Surgery for Small Cell Lung Cancer

A Retrospective Analysis of 243 Patients from Japanese Lung Cancer Registry in 2004

Hidefumi Takei, MD, Haruhiko Kondo, MD,* Etsuo Miyaoka, PhD,† Hisao Asamura, MD,‡ Ichiro Yoshino, MD,§ Hiroshi Date, MD,‖ Meinoshin Okumura, MD,¶ Hirohito Tada, MD,# Yoshitaka Fujii, MD,** Yoichi Nakanishi, MD,†† Kenji Eguchi, MD,‡‡ Hirotoshi Dosaka-Akita, MD,§§ Hideo Kobayashi, MD,‖‖ Noriyoshi Sawabata, MD,¶ and Kohei Yokoi, MD;¶¶ for the Japanese Joint Committee of Lung Cancer Registry*

Introduction: Indications for surgical resection for small cell lung cancer (SCLC) have been very limited. Because early-stage SCLC is a rare presentation of lung cancer, studies comparing surgical resection among a large number of patients are unlikely to be conducted. This study reports the most recent surgical outcomes of a large number of SCLC patients who underwent surgery in 2004.Methods: In 2010, the Japanese Joint Committee of Lung Cancer Registry performed a nationwide retrospective registry study regarding the prognosis and clinicopathologic profiles of 11,663 patients who underwent resection for primary lung cancer in 2004. Of the 11,663 patients, 243 patients with SCLC (2.1%) were included in this study. The registry data of the patients with SCLC were analyzed, and the clinicopathologic profiles and surgical outcomes of the patients were evaluated.Results: The 5-year survival rate for all cases (n = 243, 213 males, mean age 68.2 years) was 52.6%. The 5-year survival rates by c-stage and p-stage were as follows: IA, 64.3% (n = 132) and 72.3% (n = 93); IB, 45.7% (n = 36) and 61.1% (n = 51); IIA, 50.5% (n =25); and 44.8% (n = 27); IIB, 33.3% (n = 10) and 40.3% (n = 17); IIIA, 30.5% (n = 30) and 23.4% (n = 45); and IV, 0% (n = 7) and 0% (n = 9), respectively. A multivariate analysis showed that the significant prognostic factors were age, gender, c-stage, and surgical curability. A kappa value was moderate conformity between c-stage and p-stage in all cases.Conclusions: Surgical resection in selected patients with early-stage SCLC, especially stage I, had favorable results.

Key Words: Small cell lung cancer, Surgery, Registry

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Lung cancer is the leading cause of cancer-related death in the United States and in Japan. Small cell lung cancer (SCLC) represents only 13–20% of all lung cancers.[1] It is distinguished by its rapid growth rate and early dissemination to regional lymph nodes and distant sites. Therefore, SCLC represents less than 5% of cases in large surgical series.[2]

In 1973, the Medical Research Council[3] reported a postoperative survival rate that was as poor as the survival rate for nonsurgical treatment in SCLC patients. In addition, Mountain[4] reported that there was no difference in outcome between resected and non-resected cases in 368 SCLC patients. After those two studies were published, the standard treatment for SCLC became chemotherapy and/or radiation, and surgery was basically contraindicated. In 1983, the Lung Cancer Study Group[5] initiated the only randomized trial of adjuvant surgical resection after induction chemotherapy. This trial failed to show improved survival rates after surgery compared with radiation after neoadjuvant chemotherapy. Thereafter, several authors reported rather favorable surgical results in a relatively small number of patients with early-stage SCLC.[6,7] Shepherd and colleagues[8] reported in 1988 that the postoperative 5-year survival rate was 31% in 77 patients with surgery as the primary treatment for SCLC. In 2005, Japan Clinical Oncology Group reported a 68% 3-year postoperative survival rate in patients with resected clinical stage I SCLC undergoing postoperative adjuvant chemotherapy.[9] Recently, several large cohort studies of surgery for limited disease SCLC have

*Department of General Thoracic Surgery, Kyorin University, Tokyo; †Department of Mathematics, Science University of Tokyo; ‡Division of Thoracic Surgery, National Cancer Center Hospital, Tokyo; §Department of General Thoracic Surgery, Chiba University Graduate School of Medicine, Chiba; ‖Department of Thoracic Surgery, Kyoto University Graduate School of Medicine, Kyoto, ¶Department of General Thoracic Surgery, Osaka University Graduate School of Medicine, #Division of General Thoracic Surgery, Osaka City General Hospital, Osaka; **Department of Oncology, Immunology and Surgery, Nagoya City University Graduate School of Medical Science and Medical School, Nagoya; ††Department of Clinical Medicine, Research Institute for Diseases of the Chest, Faculty of Medical Sciences, Kyushu University, Fukuoka; ‡‡Department of Medical Oncology, Teikyo University School of Medicine, Tokyo; §§Department of Medical Oncology, Hokkaido University Graduate School of Medicine, Sapporo; ‖‖Division of Respiratory Disease, National Defense Medical College, Tokorozawa; and ¶¶Department of Thoracic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan.

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Address for correspondence: Hidefumi Takei, MD, Division of General Thoracic Surgery, Kyorin University, 6-20-2, Shinkawa, Mitaka, Tokyo, 181–8611, Japan. E-mail: htakei@ks.kyorin-u.ac.jp

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been reported.[10,11] An analysis of 205 clinical stage IA SCLC patients from the National Cancer Institute's Surveillance Epidemiology and End Results database who underwent radical lobectomy showed a 5-year survival rate of 50.3% without postoperative adjuvant radiotherapy.[12]

However, optimal indications for surgical resection for SCLC and the efficacy of perioperative chemotherapy have not yet been determined. Because early-stage SCLC is a rare presentation, accounting for 2.4% to 3.4% of resected lung cancer,[13] and a definite preoperative diagnosis of cell type as SCLC is rather difficult, studies prospectively comparing the significance of surgical resection in a large number of cases are unlikely to be conducted.

This study aimed to investigate recent surgical results for SCLC patients retrospectively, based on the large-volume Japanese nationwide registry database.

PATIENTS AND METHODS

Patients

In 2010, the Japanese Joint Committee of Lung Cancer Registry performed a nationwide retrospective registry study regarding the prognoses and clinicopathologic profiles of 11,663 patients who underwent resection for primary lung cancer in 2004. Of those patients, 243 with histologically confirmed SCLC (2.1%) were extracted from the database. The clinicopathologic factors and their relationship to postoperative survival were evaluated.

The following items were included for analysis: gender, age, smoking status, serum tumor markers (carcinoembryonic antigen and proGRP), clinical tumor, node, metastasis (TNM) stage (c-stage), pathological TNM stage (p-stage), surgical procedure, surgical curability (R0 and R1/R2), presence or absence of preoperative and postoperative chemotherapy, and survival time. The Union for International Cancer Control TNM staging, version 7,[14] was adopted in this study.

This study and the Japanese Joint Committee of Lung Cancer Registry registration study adhere to the Ethical Guidelines for Epidemiologic Research imposed by the Japanese Ministry of Health, Labor, and Welfare.[15]

Statistical Analysis

Survival time was defined as the time from the date of the surgery to the date of the last follow-up. Survival curves were estimated by the Kaplan-Meier method. Differences in survival were assessed by the log-rank test. A multivariate analysis by Cox's proportional hazards model was used to test the significance of prognostic factors. Statistical significance was considered to be established when the associated p value was less than 0.05.

A kappa value of conformity between c-stage and p-stage was also determined.[16] A kappa has a maximum of 1 (indicating perfect agreement) and a minimum −1 (indicating worse than chance agreement). A value of 0 indicates an agreement that is no better than chance, values above 0.4 are usually considered indicative of "moderate" agreement, and values higher than 0.6 are considered "good" agreement.

RESULTS

Patient Profiles

The clinicopathologic characteristics of the 243 patients with resected SCLC are summarized in Table 1. Of the 243 patients with resected SCLC, there were 213 (87.7%) men and 30 (12.3%) women. The mean age at the time of operation was 68.2±9.5 years. Preoperative serum proGRP levels were elevated in 58 patients (23.9%) and within normal limits in 185 (76.1%) patients. The major operative mode was lobectomy/bilobectomy (n = 174, 71.6%), followed by segmentectomy/wedge resection (n = 51, 21.0%). More than 60% of patients (n = 169, 68.6%) were diagnosed as c-stage IA or IB. As for the pathologic stage, 93 patients (38.3%) were recognized as p-stage IA, and 51 (21.0%) as p-stage IB. There were 45 (18.5%) patients in p-stage IIIA. Complete resections (R0) were achieved in 214 (88.1%) patients.

Postoperative Survival

The overall postoperative survival curve is shown in Figure 1. The 5-year survival rate of the 243 patients with SCLC was 52.6%. The postoperative survival curves according to c-stage and p-stage are shown in Figure 2. The 5-year survival rates by c-stage and p-stage were as follows: 64.3% in c-stage IA, 45.7% in c-stage IB, 50.5% in c-stage IIA, 33.3% in c-stage IIB, 30.5% in c-stage IIIA, 0% in c-stage IV, 72.3% in p-stage IA, 61.1% in p-stage IB, 44.8% in p-stage IIA, 40.3% in p-stage IIB, 23.4% in p-stage IIIA, and 0% in p-stage IV. The differences in survival were significant between c-stage IA and c-stage IB (p = 0.0423), c-stage IA and c-stage IIB (p = 0.0367), c-stage IA and IIIA (p = 0.0023), p-stage IA and p-stage IIA (p = 0.0074), p-stage IA and p-stage IIB (p = 0.0033), p-stage IA and p-stage IIIA (p = 0.0000), and p-stage IB and p-stage IIIA (p = 0.0006).

The relationship of each factor to survival, determined by univariate analysis, is shown in Table 1. Except for c-stage and p-stage, there was statistical significance in gender (women fared better than men did), serum ProGRP level (worse in elevated cases), and surgical curability (R0 patients fared better than R1/R2 patients did). In a Cox proportional hazards model to predict overall survival, the following factors persisted as significant prognostic factors: gender, age, c-stage, and surgical curability (Table 2).

Clinicopathological Results According to c-Stage

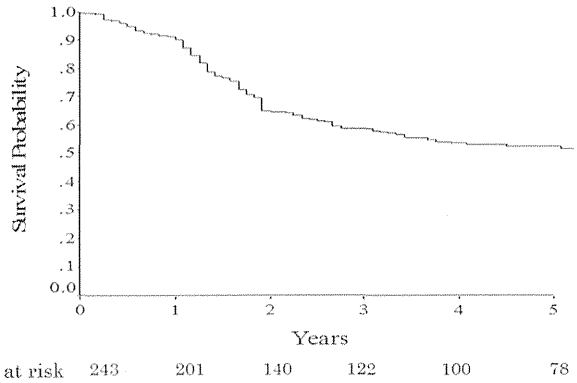
The relationship of p-stage, perioperative chemotherapy, and surgical curability to c-stage is shown in Table 3. In c-stage IA + IB, 39 of 168 cases (23.2%) were upstaged to p-stage, and eight of 30 cases (26.7%) in c-stage IIIA and two (66.7%) of three in c-stage IIIB were downstaged to p-stage I or II. A conformity of c-stage and p-stage was determined to be moderate, with a kappa value of 0.425.

As for surgical curability, in c-stage I (IA + IB), 158 cases (96.3%) underwent R0 resection and only six cases (3.7%) underwent R1/R2 resection. In c-stage II, 32 cases

TABLE 1. Characteristics of Patients with Resected Small Cell Lung Cancer and Overall Survival

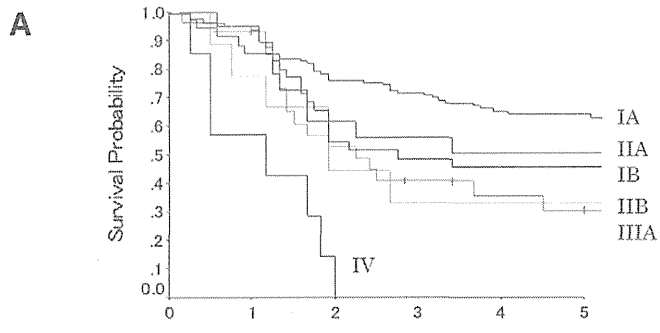
	N (%)	5-Year Survival (%)	Comparison	*p* Value
Gender				
Men	213 (87.7)	49.3		0.0190
Women	30 (12.3)	79.0		
Smoking				
Nonsmoker	22 (9.1)	41.6		
Ex-smoker	74 (30.5)	50.8	Nonsmoker vs. ex-smoker	0.5740
Smoker	124 (51.0)	56.3	Nonsmoker vs. smoker	0.2253
Unknown	23 (9.5)			
Operative mode				
Wedge resection	37 (15.2)	30.6	Wedge resection vs. lobectomy/bilobectomy	0.0019
Segmentectomy	14 (5.8)	63.6	Segmentectomy vs. lobectomy/bilobectomy	0.7848
Lobectomy/ bilobectomy	174 (71.6)	58.3		
Pneumonectomy	9 (3.7)	31.8	Pneumonectomy vs. lobectomy/bilobectomy	0.1600
Unknown	9 (3.7)			
c-stage				
IA	132 (54.3)	63.3		
IB	36 (14.3)	45.7	IB vs. IA	0.0423
IIA	25 (10.3)	50.5	IIA vs. IA	0.2531
IIB	10 (4.1)	33.3	IIB vs. IA	0.0367
IIIA	30 (12.3)	30.5	IIIA vs. IA	0.0023
IIIB	3 (1.2)	—	—	—
IV	7 (2.9)	0	IV vs. IA	0.0000
p-stage				
IA	93 (38.3)	72.3		
IB	51 (21.0)	61.1	IB vs. IA	0.1855
IIA	27 (11.1)	44.8	IIA vs. IA	0.0074
IIB	17 (7.0)	40.3	IIB vs. IA	0.0033
IIIA	45 (18.5)	23.4	IIIA vs. IA	0.0000
IIIB	1 (0.4)	—	—	—
IV	9 (3.7)	0	IV vs. IA	0.0000
Preoperative treatment				
Done	27 (11.1)			
None	215 (88.5)			
Unknown	1 (0.4)			
Adjuvant chemotherapy				
Done	158 (65.0)	52.0		0.5535
None	69 (28.4)	51.8		
Unknown	16 (6.6)			
Tumor marker				
CEA higher level	70 (28.8)	49.1		0.5631
CEA normal level	173 (71.2)	53.9		
ProGRP higher level	58 (23.9)	36.0		0.0482
ProGRP normal level	185 (76.1)	57.2		
Residual tumor				
R0	214 (88.1)	57.0		0.0000
R1/R2	23 (9.5)	10.2		
Unknown	6 (2.5)			

(94.1%) underwent R0 resection and three cases (8.8%) underwent R1/R2. In c-stageIIIA, R0 resections were done in 19 cases (65.5%). The 5 year survival rates of the patients who underwent R0 resection with c-stage IA, c-stage IB, and c-stage II (IIA+IIB) were 65.4%, 51.6%, and 44.4%, respectively.



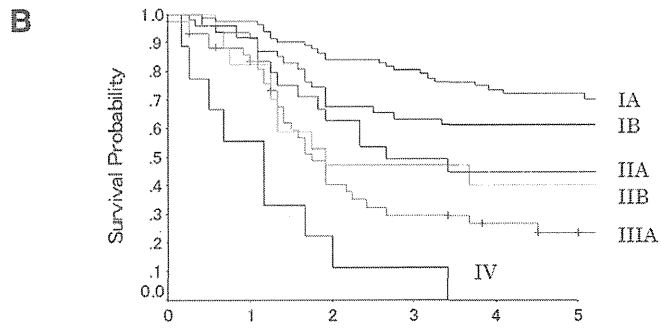
Number at risk 243 201 140 122 100 78

FIGURE 1. Overall survival curve. The 5-year survival rate of patients with small cell carcinoma was 52.6%.



Number at risk

IA	132	114	90	82	69	52
IB	36	30	19	17	15	11
IIA	25	18	11	10	9	6
IIB	10	7	4	3	3	2
IIIA	30	24	13	9	7	6
IV	7	4	1	0	0	0



Number at risk

IA	93	80	68	63	52	44
IB	51	44	31	28	27	19
IIA	27	22	15	11	9	6
IIB	17	14	8	8	4	3
IIIA	45	35	15	11	8	6
IV	9	5	1	1	0	0

FIGURE 2. Overall survival curve based on clinical stage (Union for International Cancer Control-TNM Ver. 7). The 5-year survival rates by c-stage (*A*) and p-stage (*B*) were as follows: IA, 64.3% (n = 132) and 72.3% (n = 93); IB, 45.7% (n = 36) and 61.1% (n = 51); IIA, 50.5% (n = 25) and 44.8% (n = 27); IIB, 33.3% (n = 10) and 40.3% (n = 17); IIIA, 30.5% (n = 30) and 23.4% (n = 45); and IV, 0% (n = 7) and 0% (n = 9), respectively.

DISCUSSION

This study, which included 243 patients who underwent surgery in 2004, is the largest in number of patients with SCLC who underwent surgical intervention within just 1 year. It was expected that there would be low variations in preoperative staging evaluation, surgical technique, and postoperative care for each case. For such occasions, the results of this study were meaningful.

The current standard treatment for patients with SCLC is chemotherapy and radiotherapy, except for a portion of early-stage patients. The MRC study[3] in 1973 was a randomized trial, comparing surgery versus radiation alone. In that study, the median survival rate in the surgery group was 6.5 months, compared with 10 months in the radiation group (p = 0.04). After that article was published, the standard care was changed from surgical resection to radiotherapy. However, only 34 of the 71 patients (48%) who were enrolled in the surgery arm actually underwent surgical resection. Most of the patients in the MRC study had relatively advanced disease.

Recently, several authors have reported positive results for surgery in patients with early-stage SCLC.[17,18] Shah and colleagues[19] reported on surgical resection for SCLC patients without adjuvant chemotherapy in 1992. Of 28 patients who underwent surgical resection, 14 had stage I disease, five had stage II disease, and nine had stage III disease. The actual 5-year survival rate for patients in stage I was 57.1%, whereas no patients with stage II disease survived 5 years. In half of the patients in Shah's study, the tumor was in a central position. Lim and colleagues[11] reported excellent survival rates for patients in stages I to III who underwent lung resection with nodal dissection for SCLC. A total of 59 patients in their study underwent complete R0 resection for SCLC between 1980 and 2006, and the overall 5-year survival rate was 52%. That study supports the need to reevaluate surgery as the primary treatment and the use of clinical Tumor, Node, Metastasis criteria in the selection of patients with very limited SCLC for surgery. Weksler and colleagues[20] analyzed patients in the Surveillance Epidemiology and End Results database, making a retrospective analysis of a large national database. That study examined 3566 patients with stage I or II SCLC who underwent surgery from 1988 to 2007. Patients with stage II SCLC who had a lung resection had a median survival time of 25.0 months, compared with 14.0 months in patients with stage II SCLC who did not undergo lung resection ($p < 0.0001$). Weksler's study concluded that surgical resection as a component of treatment for stage I or stage II SCLC is associated with significantly improved survival and should be considered in the management of early-stage SCLC.

The overall 5-year survival rate of the patients in our study was 52.6%. Multivariate analysis found that good prognostic factors for survival were younger age, female gender, early-stage disease, and achieved curative resection. The same trends have been previously reported.[11,20] Even though c-stage was one of the most important prognostic factors, the survival rate of the selected patients with c-stage II was favorable results. In particular, patients who underwent complete resection had good survival rates, not only with c-stage I, but also with c-stage II, compared with previous reports. In c-stage

I and II, 190 patients (95.5%) underwent R0 resection, and only nine underwent R1/R2 resection. Surgery was recommended for the c-stage I SCLC patients; however, based on these results, surgical resection might also be considered for patients with stage II SCLC.

On the other hand, in several patients in this study, c-stage did not correspond well with p-stage. Among the patients with stage I SCLC according to preoperative evaluations, 23.2% of the cases were upstaged to stage II or stage III postoperatively. A kappa value demonstrated moderate conformity between c-stage and p-stage in all cases. Vallieres and colleagues[10] reported the same trend when comparing clinical and pathological staging of SCLC, using the International Association for the Study of Lung Cancer database. The overall concordance between clinical and pathologic TNM staging was 58%. When grouping clinical stages I and II together, 19.7% were upstaged to stage pIIIA or above after resection according to the International Association for the Study of Lung Cancer database. Although there is no data on preoperative staging modality in the current study, intensive staging before considering surgical therapy is important, using such tools as positron emission tomography-computed tomography (PET-CT),[21] endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA),[22] and surgical mediastinoscopy.[23]

Large cell neuroendocrine carcinoma (LCNEC) of the lung is defined as a high-grade neuroendocrine tumor no less than SCLC in the 1999 World Health Organization classification of lung tumors.[24] Takei et al.[25] reported that 44% (24 of 55) of operated patients who were originally diagnosed with SCLC (before 1999) were reclassified as LCNEC after the pathologic review. Studies on treatment of patients with SCLC naturally included many cases of LCNEC before LCNEC had been recognized. Thus, it is necessary to be aware when comparing studies performed before and after LCNEC was defined. The subjects of the current study are patients who were operated on in 2004, when LCNEC was well recognized.

In the present study, the survival benefit of postoperative adjuvant chemotherapy was not proved. It is assumed that because of biases in treatment acceptance, the patients' backgrounds were varied, although an analysis was conducted only in p-stage I patients.

Limitations of this analysis include that it is a retrospective study; there is no randomization for adjuvant treatment; there is a lack of preoperative histopathological diagnosis data; there is a lack of information regarding preoperative staging methods; and there is no information regarding the aim of the preoperative treatment and whether the induction treatment was followed by surgery or salvage surgery.

TABLE 2. Multivariate Analysis of Overall Survival for Resected Small Cell Lung Cancer; Cox Proportional Hazards Model

	Hazard Ratio	95% CI	*p* Value
Age, per year increase	1.038	1.015–1.062	0.001
Gender			
Men	1.00		
Women	0.356	0.142–0.893	0.028
c-stage			0.029
IA	1.00		
IB	1.421	0.811–2.493	0.220
IIA	1.298	0.618–2.727	0.491
IIB	2.389	0.986–5.788	0.054
IIIA	1.514	0.797–2.876	0.205
IIIB	3.739	0.863–16.204	0.078
IV	4.557	1.769–11.741	0.002
Tumor marker			
ProGRP normal level	1.00		
ProGRP higher level	1.232	0.774–1.961	0.378
Residual tumor			
R0	1.00		
R1/R2	2.288	1.208–4.332	0.011

CI, confidence interval

CONCLUSION

Surgical resection for selected patients with early-stage SCLC, especially stage I, had good survival outcomes. Based on this result, surgery might also be considered in c-stage II SCLC. Further, a clinical trial on the surgery for patients with c-stage II SCLC was recommended.

TABLE 3. Relationships Between c-Stage, p-Stage, Surgical Curability, and Perioperative Treatment

		p Stage							Surgical Curability[a]	
		IA	IB	IIA	IIB	IIIA	IIIB	IV	R0	R1/2
c-stage	IA	80	23	10	8	11	0	0	126	3
	IB	4	21	3	1	6	0	1	32	3
	IIA	5	2	11	2	4	1	0	21	3
	IIB	0	2	1	4	2	0	1	10	0
	IIIA	4	2	0	2	21	0	1	19	10
	IIIB	0	1	1	0	0	0	1	3	0
	IV	0	0	1	0	1	0	5	3	4

R0, no residual tumor; R1/R2, microscopic or macroscopic residual tumor.
[a]Six patients data of curability were missing.

REFERENCES

1. Murren JR, Turrisi AT, Pass HI. Small cell lung cancer. In: DeVita VTJ, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice.* Philadelphia, PA: Lippincott Williams & Wilkins; 2005:820–843.
2. Masters G. The clinical presentation of small cell carcinoma. In: Pass HI, Carbone DP, Johnson DH, et al, eds. *Lung Cancer, Principles and Practice.* Philadelphia, PA: Lippincott Williams & Wilkins; 2005:304–314.
3. Fox W, Scadding JG. Medical Research Council comparative trial of surgery and radiotherapy for primary treatment of small-celled or oat-celled carcinoma of bronchus. Ten-year follow-up. *Lancet* 1973;2:63–65.
4. Mountain CF. Clinical biology of small cell carcinoma: relationship to surgical therapy. *Semin Oncol* 1978;5:272–279.
5. Lad T, Piantadosi S, Thomas P, Payne D, Ruckdeschel J, Giaccone G. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. *Chest* 1994;106(6 Suppl):320S–323S.
6. Shields TW, Higgins GA Jr, Matthews MJ, Keehn RJ. Surgical resection in the management of small cell carcinoma of the lung. *J Thorac Cardiovasc Surg* 1982;84:481–488.
7. Davis S, Wright PW, Schulman SF, Scholes D, Thorning D, Hammar S. Long-term survival in small-cell carcinoma of the lung: a population experience. *J Clin Oncol* 1985;3:80–91.
8. Shepherd FA, Evans WK, Feld R, et al. Adjuvant chemotherapy following surgical resection for small-cell carcinoma of the lung. *J Clin Oncol* 1988;6:832–838.
9. Tsuchiya R, Suzuki K, Ichinose Y, et al. Phase II trial of postoperative adjuvant cisplatin and etoposide in patients with completely resected stage I-IIIa small cell lung cancer: the Japan Clinical Oncology Lung Cancer Study Group Trial (JCOG9101). *J Thorac Cardiovasc Surg* 2005;129:977–983.
10. Vallières E, Shepherd FA, Crowley J, et al.; International Association for the Study of Lung Cancer International Staging Committee and Participating Institutions. The IASLC Lung Cancer Staging Project: proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2009;4:1049–1059.
11. Lim E, Belcher E, Yap YK, Nicholson AG, Goldstraw P. The role of surgery in the treatment of limited disease small cell lung cancer: time to reevaluate. *J Thorac Oncol* 2008;3:1267–1271.
12. Yu JB, Decker RH, Detterbeck FC, Wilson LD. Surveillance epidemiology and end results evaluation of the role of surgery for stage I small cell lung cancer. *J Thorac Oncol* 2010;5:215–219.
13. Sawabata N, Miyaoka E, Asamura H, et al.; Japanese Joint Committee for Lung Cancer Registration. Japanese lung cancer registry study of 11,663 surgical cases in 2004: demographic and prognosis changes over decade. *J Thorac Oncol* 2011;6:1229–1235.
14. International Union against Cancer; Sobin LH, Gospodrowicz MK, Wittekind CH, eds. *TNM Classification of Malignant Tumours.* 7th Ed. New York, NY: Wiley-Liss; 2009.
15. The Ethical Guidelines for Epidemiologic Research notified by Japanese Ministry of Health, Labour and Welfare. December 1, 2008. Available at: http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/ekigaku/0504sisin.html.
16. Cohen JA. A coefficient of agreement for nominal scales. *Educ Psychol Meas.* 1960;20:37–46.
17. Varlotto JM, Recht A, Flickinger JC, Medford-Davis LN, Dyer AM, DeCamp MM. Lobectomy leads to optimal survival in early-stage small cell lung cancer: a retrospective analysis. *J Thorac Cardiovasc Surg* 2011;142:538–546.
18. Schreiber D, Rineer J, Weedon J, et al. Survival outcomes with the use of surgery in limited-stage small cell lung cancer: should its role be re-evaluated? *Cancer* 2010;116:1350–1357.
19. Shah SS, Thompson J, Goldstraw P. Results of operation without adjuvant therapy in the treatment of small cell lung cancer. *Ann Thorac Surg* 1992;54:498–501.
20. Weksler B, Nason KS, Shende M, Landreneau RJ, Pennathur A. Surgical resection should be considered for stage I and II small cell carcinoma of the lung. *Ann Thorac Surg* 2012;94:889–893.
21. Bradley JD, Dehdashti F, Mintun MA, Govindan R, Trinkaus K, Siegel BA. Positron emission tomography in limited-stage small-cell lung cancer: a prospective study. *J Clin Oncol* 2004;22:3248–3254.
22. Wada H, Nakajima T, Yasufuku K, et al. Lymph node staging by endobronchial ultrasound-guided transbronchial needle aspiration in patients with small cell lung cancer. *Ann Thorac Surg* 2010;90:229–234.
23. Jett JR, Schild SE, Kesler KA, et al. Treatment of small cell lung cancer. Diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guideline. *Chest* 2013;143(suppl):e400s–e419s.
24. Travis WD, Colby TV, Corrin B, et al. *Histological Typing of Lung and Pleural Tumours.* 3rd ed. Berlin: Springer; 1999.
25. Takei H, Asamura H, Maeshima A, et al. Large cell neuroendocrine carcinoma of the lung: a clinicopathologic study of eighty-seven cases. *J Thorac Cardiovasc Surg* 2002;124:285–292.

Prognostic value of intraoperative pleural lavage cytology for non–small cell lung cancer: The influence of positive pleural lavage cytology results on T classification

Kotaro Kameyama, MD,[a] Norihito Okumura, MD,[a] Etsuo Miyaoka, PhD,[b] Hisao Asamura, MD,[c] Ichiro Yoshino, MD,[d] Hirohito Tada, MD,[e] Yoshitaka Fujii, MD,[f] Yoichi Nakanishi, MD,[g] Kenji Eguchi, MD,[h] Masaki Mori, MD,[i] Hideo Kobayashi, MD,[j] Noriyoshi Sawabata, MD,[k] Meinoshin Okumura, MD,[k] and Kohei Yokoi, MD,[l] for the Japanese Joint Committee of Lung Cancer Registry

Objective: Although positive pleural lavage cytology (PLC) has been demonstrated to be closely associated with a poor prognosis for patients with lung cancer, it has not been incorporated into the TNM staging system of the Union for International Cancer Control. The aim of our study was to retrospectively examine the clinical significance of PLC status and illustrate the recommendations of the International Pleural Lavage Cytology Collaborators (IPLCC) in a large national database.

Methods: The Japanese Joint Committee of Lung Cancer Registry database included 11,073 patients with non–small cell lung cancer who underwent resections in 2004. We extracted the clinicopathologic data for 4171 patients (37.3%) who underwent PLC. These patients were staged according to the seventh edition of the Union for International Cancer Control TNM classification and by recommendations of the IPLCC, in which T was singly upgraded up to a maximum of T4 for those who were PLC-positive. Prognoses based on these 2 systems were compared.

Results: A total of 217 patients (5.2%) were PLC-positive, which was significantly associated with a higher incidence of adenocarcinoma and advanced disease. The 5-year survival for patients with positive and negative PLC results were 44.5% and 72.8%, respectively, and this difference in survival was statistically significant ($P < .001$). Multivariate analysis showed that positive PLC status was an independent factor for a poor prognosis (hazard ratio, 1.57; $P < .001$). Significant differences in survival were also found between patients with positive and negative PLC results in the same T categories and stages, including T2a, T3, stage IB, and stage IIIA. The IPLCC recommendations adjusted the prognostic differences in all T categories and stages. The significant difference in survival disappeared between the 2 groups in all T categories and stages.

Conclusions: Our results indicate that a T category upgrade is prognostically adequate for patients who are PLC-positive. (J Thorac Cardiovasc Surg 2014;148:2659-64)

From the Department of Thoracic Surgery,[a] Kurashiki Central Hospital, Kurashiki, Japan; Department of Mathematics,[b] Science University of Tokyo, Tokyo, Japan; Division of Thoracic Surgery,[c] National Cancer Center Hospital, Tokyo, Japan; Department of General Thoracic Surgery,[d] Chiba University Graduate School of Medicine, Chiba, Japan; Division of General Thoracic Surgery,[e] Osaka City General Hospital, Osaka, Japan; Department of Oncology, Immunology, and Surgery,[f] Nagoya City University Graduate School of Medical Science and Medical School, Nagoya, Japan; Research Institute for Diseases of the Chest,[g] Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; Department of Medical Oncology,[h] Teikyo University School of Medicine, Tokyo, Japan; Department of Pulmonary Medicine,[i] Sapporo-Kosei General Hospital, Hokkaido, Japan; Division of Respiratory Disease,[j] National Defense Medical College, Saitama, Japan; Department of General Thoracic Surgery,[k] Osaka University Graduate School of Medicine, Osaka, Japan; and Department of Thoracic Surgery,[l] Nagoya University Graduate School of Medicine, Nagoya, Japan.

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Address for reprints: Kotaro Kameyama, MD, Department of Thoracic Surgery, Kurashiki Central Hospital, 1-1-1 Miwa, Kurashiki, Okayama 710-8602, Japan (E-mail: kk8724@kchnet.or.jp).

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For surgical cases of primary lung cancer, pleural lavage cytology (PLC) is a simple, easily done technique that provides a cytodiagnosis at the time of thoracotomy to evaluate subclinical pleural dissemination of cancer cells without pleural dissemination or pleural effusion. After a PLC result was first reported by Eagan and colleagues[1] in 1984, numerous studies have shown that PLC status is a prognostic factor for primary lung cancer.[2-22] In general, the frequency of positive results is <10% of patients who underwent PLC in the larger published series. In previous multiinstitution studies, a positive PLC result was suggested to be an independent prognostic factor and a predictor of tumor recurrence.[22-26]

However, PLC findings were not incorporated in the TNM Classification of Malignant Tumours.[27,28] In 2010, the

Abbreviations and Acronyms
IPLCC = International Pleural Lavage Cytology Collaborators
NSCLC = non–small cell lung cancer
PLC = pleural lavage cytology
UICC = Union for International Cancer Control

International Pleural Lavage Cytology Collaborators (IPLCC) reported the results of a meta-analysis and recommended that a single increase in the T category up to a maximum of T4 be assigned to patients with positive PLC results.[24]

The aim of our study was to retrospectively examine the clinical significance of PLC status and to illustrate the recommendations of the IPLCC. We used a large national database that were compiled by the Japanese Joint Committee of Lung Cancer Registry.[29,30]

PATIENTS AND METHODS

In 2010, the Japanese Joint Committee of Lung Cancer Registry performed a nationwide retrospective registry study on the prognosis and clinicopathologic profiles of resected lung neoplasms in Japan.[29,30] Only primary lung neoplasms that had been resected in 2004 at certified teaching hospitals in Japan were considered for the registry, which provided a follow-up period of at least 5 years. The committee received the registries of 11,663 patients from 253 teaching hospitals.

This registry followed the ethical guidelines for epidemiologic studies published jointly by the Japan Ministry of Science, Culture, and Education and the Japan Ministry of Health, Labor, and Welfare published June 17, 2002, which were revised August 16, 2007. In addition, it was approved by the institutional review board of Osaka University Medical Hospital, where the registry office is located, after discussions were published August 13, 2009 (approval No. 09124).

The patients in this study were 4171 patients who underwent PLC from among 11,073 patients with non–small cell lung cancer (NSCLC) (37.3%). Cases involving malignant pleural effusion were excluded. There were 2524 men and 1647 women. Adenocarcinoma was detected in 2977 patients, squamous cell carcinoma in 881 patients, large cell carcinoma in 149 patients, adenosquamous carcinoma in 81 patients, and other histologic types in 83 patients. The seventh edition of the Union for International Cancer Control (UICC) TNM classification system was used for the evaluations of TNM staging.[28] There were 1694 patients in stage IA, 1009 patients in stage IB, 378 patients in stage IIA, 262 patients in stage IIB, 703 patients in stage IIIA, 38 patients in stage IIIB, and 87 patients in stage IV. In our study, the PLC technique used had not been standardized. Induction therapy was performed in 199 patients (chemotherapy in 118 patients, radiation therapy in 6 patients, and chemoradiotherapy in 75 patients). Adjuvant chemotherapy was administered to 977 patients. These menus were not uniform.

To correct the prognoses according to the pathologic stages of patients with positive PLC results to patients with negative PLC results, pathologic stages were reevaluated based on the recommendations of the IPLCC: a single increase in the p-T category up to a maximum of T4 was assigned to patients with a positive PLC result (upstage).[24] Single increases in the T category upstaged T1a to T1b, T1b to T2a, T2a to T2b, T2b to T3, and T3 to T4. Pathologic stages were rearranged according to the upstaged T categories.

Categorical data are presented as frequency and continuous data are presented as means with standard deviations. Comparisons of categorical data between the 2 groups were made using χ^2 tests or Fisher exact tests where appropriate and continuous data were compared using 2-tailed t test. The survival time was measured from the date of surgery to the death date or the last follow-up date. The survival curves were estimated by using the Kaplan-Meier method. Differences in survival were assessed by the log-rank test. Multivariate analyses of prognostic factors were carried out using Cox proportional hazard regression models. A P value <.05 was considered to be significant.

RESULTS

Among 4171 patients who underwent PLC, 217 patients (5.2%) had positive PLC results (Table 1). Patients with positive PLC results had larger tumors ($P < .0001$) and more frequently adenocarcinoma in the histology ($P < .0001$), advanced stage ($P < .0001$), and pleural invasion ($P < .0001$) in comparison with those who were PLC-negative.

Sixty-five percent of patients with positive PLC and 29.2% of PLC-negative patients developed recurrence within 5 years after surgery ($P < .0001$). The 5-year survival was 44.5% for patients with positive PLC results and was 72.8% for patients with negative PLC results ($P < .0001$) (Figure 1). By multivariate analysis using a Cox proportional hazard regression model, PLC status (hazard ratio, 1.57; 95% confidence interval, 1.276-1.919; $P < .0001$) and other clinical factors (ie, gender, age, T category, N category, M category, and tumor size) were independent prognostic factors (Table 2).

Comparisons of the survival between patients with positive and negative PLC results according to T categories revealed significant differences in T2a ($P < .0001$) and T3 ($P = .0184$) (Figure 2 and Table 3). In addition, comparisons of the survival between patients with positive and negative PLC results according to pathologic stages revealed significant differences in stage IB ($P = .0062$) and stage IIIA ($P = .0115$) (Table 3). Based on the recommendations of the IPLCC, if a single increase in the T category up to a maximum of T4 was assigned to a patient with a positive PLC result, the significant difference in survival disappeared between the 2 groups in all T categories and stages. (Figure 3 and Table 4).

DISCUSSION

Body cavity fluid cytology is a simple, easily done technique that provides an intraoperative cytodiagnostic evaluation of latent dissemination of cancer cells.[31] In surgical cases of abdominal malignant tumors, PLC status is an independent prognostic factor, as reflected in the UICC TNM classification for gastric, uterine, ovarian, and fallopian tube cancers.[28] PLC status is directly involved in the treatment strategy. However, PLC findings were not incorporated in the seventh edition of the UICC TNM staging system.[28,32] It is not known to what extent the noninclusion of PLC results affects treatment strategies.

In this study, 5.2% of patients who underwent PLC had positive results. When these patients were examined by T,

TABLE 1. Clinicopathologic characteristics according to pleural lavage cytology (PLC) results

Characteristic	Positive PLC	Negative PLC	*P* value
Age (y)	66.2 ± 9.9	66.3 ± 9.8	.9040
Gender			.0640
Male	118	2406	
Female	99	1548	
Histologic type			<.0001
Adenocarcinoma	193	2784	
Squamous cell carcinoma	19	862	
Others	5	308	
Surgical procedure			.0460
Pneumonectomy	9	121	
Lobectomy	177	3239	
Segmentectomy	14	321	
Wedge resection	10	234	
Others	7	38	
T category			<.0001
T1a	14	1147	
T1b	12	771	
T2a	138	1390	
T2b	9	186	
T3	35	394	
T4	9	66	
N category			<.0001
N0	109	3040	
N1	26	318	
N2	81	584	
N3	1	12	
M category			<.0001
M0	187	3886	
M1a	27	30	
M1b	3	38	
Pathologic stage			<.0001
IA	15	1679	
IB	60	949	
IIA	23	355	
IIB	12	250	
IIIA	74	629	
IIIB	4	34	
IV	29	58	
Tumor size (cm)	3.40 ± 1.63	2.99 ± 1.80	
Pleural factor			<.0001
pl 0	47	2759	
pl 1	56	669	
pl 2	85	229	
pl 3	25	279	
Not evaluated	4	18	
Total	217	3954	

PLC, Pleural lavage cytology.

N, and M categories and by pathologic stages, significantly higher percentages of advanced cases were seen among patients with positive PLC results compared with patients with negative PLC results. Patients with positive PLC results also had significantly larger tumors than those who were PLC-negative. A significantly higher percentage of

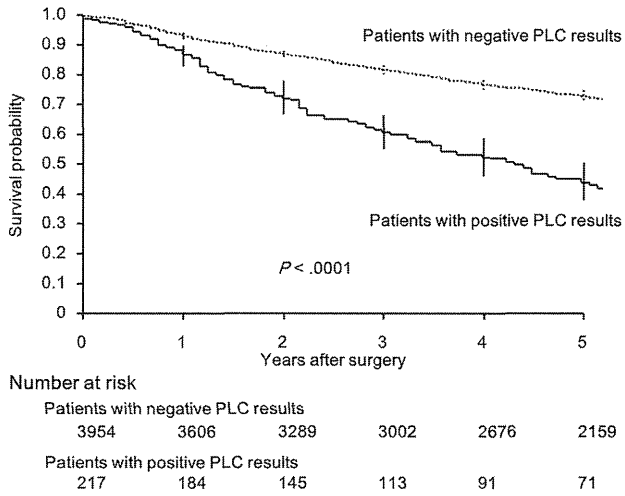

FIGURE 1. Postoperative survival curves based on pleural lavage cytology (*PLC*) status. There was a significant difference between patients with positive and negative PLC results ($P < .0001$). The *solid line* indicates patients with positive PLC results and the *dashed line* indicates patients with negative PLC results. The *vertical bars* indicate 95% confidence intervals.

pleural invasion was evident among patients with positive PLC results compared with those who were PLC-negative. These characteristics are consistent with those described in previous reports.[1,9,10,12,14,19] In our study, the 5-year survival was 44.5% for patients with positive PLC results and 72.8% for patients with negative PLC results, which indicated a significantly worse prognosis for patients with positive PLC results. A multivariate analysis revealed that PLC finding is an independent prognostic

TABLE 2. Multivariate analysis for prognostic factors

Prognostic factor	Hazard ratio	95% Confidence interval	*P* value
Positive PLC	1.57	1.276-1.919	<.0001
Male gender	1.66	1.460-1.894	<.0001
Age, per year	1.03	1.023-1.036	<.0001
T category			
T1a	1.00	—	—
T1b	1.59	1.266-1.990	<.0001
T2a	2.01	1.645-2.461	<.0001
T2b	2.79	2.048-3.794	<.0001
T3	2.94	2.271-3.807	<.0001
T4	3.87	2.692-5.564	<.0001
N category			
N0	1.00	—	—
N1	1.76	1.459-2.111	<.0001
N2	3.13	2.735-3.580	<.0001
N3	9.27	5.083-16.913	<.0001
M category			
M0	1.00	—	—
M1a	1.89	1.349-2.643	<.0001
M1b	4.02	2.601-6.206	<.0001
Tumor size (cm)	1.05	1.014-1.085	.006

PLC, Pleural lavage cytology.

GTS

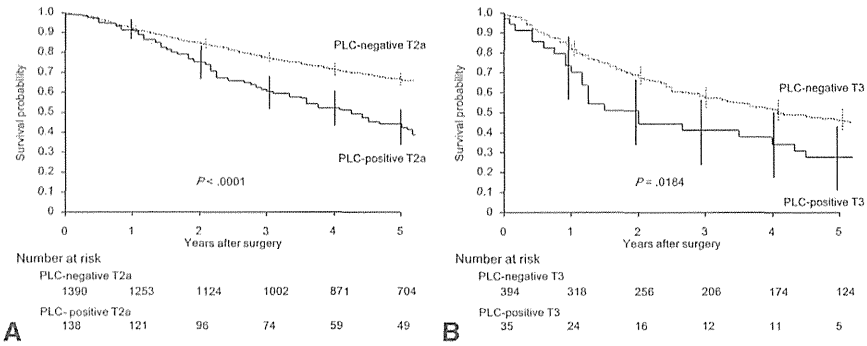

FIGURE 2. Comparisons of survival curves between patients with positive and negative pleural lavage cytology (*PLC*) results based on T categories. A, There was a significant difference between PLC-positive T2a and PLC-negative T2a ($P < .0001$). B, There was a significant difference between PLC-positive T3 and PLC-negative T3 ($P = .2261$). *Solid lines* indicate patients with positive PLC results and *dashed lines* indicate patients with negative PLC results. The *vertical bars* indicate 95% confidence intervals.

factor with a hazard ratio of 1.57. PLC status has been suggested to be an independent prognostic factor in previous reports.[6,12,14,16,19,21] Some reports only recognized certain stages as an independent factor and other reports stated that PLC status was not an independent prognostic factor.[17,18] Recent studies that used meta-analyses have shown that PLC status is an independent prognostic factor.[23,24,26] However the time periods considered in these studies covered a wide range. In our study, patients were limited to those who underwent surgery during 2004; thus, patients were evaluated and treated according to a relatively standardized procedure.

The prognoses for patients with positive and negative PLC results were compared by T category and pathologic stage based on the seventh edition of the UICC TNM classification. Significant differences in survival were found between the patients with positive and negative PLC results within the same T category and stage, including T2a, T3, stage IB, and stage IIIA. One reason for these findings may be differences in the number of patients in each group. For example, the T2a and T3 stages included more patients than the other T subclassifications. Similarly, the stage IB and stage IIIA categories included more patients than the other subgroups. Based on the sixth edition of the UICC TNM classification, the IPLCC recommended that a single increase in the T category up to a maximum of T4 be assigned to those with positive PLC results.[24] We performed a single increase in the T category based on the seventh edition of the TNM classification. The significant differences in the survival between patients with positive and negative PLC results disappeared for all T categories and stages.

TABLE 3. Comparisons of survival rates between patients with positive and negative pleural lavage cytology (PLC), according to T categories and pathologic stages

	Positive PLC		Negative PLC		
Category or stage	n	5-y survival (%)	n	5-y survival (%)	*P* value
T category					
T1a	14	76.2	1147	88.3	.2977
T1b	12	71.3	771	79.2	.1951
T2a	138	45.1	1390	67.7	<.0001
T2b	9	25.0	186	53.7	.1100
T3	35	27.7	394	46.4	.0184
T4	9	19.4	66	36.2	.9587
Pathologic stage					
IA	15	100	1679	88.8	—
IB	60	61.5	949	77.1	.0062
IIA	23	48.3	355	62.9	.0833
IIB	12	37.0	250	51.8	.5496
IIIA	74	26.4	629	42.5	.0115
IIIB	4	37.5	34	20.2	.2912
IV	29	27.8	58	30.3	.4962
Total	217	44.5	3954	72.8	<.0001

PLC, Pleural lavage cytology.

The significance of incorporating PLC findings into the TNM classification system is reflected in the treatments for upstaged patients, such as the addition of adjuvant therapy or a change to a more effective adjuvant therapy. There have been some proposals for incorporating PLC findings in the TNM classification system in which patients with positive PLC results were classified into T3 disease,[25] T4 disease,[9,21] or stage IIIB disease.[14] However there was no consensus among these proposals because most of these series were too small for detailed analysis. Moreover, because PLC status is related to multiple prognostic factors, it may be inappropriate for patients with positive PLC results to be classified into a single T category or single stage. The IPLCC recommendation should be the most reliable proposal because it is based on an exploratory statistical model using data from a multiinstitution study.

This study is associated with several limitations that should be considered when interpreting the results. First, the PLC technique has not been standardized. The IPLCC recommends that 100 mL saline be irrigated over the lung

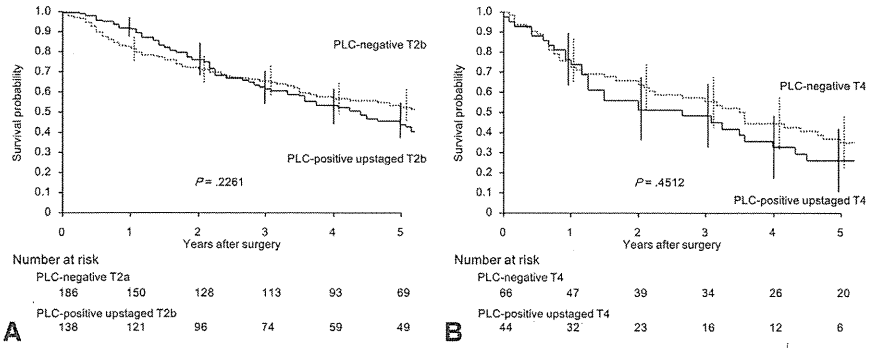

FIGURE 3. Comparisons of survival curves between patients with positive and negative pleural lavage cytology (*PLC*) results according to reevaluations based on International Pleural Lavage Cytology Collaborators recommendations. A, There was no significant difference between PLC-positive upstaged T3 and PLC-negative T3. B, There was no significant difference between PLC-positive upstaged T4 and PLC-negative T4. *Solid lines* indicate patients with positive PLC results and *dashed lines* indicate patients with negative PLC results. The *vertical bars* indicate 95% confidence intervals.

surface immediately after thoracotomy and before lung resection, after which the saline is aspirated and a sample is sent for cytologic screening for malignant cells.[24] In addition, patients with positive PLC results after pulmonary resection have a worse prognosis than those with positive PLC results immediately after thoracotomy.[16,20,21] The finding of a positive PLC result after pulmonary resection is thought to involve human factors associated with surgical manipulation,[11] and the PLC results obtained immediately after thoracotomy may more accurately reflect the biologic malignancy of lung cancer. Second, only 37.3% of NSCLC patients had PLC in this study. One reason for this finding is that the value of PLC has not been recognized in many institutions. In our study, patients who underwent PLC were not compared with the excluded patients. However, 94.8% of patients who underwent PLC were PLC-negative, with clinicopathologic characteristics similar to those of general NSCLC patients. Third, the patients with positive PLC results were significantly different from those with negative PLC results. Matching may equalize this inequality and permit true exploration of the effects of PLC in similar patients. However, we did not match the patients because the aim of our study was to retrospectively examine the clinical significance of the PLC status and illustrate the recommendations of the IPLCC based on an exploratory statistical model using data obtained from a multiinstitution study.[24] Fourth, we did not investigate the incidence of pleural recurrence, although PLC-positive patients had more episodes of recurrence than PLC-negative patients within 5 years after surgery. Patients with positive PLC results have been reported to have a high incidence of pleural recurrence.[19,25,26,33] Other reports have indicated that local intrapleural therapy is effective for local control, although this treatment does not improve survival.[18,34] Because the PLC findings affect all T, N, and M categories, the administration of systemic adjuvant chemotherapy may be effective in patients with positive PLC results. The importance of incorporating PLC results into the TNM classification will be recognized only if the effectiveness of adjuvant chemotherapy is demonstrated prospectively in patients with positive PLC results.

TABLE 4. Comparisons of survival rates between patients with positive and negative pleural lavage cytology (PLC), according to upstaged T categories and reevaluated pathologic stages

	Positive PLC		Negative PLC		
Category or stage	n	5-y survival (%)	n	5-y survival (%)	*P* value
Upstaged T category					
T1a	—	—	1147	88.3	—
T1b	14	76.2	771	79.2	.9417
T2a	12	71.3	1390	67.7	.7518
T2b	138	45.1	186	53.7	.2261
T3	9	25.0	394	46.4	.2568
T4	44	27.6	66	36.2	.4512
Reevaluated pathologic stage					
IA	8	100	1679	88.8	—
IB	7	100	949	77.1	—
IIA	62	61.2	355	62.9	.8223
IIB	21	48.0	250	51.8	.6953
IIIA	70	29.6	629	42.5	.1234
IIIB	20	23.6	34	20.2	.8662
IV	29	27.8	58	30.3	.4962
Total	217	44.5	3954	72.8	<.0001

PLC, Pleural lavage cytology.

CONCLUSIONS

PLC status was an independent prognostic factor in patients with NSCLC who had been surgically treated. Based on the recommendations of the IPLCC, if a single increase in the T category up to a maximum of T4 is assigned to a patient with a positive PLC result, the significant difference in survival disappears between the 2 groups in all T categories and stages. This recommendation appears to be an appropriate method for incorporating PLC findings into the seventh edition of the UICC TNM

classification. The implications of incorporating PLC findings into the TNM classification system is reflected in the treatments for upstaged patients, such as the addition of adjuvant therapy or a change to a more effective adjuvant therapy.

We hope that PLC findings will be incorporated in the next revision of the UICC TNM classification.

References

1. Eagan RT, Bernatz PE, Payne WS, Pairolero PC, Williams DE, Goellner JR, et al. Pleural lavage after pulmonary resection for bronchogenic carcinoma. *J Thorac Cardiovasc Surg*. 1984;88:1000-3.
2. Kondo H, Naruke T, Tsuchiya R, Goya T, Suemasu K, Yamagishi K, et al. Pleural lavage cytology immediately after thoracotomy as a prognostic factor for patients with lung cancer. *Jpn J Cancer Res*. 1989;80:233-7.
3. Buhr J, Berghauser KH, Morr H, Dobroschke J, Ebner HJ. Tumor cells in intraoperative pleural lavage. An indicator for the poor prognosis of bronchogenic carcinoma. *Cancer*. 1990;65:1801-4.
4. Okumura M, Ohshima S, Kotake Y, Morino H, Kikui M, Yasumitsu T. Intraoperative pleural lavage cytology in lung cancer patients. *Ann Thorac Surg*. 1991;51:599-604.
5. Kondo H, Asamura H, Suemasu K, Goya T, Tsuchiya R, Naruke T, et al. Prognostic significance of pleural lavage cytology immediately after thoracotomy in patients with lung cancer. *J Thorac Cardiovasc Surg*. 1993; 106:1092-7.
6. Buhr J, Berghauser KH, Gonner S, Kelm C, Burkhardt EA, Padberg WM. The prognostic significance of tumor cell detection in intraoperative pleural lavage and lung tissue cultures for patients with lung cancer. *J Thorac Cardiovasc Surg*. 1997;113:683-90.
7. Higashiyama M, Doi O, Kodama K, Yokouchi H, Tateishi R, Horai T, et al. Pleural lavage cytology immediately after thoracotomy and before closure of the thoracic cavity for lung cancer without pleural effusion and dissemination: clinicopathologic and prognostic analysis. *Ann Surg Oncol*. 1997;4:409-15.
8. Dresler CM, Fratelli C, Babb J. Prognostic value of positive pleural lavage in patients with lung cancer resection. *Ann Thorac Surg*. 1999;67:1435-9.
9. Okada M, Tsubota N, Yoshimura M, Miyamoto Y, Maniwa Y. Role of pleural lavage cytology before resection for primary lung carcinoma. *Ann Surg*. 1999; 229:579-84.
10. Ichinose Y, Tsuchiya R, Yasumitsu T, Koike T, Yamato Y, Nakagawa K, et al. Prognosis of non-small cell lung cancer patients with positive pleural lavage cytology after a thoracotomy: results of the survey conducted by the Japan Clinical Oncology Group. *Lung Cancer*. 2001;31:37-41.
11. Kotoulas C, Lazopoulos G, Karaiskos T, Tomos P, Konstantinou M, Papamichalis G, et al. Prognostic significance of pleural lavage cytology after resection for non-small cell lung cancer. *Eur J Cardiothorac Surg*. 2001;20: 330-4.
12. Okada M, Sakamoto T, Nishio W, Uchino K, Tsuboshima K, Tsubota N. Pleural lavage cytology in non-small cell lung cancer: lessons from 1000 consecutive resections. *J Thorac Cardiovasc Surg*. 2003;126:1911-5.
13. Riquet M, Badoual C, Le Pimpec Barthes F, Lhote FM, Souilamas R, Hubsch JP, et al. Visceral pleura invasion and pleural lavage tumor cytology by lung cancer: a prospective appraisal. *Ann Thorac Surg*. 2003;75:353-5.
14. Lim E, Ali A, Theodorou P, Nicholson AG, Ladas G, Goldstraw P. Intraoperative pleural lavage cytology is an independent prognostic indicator for staging non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2004;127:1113-8.
15. Vicidomini G, Santini M, Fiorello A, Parascandolo V, Calabro B, Pastore V. Intraoperative pleural lavage: is it a valid prognostic factor in lung cancer? *Ann Thorac Surg*. 2005;79:254-7.
16. Enatsu S, Yoshida J, Yokose T, Nishimura M, Nishiwaki Y, Shirakusa T, et al. Pleural lavage cytology before and after lung resection in non-small cell lung cancer patients. *Ann Thorac Surg*. 2006;81:298-304.
17. Nakagawa T, Okumura N, Kokado Y, Miyoshi K, Matsuoka T, Kameyama K. Clinical relevance of intraoperative pleural lavage cytology in non-small cell lung cancer. *Ann Thorac Surg*. 2007;83:204-8.
18. Satoh Y, Hoshi R, Ishikawa Y, Horai T, Okumura S, Nakagawa K. Recurrence patterns in patients with early stage non-small cell lung cancers undergoing positive pleural lavage cytology. *Ann Thorac Surg*. 2007;83: 197-202.
19. Higashiyama M, Oda K, Okami J, Maeda J, Kodama K, Takenaka A, et al. Prognostic value of intraoperative pleural lavage cytology for lung cancer without carcinomatous pleuritis: importance in patients with early stage disease during long-term follow-up. *Eur J Cardiothorac Surg*. 2009;35:337-42.
20. Shintani Y, Ohta M, Iwasaki T, Ikeda N, Kanou T, Tomita E, et al. Intraoperative pleural lavage cytology after lung resection as an independent prognostic factor for staging lung cancer. *J Thorac Cardiovasc Surg*. 2009;137:835-9.
21. Aokage K, Yoshida J, Ishii G, Enatsu S, Hishida T, Nishimura M, et al. The impact on survival of positive intraoperative pleural lavage cytology in patients with non-small-cell lung cancer. *J Thorac Cardiovasc Surg*. 2010;139: 1246-52.
22. Mordant P, Rivera C, Legras A, Le Pimpec Barthes F, Riquet M. Current readings: the most influential and recent studies regarding resection of lung cancer in M1a disease. *Semin Thorac Cardiovasc Surg*. 2013;25:251-5.
23. Li YN, Shi HZ, Liang QL, Yang HB, Huang GM. Prognostic significance of pleural lavage cytology in patients with lung cancer: a meta-analysis. *Lung Cancer*. 2008;60:183-92.
24. Lim E, Clough R, Goldstraw P, Edmonds L, Aokage K, Yoshida J, et al. Impact of positive pleural lavage cytology on survival in patients having lung resection for non-small-cell lung cancer: An international individual patient data meta-analysis. *J Thorac Cardiovasc Surg*. 2010;139:1441-6.
25. Kaneda M, Yokoi K, Ito S, Niwa H, Takao M, Kondo R, et al. The value of pleural lavage cytology examined during surgery for primary lung cancer. *Eur J Cardiothorac Surg*. 2012;41:1335-41.
26. Saso S, Rao C, Ashrafian H, Ghaem-Maghami S, Darzi A, Athanasiou T. Positive pre-resection pleural lavage cytology is associated with increased risk of lung cancer recurrence in patients undergoing surgical resection: a meta-analysis of 4450 patients. *Thorax*. 2012;67:526-32.
27. Goldstraw P, International Association for the Study of Lung Cancer. *Staging manual in thoracic oncology*. Orange Park, FL: Editorial Rx Press; 2009.
28. Sobin LH, Gospodarowicz MK, Wittekind C; International Union against Cancer. *TNM classification of malignant tumours*. 7th ed. Hoboken, NJ: Wiley-Blackwell; 2010.
29. Sawabata N, Asamura H, Goya T, Mori M, Nakanishi Y, Eguchi K, et al. Japanese Lung Cancer Registry Study: first prospective enrollment of a large number of surgical and nonsurgical cases in 2002. *J Thorac Oncol*. 2010;5:1369-75.
30. Sawabata N, Miyaoka E, Asamura H, Nakanishi Y, Eguchi K, Mori M, et al. Japanese lung cancer registry study of 11,663 surgical cases in 2004: demographic and prognosis changes over decade. *J Thorac Oncol*. 2011;6: 1229-35.
31. Hermanek P, Hutter RV, Sobin LH, Wittekind C. International Union Against Cancer. Classification of isolated tumor cells and micrometastasis. *Cancer*. 1999;86:2668-73.
32. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol*. 2007;2:706-14.
33. Higashiyama M, Kodama K, Yokouchi H, Takami K, Nakayama T, Horai T. Clinical value of pleural lavage cytological positivity in lung cancer patients without intraoperative malignant pleuritis. Recurrent pattern based on semiquantitative analysis of tumor cells in pleural lavage. *Jpn J Thorac Cardiovasc Surg*. 2000;48:611-7.
34. Ichinose Y, Tsuchiya R, Koike T, Yasumitsu T, Nakamura K, Tada H, et al. A prematurely terminated phase III trial of intraoperative intrapleural hypotonic cisplatin treatment in patients with resected non-small cell lung cancer with positive pleural lavage cytology: the incidence of carcinomatous pleuritis after surgical intervention. *J Thorac Cardiovasc Surg*. 2002;123:695-9.

シンポジウム

3．診療ガイドラインの社会的意義と問題点
1）ガイドライン概観
～ガイドライン作成のコンセプトと社会的意義をどう考えるか～
（1）乳癌診療ガイドライン―Web化によるメリットと今後の展望―

中村　清吾

Key words：診療ガイドライン，EBM，NCCNガイドライン

1．これまでの診療ガイドラインの特徴と問題点

乳癌診療ガイドライン策定にあたっての基本的な作業工程は，図1に示す如く，まず，臨床家がしばしば遭遇するような診療上の疑問をClinical question（CQ）として掲げることから始まる．次に，各CQに基づく文献を図書館の司書の方と連携して検索（関連する一連の文献の中から，ハイレベルエビデンス或いは臨床上重要と思われる論文を漏れなく検索）し，参考とすべき論文を取捨選択する．さらにそれらを鵜呑みにすることなく，一つ一つを批判的に吟味して推奨グレードと推奨文ならびに解説を加えたものが基本形となっている．したがって，標準治療の骨子と，その背景にあるエビデンスを学ぶには最適のツールである．また，推奨文を作成するうえで採用した論文は，エビデンスレベルが一目瞭然にわかるように構造化抄録という統一フォーマットにしたがってアブストラクトを作っている（図2）．これは，EBMを重視した作成手順で，EBM教育で有名なMcMaster大学等があるカナダのオンタリオ州で作成されているものに近く，Canadian style guidelineとも称される．2004年に，薬物療法のガイドラインが，金原出版より出版され，その翌年に，残りの4分野（外科療法，放射線療法，検診・診断，予防・疫学）のガイドラインが刊行された．そして，次の年には，5分野すべてを対象に，患者向けにガイドラインをわかり易く解説した「乳癌ガイドラインの患者向け解説」を出版し，患者教育

昭和大学外科学講座乳腺外科学部門

110th Scientific Meeting of the Japanese Society of Internal Medicine：Symposium：3. Social Impacts and Controversial Points of Clinical Practice Guidelines；1）Overview of Guidelines：Concepts of making clinical practice guidelines and discussion on their social impacts,（1）Breast cancer practice guideline.

Seigo Nakamura：Division of Breast Surgical Oncology, Department of Surgery, Showa University School of Medicine, Japan.

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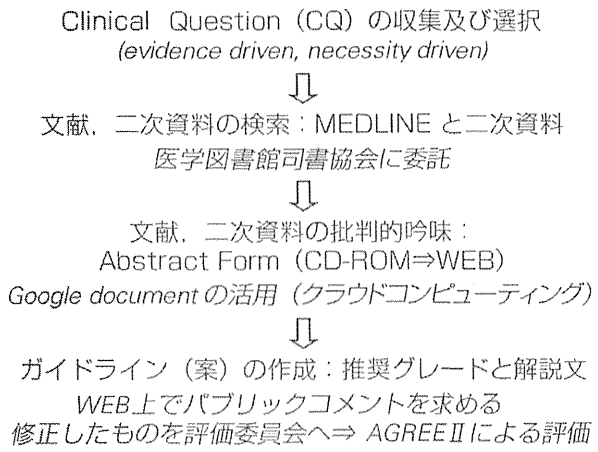

図 1．ガイドラインの作成手順 2011

や啓蒙に役立てるようにし，3 年間で一巡する仕組みとなった．これまで 7 年間で，全分野が少なくとも 2 回の改訂がおこなわれ，2010 年には，薬物療法の 3 度目の改訂がなされた．

しかし，①改訂は 3 年に 1 回のため，実診療とのギャップが生ずる②5 分冊化されており，日常診療の流れの中で使ううえで，使いにくい③本の場合には，ページ数の制限もあり，分冊化が必要となる，といった問題点が指摘されており，特に，日進月歩の薬物療法の領域では，3 年の間に標準治療の概念が大きく変わることもあり，抜本的な改善が必要であった．そこで，これらの問題点を一気に解決する手段として，Web化を進めることとなった．

2. Web化の特徴

Web版の最大の利点は，速報性にある．本の形で出す場合，その制作工程や，印刷の都合上，どんなに頑張っても年 1 回の改訂がせいぜいであるが，Web版は，原型さえ出来てしまえば，修正作業の多くは，作成者側で随時可能となり，随時一斉配信ができる．ページ数を気にする必要がないため，網羅性のある内容とすることが可能である．また，コンピュータならではの，豊富な検索機能が利用できるため，これまでの 5 分野を統合した利用が漸く実現できた（図 3）．

今回のWeb版では，NCCNのガイドライン日本語版とリンクし，フローチャートの分岐部に相当するCQがある場合は，その内容を瞬時に参照できるようにした．こうすることで，日米ガイドラインの相違点がわかり，特に早期に保険承認や適応拡大を要望すべき課題が明確化することを期待した．

また，Web版では，これまでの 5 分野ごとに作成したCQによる検索の他，キーワード入力により，関連CQ一覧を表示させ，その中から，自分が知りたいCQを参照するという方法を取り入れた他，NCCNガイドライン側から，アルゴリズムの分岐点となる根拠のCQにリンクし，その背景にある根拠を深く理解するといった使い方も可能とした．また，使用された論文は構造化抄録を参照でき，その概要やエビデンスレベル，特に主な結果を記憶に留めるのに役立つ．さらに，もっと深く理解したい場合は，PubMedにもリンクしているので，関連論文の検索や，論文そのものを入手する場合に有用である．

3. ガイドライン活用のポイント

まず，ガイドラインを理解するうえで，もっとも重要な点は，推奨グレードの意味するところである．表に日本乳がんガイドラインで採用している推奨グレードの定義を示す．

2009 年までは，A，B，C，Dの 4 段階であったが，ハイレベルエビデンスがないCQの場合，専門家のコンセンサスがどの程度得られているかを示すために，2010 年からは，グレードCをC1とC2 に分けた．さらに，C1，C2 に区分する際に，作成委員によるVotingを採用し，過半数の賛成が得られた場合をC1 とした（表）．なお，このVotingに際しては，予め提出されている日本乳癌学会が定めたCOIに該当するCQが抵触する場合は，自主的に外れてもらうようにした．

作成されたガイドラインは，AGREE（Appraisal of Guidelines for Research & Evaluation）IIとい

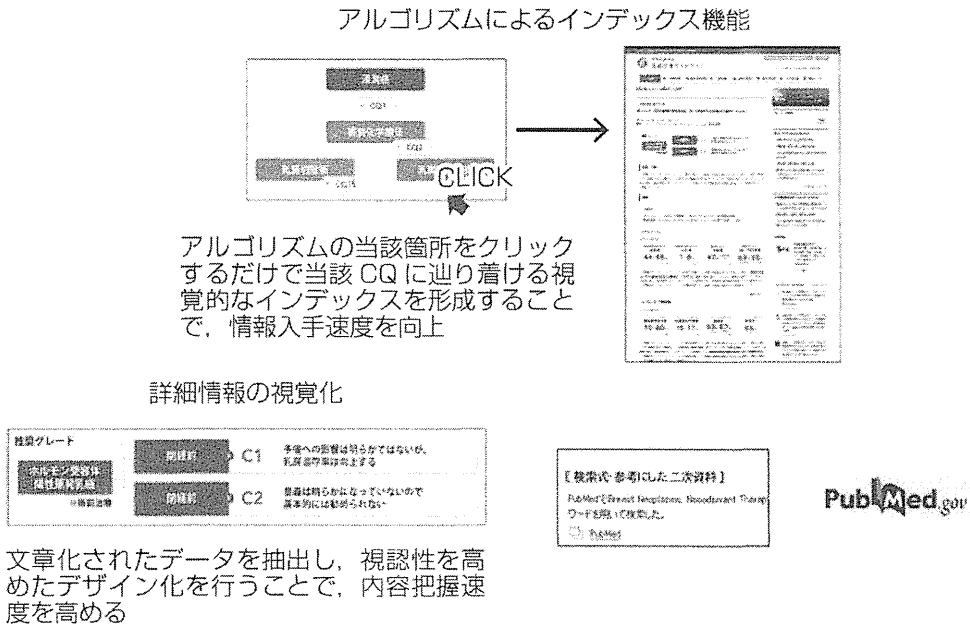

図 2.　Webの作成コンセプト：情報把握速度の向上

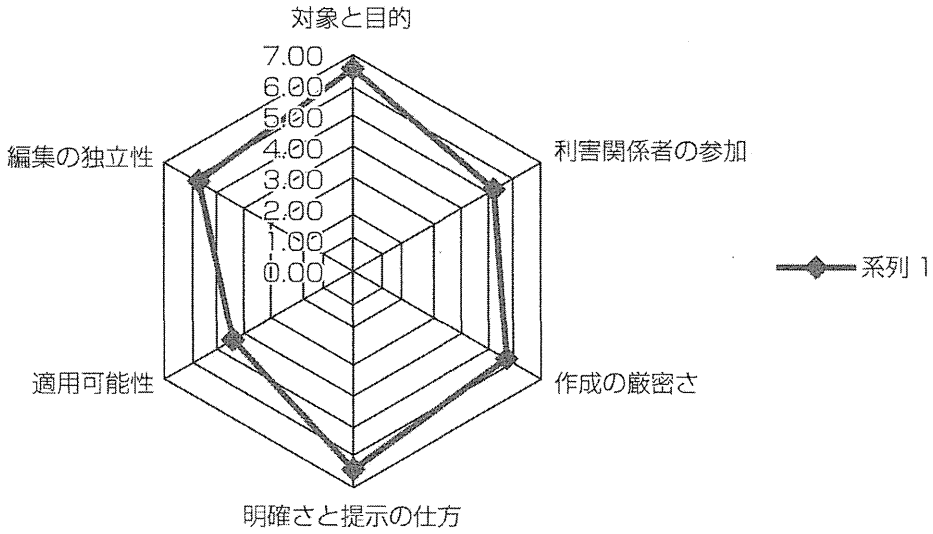

図 3.　AGREE Ⅱによる評価

うガイドラインの質的評価をするためのツールを用いて，別途独立して定められた評価委員会では，図 4 のような報告書が作成された．

また，日本乳癌学会規約委員会が作成した用語集にもリンクし，現時点でコンセンサスの得られている正しい表記が検索可能である．

4.　ガイドライン活用の実際

WEB版ガイドラインの活用法を具体的な症例をもとに紹介する．例えば，妊娠 20 週の女性が，5.4 cmという進行乳癌を呈して来院したと仮定する．妊娠期乳癌は，稀であり，その時々の標準治療を確認することは大変重要である．例えば，WEB版では，右上に，フリーワード検索という

表．乳癌診療ガイドライン推奨グレードの変更点

推奨グレード　2007年版	
A	十分なエビデンスがあり，推奨内容を日常臨床で積極的に実践するように推奨する
B	エビデンスがあり，推奨内容を日常臨床で実践するように推奨する
C	エビデンスは十分とはいえないので，日常臨床で実践する際は十分な注意を必要とする
D	患者に害悪，不利益が及ぶ可能性があるというエビデンスがあるので，日常臨床では実践しないよう推奨する
⬇	
推奨グレード　2010年版	
A	十分な科学的根拠があり，積極的に実践するように推奨する
B	科学的根拠があり，実践するように推奨する
C1	十分な科学的根拠はないが，細心の注意のもと行うことを考慮してもよい
C2	科学的根拠は十分とはいえず，実践することは基本的に勧められない
D	患者に不利益が及ぶ可能性があるという科学的根拠があるので，実践しないように推奨する

論文名	Ovarian ablation in Early Cancer : Overview.....
エビデンスレベル	1a
著者	EBCTCG
論文名，発行年，掲載ページ	Lancet 1996 : 348 : 1189-96
目的	早期乳癌に対する卵巣機能抑制の効果を.....
実施機関	EBCTCG
研究期間	1980-1995
対象患者	12のランダム化比較試験に登録された50歳未満の早期乳癌患者
介入	12のランダム化比較試験における，卵巣機能抑制群と無治療群のメタアナリシス（1995時点）
主たる評価項目	15年生存率，無病生存率
結果	卵巣機能抑制 対 無治療：52.4%：46.1% 2p=0.001.....
結論	卵巣機能抑制は，有意に15年生存率を高め.....
評価者	向井博文
コメント	12のランダム化比較試験をもとにしたメタアナリシスでは，卵巣切除を含む卵巣機能抑制は....

図4．構造化抄録の例

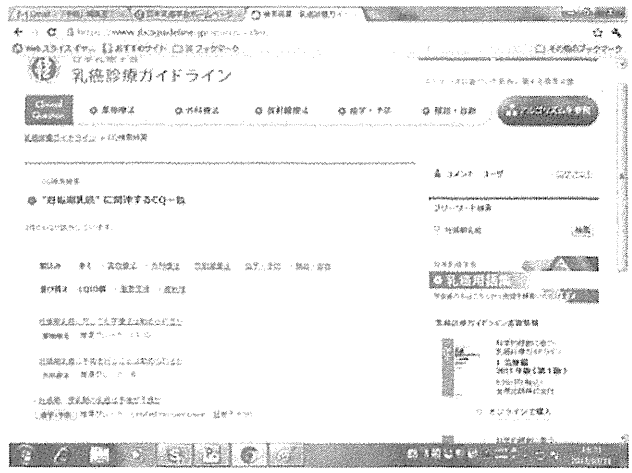

図5．Web版診療ガイドラインにおけるCQの検索例

カラムがあり，ここに「妊娠期乳癌」というキーワードを入れて検索してみる．すると，図5の如く，「妊娠期乳癌」という言葉が使われているCQの一覧が表示される．従来の書籍では，「薬物療法」「手術療法」等5分冊となっていたため，それぞれの本の索引から検索しなければならなかったが，今回のWEB版では，「妊娠期乳癌」というキーワードで一括検索が瞬時に可能となった．よく，妊娠期には化学療法は禁忌ではないかと誤解する向きがあるが，妊娠中期以降では，FACやPacritaxelなどを，投与することが可能であることが記載されている．手術に関しても妊娠中期以降であれば同様である．予防・疫学のガイドラインでは，Stageを合わせて比較すると，その予後は通常の乳癌と同様ではないかというエビデンスも紹介されている．また，本ガイドラインは，日本乳癌学会規約委員会で作られた用語集ともリンクしており，論文を記載する際，正しい用語を確認する等の場面で，大変便利である．この他，前述の如く，参考文献の構造化

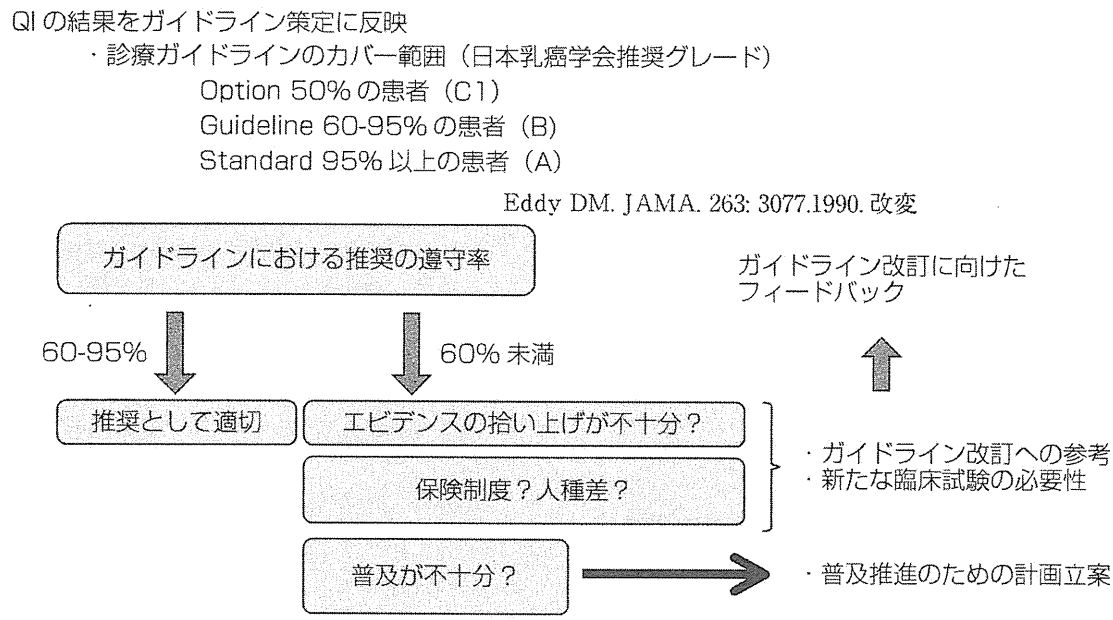

図6. 診療ガイドラインとQIの関係

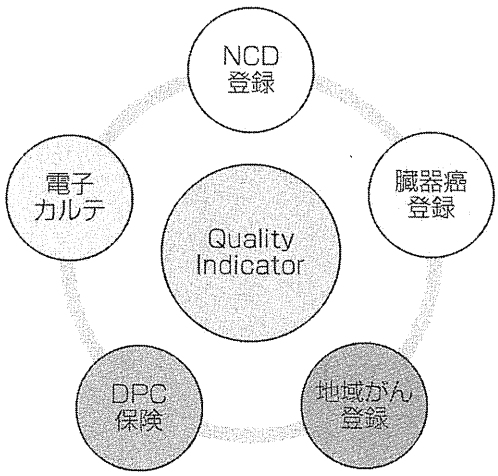

図7. 癌診療の質を測る指標の統合

抄録を参照したり，PubMed検索とのリンクもできるようになっている．さらに，NCCNの日本語版のフローチャートともリンクしているため，日常診療の流れから，該当CQを検索したり，海外の標準治療との相違を見比べることも可能である．

5. Quality Indicatorの設定と定期的な算出に向けて

日本乳癌学会では，診療ガイドラインが医療の質の向上に寄与しているか否かを把握するために，診療ガイドラインの中で，推奨レベルがAないしはBに相当するものが，どの程度遵守されているかを把握し，病院間の相違を公開（病院名は非公開）することで，年余を経てばらつきの是正につながることを期待した活動（QI小委員会）が始まった．第一段階として，CQの中から，QIに相応しいものを抽出し，それが，乳癌登録のデータから自動抽出ができるか否かの検討を行った(図6)．このことは，推奨グレードの見直しや，CQそのものの設定の是非を検討するうえでも役に立つ．

また，乳癌登録として設定した入力項目の改訂にも有用である．さらに，この作業を通じて，日本で行われている様々な登録システムにおける重複入力などの無駄を省き，連携を図ることの必要性を痛感した（図7）．

さいごに

診療ガイドラインのWeb化により，閲覧性の向上，情報検索の効率化が図られた．今後は，診療ガイドラインの順守率をもとに，QI値を定期的に算出及び公開し，医療の質の向上につなげるようにしていきたい．

著者のCOI(conflicts of interest)開示：中村清吾；講演料(アストラゼネカ，エーザイ，グラクソスミスクライン，大鵬薬品工業，中外製薬，ファイザー)，研究費・助成金(協和発酵キリン，日本癌治療学会)，寄付金(アストラゼナカ，エーザイ，大鵬薬品工業，中外製薬，バイエル薬品)

参考文献

1) https://www.jbcsguideline.jp/
2) 日本乳癌学会編：科学的根拠に基づく乳癌診療ガイドライン治療編 2011 年版．金原出版，2011.
3) 日本乳癌学会編：科学的根拠に基づく乳癌診療ガイドライン疫学・診断編 2011 年版．金原出版，2011.
4) 中村清吾：がん診療における医療の質の評価．昭和医学会雑誌　72：203–208, 2012.
5) 中村清吾：乳癌の治療戦略：概論(ガイドラインのアルゴリズム解説)，乳癌（第 2 版）日本臨床．70：489–492, 2012.
6) 中村清吾：Web化された乳癌診療ガイドラインの使い方．Cancer Board乳癌　4：193–196, 2011.

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2013 clinical practice guidelines (The Japanese Breast Cancer Society): history, policy and mission

Hirofumi Mukai · Shinzaburo Noguchi · Futoshi Akiyama · Hideo Inaji · Hirotaka Iwase · Jun Horiguchi · Junichi Kurebayashi · Koichi Hirata · Masakazu Toi · Masafumi Kurosumi · Norio Kohno · Reiki Nishimura · Seigo Nakamura · Shigeru Imoto · Takuji Iwase · Tokiko Endo · Toshiaki Saeki · Yasuhiro Ogawa · Yoshinori Ito · Yutaka Tokuda · Tadashi Ikeda

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History of breast cancer clinical practice guidelines

The breast cancer clinical practice guidelines, which were the first comprehensive guidelines for breast cancer in Japan, were developed with funding by a grant from the Ministry of Health, Labor and Welfare in 2002. It was decided that revisions of the guidelines should be made by the Japanese Breast Cancer Society thereafter.

The Japanese Breast Cancer Society established a clinical practice guidelines committee which also has a surgical therapy subcommittee, a screening and diagnosis subcommittee, a systemic therapy subcommittee, a radiation therapy subcommittee, an epidemiology and prevention subcommittee, and an evaluation subcommittee. The Japanese Breast Cancer Society published "Breast cancer clinical practice guidelines (1) systemic therapy" in 2004. Since then, the systemic therapy guidelines have been revised every 3 years for a total of four times. Guidelines for (2) surgical therapy, (3) radiation therapy, (4) screening and diagnosis, and (5) epidemiology and prevention have also been revised every 3 years for a total of three times since 2005. In 2006, inclusive "guidelines for patients" were developed covering all five areas. The guidelines for patients have also been revised twice so far. In 2011, the web version of the guidelines that integrates all areas was created to cover the remarkable changes in medical technology and systemic therapy in recent years (formally made available to the public on September 1, 2011). In addition, a print version has been published in two volumes of (1) treatment and (2) epidemiology and diagnosis since

This article is an English digested edition of the Nyugan Shinryo guideline 2013 nen ban, published by Kanehara & Co., LTD.

H. Mukai (✉)
Division of Breast and Medical Oncology, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa-shi, Chiba, Japan
e-mail: hrmukai@east.ncc.go.jp

S. Noguchi
Department of Breast and Endocrine Surgery, Osaka University Graduate School of Medicine, Osaka, Japan

F. Akiyama
Department of Pathology, The Cancer Institute Hospital of Japanese Foundation of Cancer Research, Tokyo, Japan

H. Inaji
Department of Breast Surgery, Kaizuka City Hospital, Osaka, Japan

H. Iwase
Department of Breast and Endocrine Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

J. Horiguchi
Department of Thoracic and Visceral Organ Surgery, Graduate School of Medicine, Gunma University, Maebashi, Japan

J. Kurebayashi
Department of Breast and Thyroid Surgery, Kawasaki Medical School, Okayama, Japan

K. Hirata
Department of Surgery, Surgical Oncology and Science, Sapporo Medical University School of Medicine, Sapporo, Japan

M. Toi
Department of Surgery (Breast Surgery), Graduate School of Medicine Kyoto University, Kyoto, Japan

M. Kurosumi
Department of Pathology, Saitama Cancer Center, Saitama, Japan

2011 in accordance with the web version so that it is easier to use in clinical practice.

Procedure for developing the 2013 edition

In 2011, it was decided to revise the guidelines every 2 years instead of the previous cycle of 3 years. The development of the 2013 edition started in October 2012. The specific steps are described below.

Steps 0 and 1 creation and decision of CQ

First, a policy meeting was held and a consensus for the work needed was reached among all the committee members. Thereafter, the work was performed in parallel in the following six areas: "systemic therapy", "surgical therapy", "radiation therapy", "epidemiology and prevention", "screening and imaging diagnostic", and "pathological diagnosis". Clinical questions (CQ) were determined by referring to the CQ of the 2011 edition and organizing them in discussions in each area.

Step 2 literature search

One committee member was in charge of 2–6 CQs. The committee members selected key words related to the CQs under consideration and these were presented to researchers (examples of key words: breast neoplasms, drug therapy, trastuzumab). Seven people from the Japan Medical Library Association were engaged as researchers. The key words were subjected to exhaustive searches until October, 2012. In addition to the searches described above, significant items from the literature were added by manual searches so as not to leave out relevant material. PubMed was used as the search database.

Step 3 thorough review of the literature and creation of the text

The committee members reviewed the retrieved literature and created commentary sentences for the CQs based on their reviews. During the comment preparation stage, guidelines that were already in existence in Japan and overseas and information from electronic media was actively utilized for the purpose of confirming the validity of the contents.

Step 4 mutual reviews by the committee members and completion of the final version

The draft created by each committee member was reviewed by another member within the same area. Then, the contents were reviewed by all the members covering that area to give a final version approved by the subcommittee.

Recommendation grades, evidence grades

Recommendation grades are shown in Table 1. Recommendation grades were determined based on the level of evidence of the key literature and the agreement of all committee members. As for recommendation grade C, either C1 or C2 was chosen by the votes of all members.

To clarify the interpretation of the grades of recommendations, the following were considered in the determination for each CQ.

N. Kohno
Department of Breast Oncology, Tokyo Medical University Hospital, Tokyo, Japan

R. Nishimura
Department of Breast and Endocrine Surgery, Kumamoto City Hospital, Kumamoto, Japan

S. Nakamura
Division of Breast Surgical Oncology, Department of Surgery, Showa University School of Medicine, Tokyo, Japan

S. Imoto
Department of Breast Surgery, School of Medicine, Kyorin University, Tokyo, Japan

T. Iwase
Department of Breast Surgical Oncology, Breast Oncology Center, The Cancer Institute Hospital of Japanese Foundation of Cancer Research, Tokyo, Japan

T. Endo
Department of Radiology, Nagoya Medical Center, Aichi, Japan

T. Saeki
Department of Breast Oncology, International Medical Center, Saitama Medical School, Saitama, Japan

Y. Ogawa
Department of Radiology, Kochi Medical School, Kochi, Japan

Y. Ito
Breast Medical Oncology, Breast Oncology Center, The Cancer Institute Hospital of Japanese Foundation of Cancer Research, Tokyo, Japan

Y. Tokuda
Department of Breast and Endocrine Surgery, Tokai University School of Medicine, Kanagawa, Japan

T. Ikeda
Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan