19	—		—		3	18	—		Died of cancer	22	
10	2	14	—		—		2	14	—		Died w/o cancer	15	Sudden death
11	2	8	—		—		2	8	2	5	Died of cancer	16	
12	2	42	—		—		2	42	—		Alive/NED	64	
13	2	25	—		—		2	25	—		Alive/NED	85	
14	2	3	—		—		2	3	—		Alive/NED	78	
15	2	33	—		—		—		—		Alive/NED	56	
16	2	19	—		—		—		—		Alive/NED	55	
17	—		—		5	40	—		—		Died w/o cancer	40	Myocardial infarction
18	—		—		5	30	—		—		Died w/o cancer	30	Myocardial infarction
19	—		—		—		3	5	3	5	Died w/o cancer	24	Pneumonia
20	—		—		—		3	31	—		Alive/NED	45	
21	—		—		—		3	18	—		Alive/NED	66	
22	—		—		—		3	7	3	7	Alive/NED	45	
23	—		—		—		2	40	—		Alive/NED	44	
24	—		—		—		—		3	4	Alive/NED	55	

Abbreviations: RTOG, Radiation Therapy Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; NED, no evidence of disease; w/o, without.

pleural effusions were manageable with only diuretics for various periods (4 to 75+ months).

Four patients required corticosteroid therapy for radiation pneumonitis. The median time to symptomatic radiation pneumonitis was 5 months (range, 4 to 7 months). Three of the four patients subsequently required oxygen support and one patient died without cancer recurrence 19 months later.

In total, eight patients died without cancer recurrence, and these causes of death may have been related to cardiopulmonary toxicity.

DISCUSSION

In the last decade, the number of patients receiving definitive CRT has been increasing worldwide. However, the long-term survival and late toxicity for these patients have not been reported precisely. Although our study, including 72 patients with T4 or M1 lymph node (or both), was retrospective and may be biased, the results with 3- and 5- year survivals of 38% and 29%, respectively, were comparable with the reported trials of CRT, including RTOG 85–01 and intergroup study (INT) 0123/RTOG 94–05.[15,16] The pattern of failure in the present analysis showed that local failure was still dominant. The INT 0123 study also showed a similar pattern of failure and the tumor control probability of current CRT approaches seems to have reached a plateau. We should make further efforts to improve local control, which may affect survival. The dose-escalation strategy of radiotherapy was not proven to be effective in the INT 0123 study, and we may need newer cytotoxic drugs or molecular targeted therapy in combination with radiotherapy.

Radiation-induced heart disease is one of the complications in patients who undergo thoracic radiotherapy.[17,18] Pericardial disease is the most common manifestation of radiation-induced heart disease. There have been many reports of pericardial disease after thoracic radiotherapy in patients with Hodgkin's lymphoma.[19-21] According to recent observations, coronary artery disease after thoracic radiotherapy is not negligible and it should be considered in the radiotherapy treatment planning.[22-24] We also observed two patients with acute myocardial infarction, although we were not sure whether these were related to the treatment. There have been few reports on pericardial disease in patients with esophageal cancer, because of the dismal prognosis.[25,26] However, the number of reports will increase with the prevalence of definitive CRT and with improved survival. The incidence of grade ≥ 3 pericarditis in our study was 10% (eight of 78 patients) and seemed to be substantial. One cause of this, in addition to the concurrent use of chemotherapy, may be the wide elective nodal irradiation up to 40 Gy with anteroposterior-posteroanterior opposed portals. This means that more than 60% of the entire heart volume received at least 40 Gy in most patients. It is clear that a precise analysis using dose-volume histogram and normal tissue complication probability is necessary, and this will be reported elsewhere.

Treatment of pericardial effusion includes medication, pericardiocentesis, and pericardial window placement, which are thought to be manageable;[17,27] however, some patients died as a result of heart failure in our study, and the obvious best treatment is prevention. Three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, and proton therapy have potential advantages over traditional anteroposterior-posteroanterior treatment in reducing doses to the heart, and their incorporation may thus be beneficial.

Pleural effusion after thoracic radiotherapy also has been reported, mainly in Hodgkin's lymphoma.[28,29] The main cause of benign pleural effusion after thoracic radiotherapy is thought to be lymphatic obstruction resulting from mediastinal fibrosis and, in some cases, it may be related to heart disease, such as heart failure and pericardial effusion. The incidence of grade ≥ 2 benign pleural effusion in our study was 19% (15 of 78 patients), and we note that patients with benign pleural effusion after definitive CRT in esophageal cancer are common. The treatment of pleural effusion after thoracic radiotherapy includes medication, pleurocentesis, and pleurodesis. This treatment may not directly affect survival, but it clearly affects the quality of life as influenced by medical intervention. We should make every effort to reduce toxicity, and conformal radiotherapy techniques may also be helpful.

REFERENCES

1. Editorial Board of the Cancer Statistics in Japan (ed). Cancer statistics in Japan 2001: Foundation for promotion of cancer research. http://www.ncc.go.jp/en/statistics/2001/tables.html

2. Registration Committee for Esophageal Cancer (ed). Comprehensive registry of esophageal cancer in Japan: The Japan Society for Esophageal Diseases. http://plaza.umin.ac.jp/~jsed/

3. Okawa T, Kita M, Tanaka M, et al: Results of radiotherapy for inoperable locally advanced esophageal cancer. Int J Radiat Oncol Biol Phys 17:49-54, 1989

4. Slevin NJ, Stout R: Carcinoma of the oesophagus: A review of 108 cases treated by radical radiotherapy. Clin Radiol 40:200-203, 1989

5. Hyden EC, Langholz B, Tilden T, et al: External beam and intraluminal radiotherapy in the treatment of carcinoma of the esophagus. J Thorac Cardiovasc Surg 96:237-241, 1988

6. Coia LR: Chemoradiation as primary management of esophageal cancer. Semin Oncol 21:483-492, 1994

7. Forastier AA, Orringer MB, Perez-Tamayo C, et al: Preoperative chemoradiation followed by transhiatal esophagectomy for carcinoma of the esophagus: Final report. J Clin Oncol 11:1118-1123, 1993

8. Herskovic A, Martz K, Al-Sarraf M, et al: Combined chemotherapy and radiotherapy in patients with cancer of the esophagus. N Engl J Med 326:1593-1598, 1992

9. Al-Sarraf M, Martz K, Herskovic A, et al: Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: An intergroup study. J Clin Oncol 15:277-284, 1997

10. Ohtsu A, Yoshida S, Boku N, et al: Concurrent chemotherapy and radiation therapy for locally advanced carcinoma of the esophagus. Jpn J Clin Oncol 25:261-266, 1995

11. Ohtsu A, Boku N, Muro K, et al: Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. J Clin Oncol 17:2915-2921, 1999

12. Tobinai K, Kohno A, Shimada Y, et al: Toxicity grading criteria of the Japan Clinical Oncology Group. Jpn J Clin Oncol 23:250-257, 1993

13. Kaplan EL, Meier P: Non-parametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

14. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163-170, 1966

15. Cooper JS, Guo MD, Herskovic A, et al: Chemoradiotherapy of locally advanced esophageal cancer: Long-term follow-up of a prospective randomized trial (RTOG 85-01). JAMA 281:1623-1627, 1999

16. Minsky BD, Pajak TF, Ginsberg RJ, et al: INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: High-dose versus standard-dose radiation therapy. J Clin Oncol 20:1167-1174, 2002

17. Stewart JR, Fajardo LF, Gillette SM, et al: Radiation injury to the heart. Int J Radiat Oncol Biol Phys 31:1205-1211, 1995

18. Veinot JP, Edwards WD: Pathology of radiation-induced heart disease: A surgical and autopsy study of 27 cases. Hum Pathol 27:766-773, 1996

19. Byhardt R, Brace K, Ruckdeschel J, et al: Dose and treatment factors in radiation-related pericardial effusion associated with the mantle technique for Hodgkin's disease. Cancer 35:795-802, 1975

20. Tötterman KJ, Pesonen E, Siltanen P: Radiation-related chronic heart disease. Chest 83:875-878, 1983

21. Cosset JM, Henry-Amar M, Pellae-Cosset B, et al: Pericarditis and myocardial infarctions after Hodgkin's disease therapy. Int J Radiat Oncol Biol Phys 21:447-449, 1991

22. Boivin JF, Hutchinson GB, Lubin JH, et al: Coronary artery disease mortality in patients treated for Hodgkin's disease. Cancer 69:1241-1247, 1992

23. Corn BW, Trock BJ, Goodman RL: Irradiation-related ischemic heart disease. J Clin Oncol 8:741-750, 1990

24. Joensuu H: Acute myocardial infarction after heart irradiation in young patients with Hodgkin's disease. Chest 95:388-390, 1989

25. Cwikiel M, Albertsson M, Hambraeus G: Acute and delayed effects of radiotherapy in patients with oesophageal squamous cell carcinoma treated with chemotherapy, surgery and pre- and postoperative radiotherapy. Acta Oncol 33:49-53, 1994

26. Gergel T, Proulx G, Leichman L: Diagnostic dilemmas in oncology: Case 3—Pericardial effusion after esophageal radiation. J Clin Oncol 19:4344-4345, 2001

27. Veeragandham RS, Goldin MD: Surgical management of radiation-induced heart disease. Ann Thorac Surg 65:1014-1019, 1998

28. Rodríguez-García JL, Fraile G, Moreno MA, et al: Recurrent massive pleural effusion as a late complication of radiotherapy in Hodgkin's disease. Chest 100:1165-1166, 1991

29. Morrone N, Gama e Silva Volpe VL, Dourado AM, et al: Bilateral pleural effusion due to mediastinal fibrosis induced by radiotherapy. Chest 104:1276-1278, 1993

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Lecture

解　説

放射線治療の多施設共同研究における quality assuranceとquality control*

石　倉　　聡**

Key Words：multi-institutional clinical trial, radiation therapy, quality assurance, quality control

Quality assurance，quality controlとは

近年，多施設共同臨床試験の重要性が強調されるようになったが，それと同時にquality assurance(QA：品質保証)，quality control(QC：品質管理)の重要性が認識されるようになっている．従来，日本においてはQA, QCは主として工業，製造業の分野で使われてきたが，業種を問わずサービス業，医療の分野でも使用できる概念である．簡単に言うと，QAとは確実な仕事をして品質のよい結果が確実に得られるような品質マネージメントシステムを確立し，その情報を第三者に示して「十分な信頼感」を与えることを目的とした事後的な活動である．臨床試験においてQAの具体的活動と位置づけられるのが「監査(audit)」であり，医療機関などに対して第三者が「プロセスの評価」と「抜き取り検査」を行う．一般に，参加医療機関を訪れる施設訪問監査(site visit auditまたはquality assurance site visit)が中心であり，施設から報告されたデータと，カルテなどの原資料のデータ(原データ)との照合(source document verification；SDV)のほか，施設IRBのプロトコール承認文書および患者の同意文書の存在と日付も確認し，科学・倫理両面から品質を保証するものである．よく監査と「査察(inspection)」は混同されるが，「audit」は「examine and certify：調べて保証する」であり，「inspection」は「examine critically/officially：疑って公式に調べる」であるから両者の意味合いは異なる．何か不正行為が疑われた時に罰則を与えるかどうかを決めるために「規制当局が抜き打ちで調べに入る」のが「査察」であって，逆にルーチンで行われ，「品質にお墨付を与える」ものが「監査」である．

QAが結果の信頼性を確認するために「既になされたプロセスや製品をチェックする」という事後的な行為であるのに対して，QCは最終的に規格に合った製品(正しい結論)が得られ，その証明としてのQAに耐えるように各プロセスのエラーを低く押さえる同時・介入的な行為である．チェックの目的が「問題点の発見と改善」であって，試験の実施中にフィードバックをかける点がQAと異なる．また抜き取り検査が中心のQAよりもきめ細かいチェック(たとえば全例の全データが対象)がなされることが一般的である．QCの具体的活動がモニタリングであり，試験の実施中に，登録の進捗，データの正確性，有害事象の頻度や程度，不適格例やプロトコール逸脱などをチェックし，それらの情報を試験の管理にフィードバックしつつ試験がプロトコールどおりに(科学的倫理的に)行われるようにしむけていく一連の作業を指す．

これらQAおよびQCの両者があってはじめて多施設共同研究の質(科学性，倫理性)が保たれているといえる．

放射線治療におけるQA・QCの必要性

放射線治療は手術，化学療法とともにがん治療の3本柱の1つである．身体侵襲が少なく形

* Quality assurance and quality control in a multi-institutional clinical trial employing radiation therapy.

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態・機能温存を図れること，社会の高齢化とquality of lifeの視点などにより放射線治療を受ける患者数は年々増加している．日本放射線腫瘍学会が行った構造調査結果によると1990年から1999年の10年間で放射線治療件数は約40％の増加がみられ，とくにここ3年間の増加傾向は顕著である．

放射線治療の実施過程は複雑であり治療に先立つ計画の段階においては，放射線照射の部位，放射線照射の方法，投与する線量の決定，またモニターユニット値という放射線照射量の算出など多くの過程が存在する．モニターユニット値の算出においても多くの係数が関与し，その係数も施設の放射線治療装置に固有のものである．また放射線照射の部位の決定ひとつとってみても，病巣進展範囲の認識や手術におけるリンパ節隔清にあたる予防照射領域の設定には治療計画者の判断によりばらつきが生じるところである．そのため放射線治療の実施にあたっては，もちろん放射線照射装置の精度そのものの管理も必要であるが，その一連の過程に対するQA・QC活動が必須となる[1]．

ひとつの悪い例として，米国Southwest Oncology Group (SWOG)で過去に行われたホジキン病に対する臨床試験をあげる．この臨床試験では登録された症例のうち，36％の症例で放射線治療のプロトコール規定の逸脱が認められた．その結果，プロトコールの規定を遵守していた症例では10％であった再発率が逸脱例では44％にも及んだことが報告がされている[2]．そのほかの臨床試験においてもプロトコール規定の逸脱による治療成績の低下が報告されている[3]．臨床試験が科学的結果を出すためには，異なる施設間において治療内容を比較することが可能でなければならないが，臨床試験に限らず一般診療においても，放射線治療における技術面を含めた治療の標準化は欠かせないものである．逆に公表された臨床試験の結果が科学的に評価されて標準治療として受け入れられるためには，放射線治療も含めてプロトコールで規定した治療がどの程度のレベルで遵守されているかがカギとなる．そのため，試験終了後にQAを実施することが重要である．その一方で，試験中の組み入れられた患者に対する安全を確保する，すなわち毒性の増強や効果の低減を防止する観点から定期的にプロトコール治療が実施されているかモニターするQCも重要である．

国外におけるQA・QC活動

米国においては放射線治療のQA/QCプログラムが確立されている．歴史的には1969年にNational Cancer Institute (NCI)の補助金を受けRadiological Physics Center (RPC)が活動を始めた[4]．その役割は，多施設共同臨床試験に参加している施設の間で技術的に大きな乖離がないことと，適切なQCシステムにより施設間で比較可能な放射線治療が行われていることを，第三者的に保証することである．RPCでは主として物理的な精度管理，すなわち施設間の線量のばらつきを解消するため，郵送可能な線量計を用いたoff-site auditによるスクリーニングや施設訪問による線量測定，施設のQA/QCプログラムの確認といったon-site auditを全米に約1,800存在する放射線治療施設のうち，NCIスポンサーの臨床試験に参加する全施設を含め，約1,350の施設を対象に実施している．欧州においてもほぼ同時期から同様の活動がInternational Atomic Energy Agency (IAEA)/WHOが発展途上国を中心に115か国，約1,200施設に，European Society for Therapeutic Radiology and Oncology (ESTRO)/ European Institute for Quality Assurance in Radiotherapy (EQART)が27か国，約450施設にoff-site auditを行っている．

ここで臨床試験における放射線治療のQA/QC活動の草分け的存在であるQuality Assurance Review Center (QARC)による活動の歴史を紹介する[5]．QARCは多施設共同研究グループであるAcute Leukemia Group B (ALGB)の放射線治療委員会により1972年に設立された組織である．当時，臨床試験実施計画における放射線治療の項目は臨床腫瘍医にとって，同時に放射線腫瘍医にとっても，いわばブラックボックスであった．臨床試験実施計画書には放射線治療の詳細については記載されておらず，実際に患者がどのような放射線治療を受けたかについてほとんど知られることはなかった．また実際に行われ

表1 プロトコール違反/逸脱(n=45)

	違反	逸脱*
照射野辺縁		
GTV primary	17(38%)	22(49%)
GTV node	15(33%)	1(2%)
CTV subclinical	31(69%)	1(2%)
総線量(GTV primary)	1(2%)	0
分割法	1(2%)	0
総合判定(GTV primary/node)	27(60%)	16(36%)

*逸脱：遵守ではないが許容範囲として判定.
GTV：gross tumor volume, CTV：clinical target volume

た治療内容を評価しようにも利用できる放射線治療の情報は20%にも至らなかった．そのため，ALGBの放射線治療委員会は，放射線治療の研究プログラムの策定のみならず，臨床試験に参加しているすべての施設研究者が確立されたガイドラインに従って均一な放射線治療が行えるように放射線治療手順を明確に規定することから着手した．同時に治療の適切さを評価するため，放射線治療にかかわる資料を系統的かつ適切な時期に収集するシステムを確立した．これにより評価できる放射線治療の情報を2年間で30%未満から70%以上に上昇させ，5年間では90%以上としたが，これらの情報が集積された結果，多施設共同研究においては治療の均一性が達成されていないことが明らかになった．この事実を受けて放射線治療委員会では「プロトコール実施における問題点と落とし穴」と題した教育プログラムを定期的に実施し，その後のプロトコール規定の遵守率は3年間で40%から70%へと改善し，その後も堅調に上昇が認められた．

このような放射線治療の質の改善がきっかけとなって他の多施設共同研究グループにおいても同様のプログラムが実施されるようになり，同様の改善が示された[6][7]．その一方で，それぞれの多施設共同研究グループから，QA/QCプログラムを標準化し，同一の組織，均一な手順で実施する要求が高まり，1980年にQARCが正式に設立された．またその活動内容から，QARCは多施設研究グループからは独立してNCIから運営資金を得ている．また，欧州でもほぼ同時期より同様の活動がIAEA, European Organisation for Research and Treatment of Cancer(EORTC), ESTROなどを中心として行われており，放射線治療の臨床試験においてQA/QCを行うことはglobal standardとして必須のものと認識されている[8)~10)]．

表2 JCOGにおける放射線治療のQA/QC

JCOG放射線治療委員会

結果の報告
- 参加資格に関する指針の作成
- QA/QCガイドラインの作成
- プロトコール作成支援(検討委員の推薦)
- プロトコール審査(臨床試験審査委員会)
- 施設訪問監査(JCOG監査)
- 教育活動

放射線治療品質保証センター(RTQAC)

- 適合性検討(治療開始後早期)
- 最終検討(治療終了後)
- 治療機器の物理技術的QA/QC

放射線腫瘍医
医学物理士
事務スタッフ

国内の状況および今後の展望

一方でわが国においては，「線量計の校正」といった一部のQA/QC活動を除くと，最近まで全国規模の体系的なQA/QC活動のシステム構築がまったくなされてこなかった．そのため，わが国の放射線治療の質あるいは臨床試験の質はいまだにブラックボックスのままであり，国際的に信頼性を得ることができていないという深刻な状況にあった．日本臨床腫瘍研究グループ(Japan Clinical Oncology Group；JCOG)ではこれらの状況を踏まえて2000年に放射線治療委員会を立ち上げた．2001年には1つのランダム化比較試験において放射線治療のプロトコール規定の遵守に関する評価を行ったが，遵守率は40%にとどまっており(表1)，わが国においても積極的にQA/QCプログラムを導入することが必要であることが認識された[11)]．2002年には放射線治療委員会の下にJCOG放射線治療品質保証センターを立ち上げ(表2)，最近の臨床試験においてはプロトコール作成の段階から放射線治療規定の明確化をはかるとともに，臨床試験が開始されてからは登録症例における放射線治療の開始後早期に治療内容の評価を行い(図1)，その評価の結果を各施設にフィードバックを行うQCプログラムを導入している[12)]．これによりQARCの経験同様，今後短期間のうちにプロトコール規定の遵守率

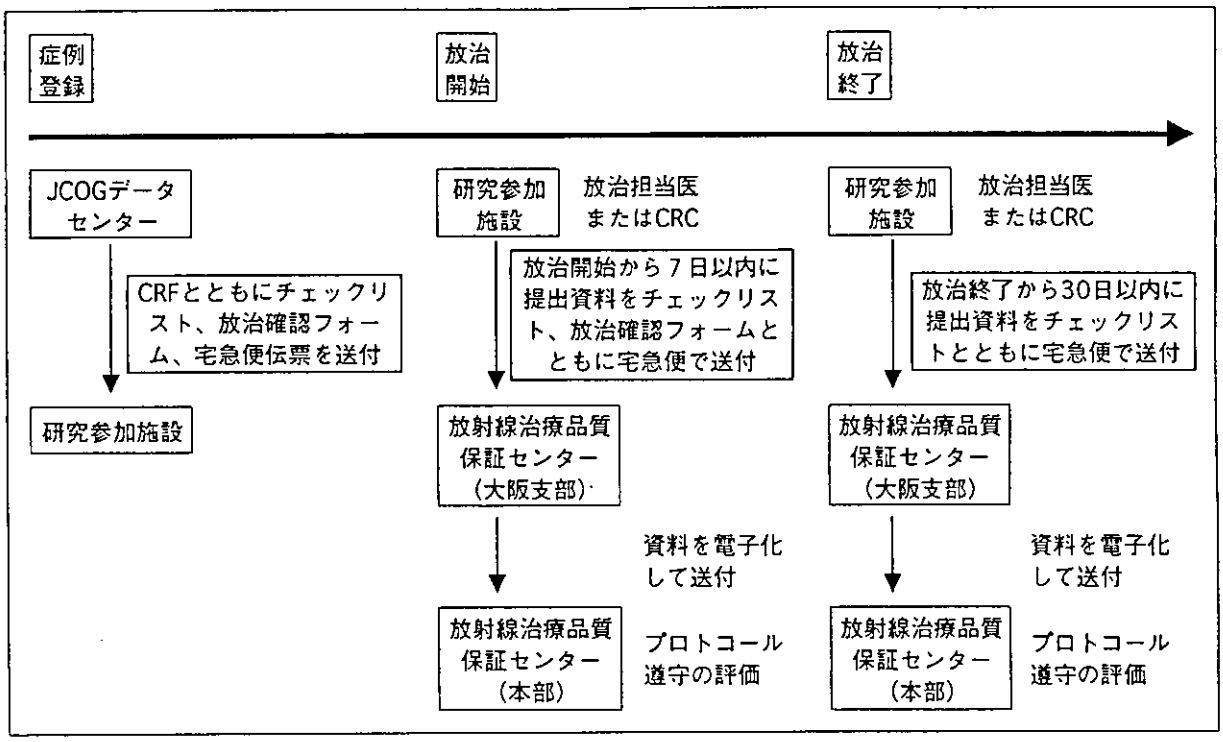

図1 JCOGにおける放射線治療，QCプログラム

が改善することが期待される．また，現在米国NCIと欧州EORTCとの間でQA/QCプログラムの標準化に関する検討がなされており，JCOGにおいても標準化プログラムの策定に向けてNCIと情報交換を行っている．

一方で，米国RPCに代表される物理的QC/QAについては厚生労働科学研究費補助金，効果的医療技術の確立推進臨床研究事業による「放射線治療の技術評価及び品質管理による予後改善のための研究」班ではRPCやIAEAの手法に準じてガラス素子線量計を用いた郵送法によるoff-site auditおよび施設訪問によるon-site auditを開始している．現時点では研究班を基盤とした活動であるためマンパワーに限りがあり，おのずと対象施設数は限られているが，その中でも各施設間で放射線照射線量のばらつきが許容範囲を超えて存在することが判明している．近い将来，物理的QA/QCに関する公的機関を設け全国規模で活動を行うことが緊急の課題である．また，物理的QA/QCも欧米においては標準化が図られており，この研究班ではRPC, IAEA, EQARTとも定期的に人的交流と情報交換を行い，標準化に対応すべく準備が進められている．

まとめ

最近ではinformation technologyの発達により放射線治療技術は急速に進歩しているが，一方でその過程は従来の何倍にも複雑となっている．体系的なQA/QCプログラムを欠いては新技術の導入は危険であるのみでなく，新技術の発展，普及を阻害することにもなる．わが国のがん治療の未来のためにも，一日も早く体系的なQA/QCプログラムが実施され，多施設共同研究に限らず一般診療においても放射線治療が安全かつ有効にその役割を果たせる日がくることを願って稿を終える．

文献

1) 加藤洋一．ISO9000による品質保証の基本的な考え方．臨床評価 2000；28：33.
2) Fabian CJ, Mansfield CM, Dahlberg S, et al. Low-dose involved field radiation after chemotherapy in advanced Hodgkin disease. A Southwest Oncology Group Randomized Study. Ann Intern Med 1994；120：903.
3) White JE, Chen T, McCracken J, et al. The influence of radiation therapy quality control on survival,

response and sites of relapse in oat cell carcinoma of the lung : preliminary report of a Southwest Oncology Group study. Cancer 1982 ; 50 : 1084.
4) http://rpc.mdanderson.org/rpc/
5) http://www.qarc.org/
6) Wallner PE, Lustig RA, Pajak TF, et al. Impact of initial quality control review on study outcome in lung and head/neck cancer studies-review of the Radiation Therapy Oncology Group experience. Int J Radiat Oncol Biol Phys 1989 ; 17 : 893.
7) Schaake-Koning C, Kirkpatrick A, Kroger R, et al. The need for immediate monitoring of treatment parameters and uniform assessment of patient data in clinical trials. A quality control study of the EORTC Radiotherapy and Lung Cancer Cooperative Groups. Eur J Cancer 1991 ; 27 : 615.
8) http://www.iaea.or.at/
9) http://www.eortc.be/
10) http://www.estro.be/estro/Frames/QA.html
11) Ishikura S, Teshima T, Ikeda H, et al. Initial experience of quality assurance in radiotherapy within the Japan Clinical Oncology Group (JCOG) [abstract]. Radiother Oncol 2002 ; 64 : S224.
12) http://www.jcog.jp/SHIRYOU/29_policy.pdf

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特集：最新 進行食道癌の治療

3. 進行食道癌に対する化学療法

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南　江　堂

3. 進行食道癌に対する化学療法*

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〔要旨〕食道癌に対する化学療法単独治療は遠隔転移を有する(M1)切除不能進行食道癌あるいは術後再発食道癌が対象で，現在はCDDP＋5-FUが標準治療となっている．2nd lineとして，paclitaxelやnedaplatinを加えた多剤併用療法が検討されている．手術補助療法としての化学療法は，欧米では術前に，本邦では術後に行うケースが多い．欧米での大規模なRCTの結果には相反するものがあり，術前化学療法の有効性はcontroversialである．本邦において，RCTで術後補助化学療法による再発予防効果が証明された．

はじめに

食道癌は他の消化器癌と比較して化学療法に対する感受性がよく，化学療法は食道癌の治療に積極的に応用されている．食道癌治療における化学療法の位置付けは，①化学放射線療法，②化学療法単独治療，③術前・術後の補助療法があげられる[1]．①の化学放射線療法に関しては他稿に委ね，本稿は②，③について解説する．

I. 食道癌に対する化学療法単独治療

遠隔転移を有する(M1)切除不能進行食道癌あるいは術後再発食道癌に対し適応がある．

キーワード：食道癌，化学療法，術前化学療法，術後補助化学療法

* Chemotherapy for advanced esophageal cancer

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1. 単剤での治療効果

食道癌に対して単剤で20%以上の奏効率が確認された薬剤は，5-fluorouracil(5-FU)，mitomycin C(MMC)，cisplatin(CDDP)，bleomycin(BLM)，methotrexate(MTX)，vindesine(VDS)，adriamycin(ADR)，nedaplatin(NDP)，paclitaxel(TXL)，vinorelbine(VNB)などである[2,3]．

MMCは蓄積性の骨髄毒性のためBLMは肺毒性のため使用されなくなってきている．CDDPは固形癌に対する効果が広く確認されており，食道扁平上皮癌に対する奏効率は約24%であった．骨髄抑制が少なく他剤との併用も容易であることから，後述する食道癌に対する多剤併用療法のkey drugになっている[3]．近年TXL，docetaxel，VNB，NDPが新薬として注目されている．TXL単独の第II相試験で，食道腺癌に34%，食道扁平上皮癌に28%の奏効率が報告[4]され，VNBでは20%の奏効率が報告[5]された．NDPは本邦で

表1. 食道癌に対する多剤併用化学療法

報告者(年)	薬剤	組織型	症例数	奏効率(%)
Kelsen ら (1983)	CDDP + BLM + VDS	S	26	33
Dinwoodie ら (1986)	CDDP + BLM + VDS	S	27	29
Kies ら (1987)	CDDP + 5-FU	S	26	42
Iizuka ら (1991)	CDDP + VDS	S	31	16.1
Iizuka ら (1992)[9]	CDDP + 5-FU	S	39	35.9
Bleiberg ら (1997)	CDDP + 5-FU	S	44	35
Kelsen ら (1997)[13]	CDDP + TXL	A & S	37	49
Ilson ら (1998)[14]	CDDP + 5-FU + TXL	A & S	60	48
Ilson ら (1999)[15]	CDDP + CPT-11	A & S	35	57
Muro ら (2003)[17]	CDDP + 5-FU	S	42	39.5
Livingston (2003)	CPT-11 + MMC	A & S	25	48
Scullin ら (2004)[16]	CDDP + GEM	A & S	42	45

開発されたプラチナ誘導体であり食道癌に対し52%と高い奏効率の報告がある[6]．さらに欧米ではirinotecan(CPT-11)，gemcitabine，gefitinib[7]の臨床試験も展開中であり[3]今後が期待されている．

しかし，単剤ではCR例はきわめてまれで治療には限界があることより，これらの薬剤を組み合せた多剤併用療法が化学療法の主流となっている．

2. 多剤併用療法

1980年代のCDDPの登場以来，CDDPを中心とした多くの多剤併用療法のレジメンが報告されてきた(表1)が，現在ではchemical modulationの理論に基づくCDDP＋5-FU療法が標準治療となっている．その奏効率は局所進行食道癌で50%，遠隔転移例で35%と報告されており[8]，日本臨床腫瘍研究グループ(JCOG)食道がんグループ(JEOG)の第II相試験でも奏効率36%の結果であった[9]．投与量は，本邦ではCDDP 80 mg/m² 1日，5-FU 800 mg/m² 1～5日持続が一般的で21～28日ごとに投与される．奏効率の向上と副作用の軽減を目的としてCDDPの少量分割投与(20 mg/m²/日)が試みられたが，その有効性は証明されなかった[10]．頭頸部領域癌に対するCDDP＋5-FU＋leucovorinの高い奏効率の報告[11]をもとに，食道癌に対してもJEOGで第II相試験が行われ，奏効率41.7%でCRが36例中2例に認められた[12]．

3. 期待される多剤併用療法

CDDP＋5-FU療法後の無効・再燃例に対して2nd lineのレジメンの開発が望まれる．欧米ではTXL単剤での比較的良好な奏効率をもとにTXL＋CDDP[13]，TXL＋CDDP＋5-FU[14]の第II相試験が展開され，それぞれ49%と48%の良好な奏効率が報告されている．その他ではCPT-11＋CDDPの第II相試験での奏効率57%[15]やgemcitabine＋CDDPの第II相試験での奏効率45%[16]などが報告されている．本邦においてはNDP＋5-FUの第II相試験が行われ奏効率は39.5%であった[17](表1)．

II. 手術補助療法としての化学療法

頸胸腹3領域郭清を含む外科手術のみではこれ以上の遠隔成績の改善が見込めない現状では，進行食道癌に対して有効な手術補助療法の開発が必要である．補助療法としての化学療法の施行時期は，術前あるいは術後が考えられるが，現時点ではどちらが効果的であるか証明されていない．欧米では術前補助化学療法を行うケースが多く，本邦では術後に行うケースが多かった．術前補助化学療法の有利な点は，down stagingの可能性があること，切除検体の組織学的検索により*in*

表2. 食道癌に対する術後補助化学療法のRCT

報告者(グループ名)〔年〕	レジメン	症例数	MST(月)	5年生存率(%)
Iizuka ら(JEOG) 〔1993〕[18]	CDDP + VDS × 2 vs RT 50 Gy	130 vs 128	—	42 vs 44
Ando ら(JEOG) 〔1997〕[19]	CDDP + VDS × 2 vs 手術単独	105 vs 100	—	48.1 vs 44.9
Ando ら(JEOG) 〔2003〕[20]	CDDP + 5-FU × 2 vs 手術単独	120 vs 122	—	61 vs 52 *(55 vs 45)
Pouliquen ら(FASR) 〔1996〕[21]	CDDP + 5-FU × 6 ～ 8 vs 手術単独	52 vs 68	13 vs 14	—

*: (5 years disease free survival)

表3. 食道癌に対する術前補助化学療法のRCT

報告者(年)	レジメン	症例数	MST(月)	生存率(%)
Roth ら (1988)[22]	CDDP + BLM + VDS × 2 vs 手術単独	19 vs 20	9 vs 9	25 vs 5(3年)
Kelsen ら (1990)	CDDP + BLM + VDS × 3 vs RT 55 Gy	48 vs 48	10.4 vs 12.4	—
Schlag ら (1991)	CDDP + 5-FU × 3 vs 手術単独	29 vs 40	8 vs 9	—
Law ら (1997)[23]	CDDP + 5-FU × 2 vs 手術単独	74 vs 73	16.8 vs 13	44 vs 31(2年)
Kelsen ら (1998)[24]	CDDP + 5-FU × 3 vs 手術単独	213 vs 227	14.9 vs 16.1	35 vs 37(2年)
Girling ら (2002)[25]	CDDP + 5-FU × 2 vs 手術単独	400 vs 402	16.8 vs 13.3	43 vs 34(2年)

vivo における正確な化学療法感受性試験が可能であることがあげられる．一方，不利な点としては薬剤耐性の獲得を促す，術前化学療法期間中に転移による広がりを助長する，術後合併症のリスクを助長するなどが理論的に考えられる[1]．現在，手術補助化学療法の有効性を検討するために欧米を中心に大規模な臨床試験が展開されている．本邦の食道癌は，欧米と比較してその組織型や局在が大きく異なり，また手術術式やリンパ節郭清範囲も異なるため，欧米における臨床試験の結果をそのまま適用することはできない．

1. 術後補助化学療法

本邦では，有効な手術補助療法を開発するためにJEOGにおいて多施設共同のRCTが行われてきた(表2)．第3次研究(1984～1987年)で術後照射(50 Gy)群と術後化学療法(CDDP 70 mg/m² + VDS 3 mg/m², 2コース)群とのRCTを行った結果，両治療法による遠隔成績に明らかな差は認められず[18]，補助療法が放射線照射から化学療法へと変換していった．このころより普及し始めた上縦隔郭清の徹底化や3領域郭清など外科手術の進歩により，食道癌の術後5年生存率の向上が認められた．そこで，補助化学療法が手術単独治療に対し生存率の向上に寄与しているか否かを検討することが必要になった．第4次研究(1988～1991年)では手術単独群と術後化学療法群(CDDP 70 mg/m² + VDS 3 mg/m², 2コース)でRCTが行われたが，両群間で有意差は認められなかった[19]．続いて行われた第5次研究(1992～1997年)では術後補助療法として現在の化学療法の標準治療となっているCDDP 80 mg/m² + 5-FU 800 mg/m², 2コースを用いて手術単独群とRCTを行った[20]．5年無再発生存率では45%/55%，とくにリンパ節転移陽性例では38%/52%と術後化学療法群のほうが有意に良好であり，CDDP+5-FUの術後化学療法による再発予防効果が認められた．現在，適切な化学療法の時期を検討する目的で，2000年より第6次研究として術後化学療法と術前化学療法をRCTにて比較検討しており，結果が待たれる．

欧米における術後化学療法の臨床試験の報告は少ないが，フランスでのRCTにおいてCDDP/5-FUによる術後化学療法は有用ではないと報告されている[21]．しかし，対象例には完全切除例と不

完全切除例が混在しCDDPの投与方法も統一されておらず，結果の解釈には慎重を要する．

2. 術前化学療法

欧米では術前化学療法(neoajduvant chemotherapy)が主流となっている(表3)．初期の単一施設での臨床試験の結果，術前化学療法により治療関連死亡は増えないことや，化療有効例では生存期間が有意に延長することなどが報告された[22,23]．近年，多施設共同による大規模なRCTの成績が報告されている．米国ではRadiation Therapy Oncology Group(RTOG)，Cancer and Acute Leukemia Group B(CALGB)，Southwest Oncology Group(SWOG)，Eastern Cooperative Oncology Group(ECOG)共同のRCT(手術単独 vs CDDP+5-FU，3コース術前化療)が行われ，生存率，無再発生存率ともに両群間に差が認められなかった[24]．一方，英国Medical Research Council(MRC)から報告された最新のRCT(手術単独 vs CDDP+5-FU，2コース術前化療)では，MSTが13.3/17.3ヵ月，2年生存率が34%/43%で有意に術前化療群が良好であった[25]．このように大規模なRCTをみても相反する結論が導き出されており，術前補助化学療法の有効性はいまだcontroversialである．

おわりに

進行食道癌に対する化学療法について解説した．食道癌に対する治療は，手術中心の治療から，手術，化学療法，放射線療法，化学放射線療法を用いた集学的治療へと多様化してきている．しかし，治療の優劣にはいまだ不明の部分が残されており，今後の臨床試験の結果が待たれている．さらに，抗癌薬や放射線の感受性予測因子が解明されれば，将来の食道癌治療において飛躍的な進歩がもたらされるであろう．

◆◆◆ 文献 ◆◆◆

1) 安藤暢敏，石志　紘：食道癌診療の現況と展望，食道癌の治療，食道癌の化学療法．日外会誌 103：359-363，2002
2) Ajani JA：Current status of new drugs and multidisciplinary approaches in patients with carcinoma of the esophagus. Chest 113 [1 Suppl]：112-119, 1998
3) 長瀬通隆，大津　敦：切除不能あるいは再発食道癌の化学療法および放射線化学療法．消病セミナー80：43-52，2000
4) Ajani JA, Ilson DH, Daugherty K et al：Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. J Natl Cancer Inst 86：1086-1091, 1994
5) Conroy T, Etienne PL, Adenis A et al：Phase II trial of vinorelbine in metastatic squamous cell esophageal carcinoma. J Clin Oncol 14：164-170, 1996
6) 田口鐵男，涌井　昭，鍋谷欣市ほか：254-S (Cis-diammine glycolato platinum)の消化器癌に対する第II相臨床試験．癌と化療19：483-488，1992
7) Ferry DR, Anderson M, Beddows K et al：Phase II trial of gefitinib(ZD1839) in advanced adenocarcinoma of the oesophagus incorporating biopsy before and after gefitinib. J Clin Oncol 22 [Suppl]：318, 2004
8) Ilson DH, Kelsen DP：Combined modality therapy in the treatment of esophageal cancer. Semin Oncol 21：493-507, 1994
9) Iizuka T, Kakegawa T, Ide H et al：Phase II evaluation of cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the esophagus；a Japanese esophageal oncology group trial. Jpn J Clin Oncol 22：172-176, 1992
10) Hayashi K, Ando N, Watanabe H et al：Phase II evaluation of protracted infusion of cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the esophagus；a Japan esophageal oncology group(JEOG) trial(JCOG9407). Jpn J Clin Oncol 31：419-423, 2001
11) Vokes EE, Choi KE, Schilsky RY et al：Cisplatin, fluorouracil, and high-dose leucovorin for recurrent or metastatic head and neck cancer. J Clin Oncol 6：618-626, 1988
12) 安藤暢敏，小澤壮治，北島政樹ほか：食道癌に対する化学療法と集学的治療．癌と化療22：869-876，1995
13) Kelsen D, Ginsberg R, Bains M et al：Phase II trial of paclitaxel and cisplatin in patients

with locally advanced metastatic esophageal cancer ; a preliminary report. Semin Oncol 24 : 77-81, 1997
14) Ilson DH, Ajani J, Bhalla K et al : Phase II trial of paclitaxel, fluorouracil, and cisplatin in patients with advanced carcinoma of the esophagus. J Clin Oncol 16 : 1826-1834, 1998
15) Ilson DH, Saltz, Eizinger P et al : Phase II trial of weekly irinotecan plus cisplatin in advansed esophageal cancer. J Clin Oncol 17 : 3270-3275, 1999
16) Scullin P, Millar J, Dunlop et al : A phase II trial of gemcitabine(gem) & cisplatin(cis) in advanced esophageal cancer(AEC). J Clin Oncol 22 [Suppl] : 322, 2004
17) Muro K, Ando N, Nishimaki T et al : A phase II study of nedaplatin and 5-fluorouracil in metastatic squamous cell carcinoma of the esophagus ; the Japan Clinical Oncology Group(JCOG) trial(JCOG 9905). Proc ASCO 22 : 277, 2003
18) Japanese Esophageal Oncology Group : A comparison of chemotherapy and radiotherapy as adjuvant treatment to surgery for esophageal carcinoma. Chest 104 : 203-207, 1993
19) Ando N, Iizuka T, Kakegawa T et al : A randomized trial of surgery with and without chemotherapy for localized squamous carcinoma of the thoracic esophagus ; the Japan clinical oncology group study. J Thorac Cardiovasc Surg 114 : 205-209, 1997
20) Ando N, Iizuka T, Ide H et al : Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus ; a Japan Clinical Oncology Group Study(JCOG9204). J Clin Oncol 21 : 4592-4596, 2003
21) Pouliquen X, Levard H, Hay JM et al : 5-fluorouracil and cisplatin therapy after palliative surgical resection of squamous cell carcinoma of the esophagus ; a multicenter randomized trial. Ann Surg 223 : 127-133, 1996
22) Roth JA, Pass HI, Flanagan MM et al : Randomized clinical trial of preoperative and postoperative adjuvant chemotherapy with cisplatin, vindesine, and bleomycin for carcinoma of the esophagus. J Thorac Cardiovasc Surg 96 : 242-248, 1988
23) Law S, Fok M, Chow S et al : Preoperative chemotherapy versus surgical therapy alone for squamous cell carcinoma of the esophagus ; a prospective randomized trial. J Thorac Cardiovasc Surg 114 : 210-217, 1997
24) Kelsen DP, Ginsberg R, Pajak TF et al : Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 339 : 1979-1984, 1998
25) Medical Research Council Oesophageal Cancer Working Party : Surgical resection with or without preoperative chemotherapy in oesophageal cancer ; a randomized controlled trial. Lancet 359 : 1727-1733, 2002

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

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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.

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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

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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 radiation 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. Thee-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-μm 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-μm 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 ± 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 2-field (%)	3-field (%)	P value*
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.