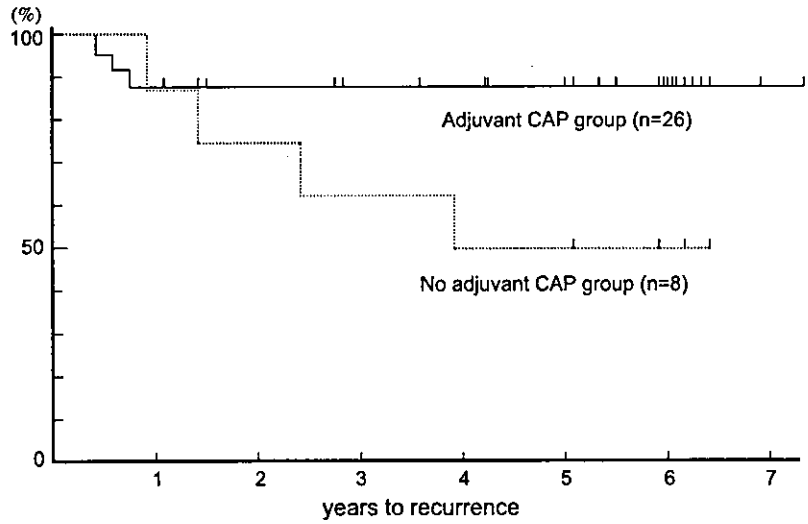

Fig. 2. Kaplan–Meier curve comparing disease-free survival in the high-risk group patients. The 5-year disease-free survival for patients treated with adjuvant chemotherapy was 88.5%, which was significantly better than 50.0% for patients without adjuvant chemotherapy ($P = 0.0150$).

cases. However, no toxic death occurred during the study period.

Discussion

There is consensus that patients with low-grade, noninvasive endometrial cancer should receive no further therapy. Adjuvant treatment for intermediate- or high-risk early stage endometrial cancer in improving survival has never been clearly proven, which may include the use of radiation, progestins, or cytotoxic chemotherapeutic agents, although which modality is best is still controversial. Most studies of adjuvant treatment have focused on external-beam irradiation. Expanding evidence exists to suggest that in node negative disease treatment planning can be more conservative to reduce patient morbidity while maintaining excellent survival. The trials performed include limiting postoperative radiotherapy to vault brachytherapy [10–12] or eliminating any adjuvant radiation. [13–15]. Growing trends are evident toward omission of any postoperative radiotherapy [16–19].

In most series of early endometrial cancer, however, distant recurrences have not been characterized in detail, or information correlating distant failure has not been provided. As shown in Table 4, local and distant recurrences occurred in 4.8% and 5.2%, respectively, in patients with surgical stage I and II using postoperative adjuvant radiation [11,16–18,20–29]. Furthermore, the fact that adjuvant radiotherapy is not effective in preventing distant disease is clearly demonstrated by two prospective randomized studies [17,30], which found that the rate of distant failure was not significantly higher in patients who did not receive adjuvant radiotherapy.

Pathologic factors suggested by many authors to have prognostic significance for patients with stage I and II disease have included the tumor grade, LVSI, the depth of myometrial invasion, cervical invasion, and the age of the

Table 2
Sites of recurrence by the risk group

Site of recurrence	No. of case				
	Low-risk group[a]		High-risk group[b]		
	CAP[c] (−) (n = 121)	CAP (+) (n = 15)	CAP (−) (n = 8)	CAP (+) (n = 26)	Total
Loco-regional					
Vaginal wall, stump	3	0	0	2	5
Distant					
Lung	0	0	3	1	4
Para-aortic nodes	0	0	1	0	1
Total	3	0	4	3	10

[a] Patients with no or one risk factor.
[b] Patients with two or more risk factors.
[c] Cyclophosphamide, doxorubicin, cisplatin.

Table 3
Chemotherapy-related toxicity

Toxicity	Grade* (n = 41)				
	0	1	2	3	4
Nausea or vomiting	9	19	11	2	0
Leucocytopenia or neutropenia	1	6	14	15	5
Anemia	10	20	9	2	0
Thrombocytopenia	24	11	4	2	0
Alopecia	3	28	10		–
Neurologic	31	8	2	0	0

* National Cancer Institute Common Toxicity Criteria, Ver. 2.

Table 4
Sites of recurrence in patients with surgical stage I or II endometrial carcinoma

Author	Stage	No. of patients	No. of adjuvant radiation received	Recurrent site		
				Local	Local + distant	Distant
DiSaia et al. [20]	I, II	174	27	4		9
Morrow et al. [3,21]	I, II	400	142	12		18
Anderson et al. [22]	I, II	64	64	2		3
Mariani et al. [23]	IB, IC	228	65	8		14
Creutzberg et al. [17]	IB, IC	714	354	59		51
Rittenberg et al. [24]	I	172	172	1	1	2
Ng et al. [11]	IB, IC	77	77	8		3
Straughn et al. [15,16]	IC	220	99	8		12
Horowitz et al. [25]	IB to IIB	164	164	3	1	9
Roberts et al. [18]	I, II	392	190	21	4	19
Ayhan et al. [26]	I	196	29	2	1	2
Alektiar et al. [27]	IB	251	22	6		11
Algan et al. [28]	I, II	98	98	6	7	4
Descamps et al. [29]	I, II	201	9	14		14
Total		3342	1512	155 (4.6%)	28 (0.8%)	175 (5.2%)

patients. The depth of myometrial invasion has been demonstrated to be a strong predictor of prognosis and distant recurrences in patients with stage I endometrial cancer [20,21,31,32]. Mariani et al. [23] reported that stage I endometrial cancer patients with myometrial invasion ≧66% are at significant risk for distant failure and death and should be considered candidates for new randomized trials of adjuvant systemic therapy. In the present analysis, because 33 of 40 patients with outer half of myometrial invasion received adjuvant CAP therapy, we could not find that deep myometrial invasion was a predictor of poor prognosis. LVSI has also previously demonstrated to be an important prognostic factor and a strong predictor of poor prognosis with distant failure in the subgroup of patients with superficial myometrial invasion and low-grade tumor [33]. In our series, multivariate analysis showed only LVSI was an independent prognostic factor. Among 29 patients with LVSI, 22 patients received postoperative chemotherapy, in which only three patients had recurrence (two local and one distant recurrence). However, the remaining seven patients who did not receive adjuvant CAP had three recurrences (two pulmonary and one para-aortic node). That is, the possibility of adjuvant CAP may prevent distant failure in patients with LVSI.

Because recurrent or metastatic endometrial tumors often respond to salvage treatment with cytotoxic agents [3–5], we have been using systemic CAP chemotherapy as a postsurgical adjuvant treatment for high-risk endometrial cancer patient instead of irradiation therapy. Adjuvant CAP therapy for FIGO surgical stage III patients achieved a favorable outcome in our institution [34], in which we also had relatively better 5-year disease-free survival rate of 78.9% and lower recurrence rate of 13/61 (21.3%) as compared to previous reports in which patients were treated with irradiation as postsurgical adjuvant therapy [35–37].

To select a high-risk subgroup that might benefit from adjuvant systemic therapy in patients with FIGO stage I or II, we divided stage I or II patients into low-risk group and high-risk group based on four prognostic factors (LVSI, tumor grade, cervical invasion, and depth of myometrial invasion). Survival in the low-risk group was excellent because only 3 isolated vaginal recurrences out of 136 patients occurred, in which these three patients did not receive adjuvant CAP. The 5-year disease-free survival and the 5-year overall survival for the low-risk group were 97.4% and 100%, respectively. In the low-risk 136 patients, 15 cases were treated with postoperative chemotherapy. Eleven patients had only deep myometrial invasion, three had only LVSI, and one had only grade 3 tumor as their adverse pathologic factor. Also, 15 patients with only one adverse pathologic factor did not receive adjuvant CAP, in which nine patients had grade 3 tumor, three had deep myometrial invasion, two had LVSI, and one had cervical involvement. There is a possibility that postoperative adjuvant CAP may be omitted in surgical stage I or II endometrial cancer patients with only one prognostic factor.

In the high-risk group, on the other hand, disease-free survival and overall survival rates were significantly much lower as compared to the low-risk group ($P < 0.001$). Among high-risk group patients, 26 patients treated with adjuvant chemotherapy had significantly more favorable prognosis as compared to eight cases that underwent only surgery. Disease recurrence occurred in 7 (20.6%) of 34 high-risk group patients. Four of seven recurrences occurred in patients who did not receive postoperative chemotherapy, in which all four were distant failure. In the remaining three patients who were in the CAP group, two had vaginal wall recurrence and only one had pulmonary recurrence. The high-risk group of patients should be treated with postoperative adjuvant CAP to decrease distant failure and improve prognosis. Clearly, the relatively small number of patients seen in this study will limit the power of these conclusions. Further investigation should be required to define the

subgroup of patients who benefit from postoperative adjuvant chemotherapy.

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British Journal of Cancer (2004) 90, 646–651

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Epidemiology

Filter cigarette smoking and lung cancer risk; a hospital-based case–control study in Japan

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Recent changes in the histology of lung cancer, namely a relative increase of adenocarcinoma compared to squamous cell carcinoma, might be due to a temporal shift from nonfilter to filter cigarettes. To investigate the association between type of cigarette and lung cancer by histological type, we conducted a case–control study in Japan, comprising 356 histologically confirmed lung cancer cases and 162 controls of male current smokers, who provided complete smoking histories. Overall, logistic regression analysis after controlling for age and prefecture revealed decreased risk, as shown by adjusted odds ratios, for both squamous cell carcinoma and adenocarcinoma among lifelong filter-exclusive smokers as compared to nonfilter or mixed smokers. This decrease was greater for squamous cell carcinoma than for adenocarcinoma. Among men under 54 years, filter-exclusive smokers displayed increased risk of adenocarcinoma, but decreased risk of squamous cell carcinoma. The recent shift in histology from squamous cell carcinoma to adenocarcinoma, particularly among younger smokers, might be due to changes in cigarette type. However, among subjects aged 65 years or more, no differences in histological type appeared related to type of cigarette smoked, implying that other factors are associated with increases in adenocarcinoma among older Japanese population.
British Journal of Cancer (2004) **90,** 646–651. doi:10.1038/sj.bjc.6601565 www.bjcancer.com

Keywords: lung cancer; histological type; filter and nonfilter cigarettes; hospital-based case–control study; Japan

Recently, the overall incidence of lung cancer has increased in Japan. However, incidence by histological type has shown a changing pattern. A relative increase in incidence of adenocarcinoma (AC), as compared to squamous cell carcinoma (SCC), has been observed, particularly for the younger age group (Tanaka *et al*, 1988; Yoshimi *et al*, 2003). While the same trends have been demonstrated in Western countries (Levi *et al*, 1997; Russo *et al*, 1997; Skuladottir *et al*, 2000; Janssen-Heijnen *et al*, 2001), AC accounts for a larger proportion of all lung cancer in Japan (Parkin *et al*, 1992). These relative increases in AC do not appear attributable to changes in pathological diagnosis alone (Charloux *et al*, 1997).

Changes in the composition of cigarettes, such as content of tar and nicotine, might influence lung cancer trends. The market share held by high-tar nonfilter cigarettes was almost completely taken over by low-tar filter cigarettes in the 1960s in both Japan and Western countries (Wynder *et al*, 1991). The links between changes in histology of lung cancer and type of cigarettes have led to the hypothesis that the type of cigarette, that is, filter or nonfilter, is associated with changing histological patterns of lung cancer. Several epidemiological studies have found that the effect of low-tar filter cigarettes on lung cancer risk differs according to histological type of tumour (Wynder and Kabat, 1988; Stellman *et al*, 1997). However, to date, no studies have examined possible relationships between type of cigarette and lung cancer risk by histological type in Asian populations. The present study explored the relationship between type of cigarettes smoked and lung cancer histology in Japan, focusing on differences between SCC and AC, by means of a multicentre, hospital-based case–control study.

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Received 12 September 2003; revised 12 November 2003; accepted 12 November 2003

MATERIALS AND METHODS

A multicentre, hospital-based case–control study was conducted in 17 hospitals that participated in the Osaka Anti-Lung Cancer Association in Osaka prefecture, two hospitals in Okinawa prefecture, and one hospital in Nagano prefecture in Japan. In participating hospitals, patients were recruited from all lung cancer wards, in addition to one or more wards for other diseases. Study subjects comprised patients who were newly admitted to the participating hospitals from January 1996 to December 1998. A total of 1324 patients (945 men and 379 women) were admitted with newly diagnosed lung cancer. All lung cancer cases were confirmed microscopically. Controls comprised 3600 patients (2169 men and 1431 women) who were admitted to the same

hospitals during the same period with diseases other than lung cancer. Of the 3600 controls, 2348 patients with diseases related to smoking were excluded, that is, no patients with respiratory tuberculosis (ICD-10: A15, 16, 19, B90), respiratory infection (A31), neoplasm (C00-D48), inguinal hernia (K40), ischaemic heart disease (I20-I25), subarachnoid haemorrhage (I60), arterial disease (I70-I73), respiratory disease (J00-J99), peptic ulcer (K25-K27), or respiratory symptoms (R04, R06, R09) were included in the study. After further exclusion of subjects $\leqslant 39$ or $\geqslant 80$ years (65 cases and 286 controls) and subjects who did not provide complete information on current smoking habits (104 cases and 86 controls), 1115 lung cancer cases and 880 controls remained for analysis.

Among the 880 controls, distribution of diagnoses was as follows: 19% ear and mastoid (H60-H95); 16% digestive system (K00-K93); 12% nervous system (G00-G99); 9% circulatory system (I00-I99); 9% endocrine, nutritional and metabolic (E50-90); 8% symptoms, signs, and abnormal clinical and laboratory findings not elsewhere classified (R00-R99); 5% infectious and parasitic (A00-B99); 5% musculoskeletal system and connective tissue (M00-M99); 4% genitourinary system (N00-N99); 4% injury, poisoning, and certain other consequences of external causes (S00-T98); 3% blood and blood-forming organs and certain disorders involving the immune mechanisms (D50-D89); 3% skin and subcutaneous tissue (L00-L99), 3% congenital malformations, deformations, and chromosomal abnormalities (Q00-Q99) and less than 2% for other categories.

Information on smoking history and other lifestyle factors was obtained by means of a self-administered questionnaire completed during admission. Current smoking status was confirmed using a closed question. Detailed smoking histories were then obtained from current and former smokers by means of open questions regarding ages at which smoking habits changed substantially; information on number of cigarettes smoked per day and type of cigarettes (filter, nonfilter, or others) was requested for each period.

To investigate associations between type of cigarette (filter/nonfilter) and histological type of lung cancer, we further examined male current smokers (356 cases and 162 controls) for whom complete smoking histories regarding filter/nonfilter cigarettes were available. Owing to the small number of female current smokers with complete smoking histories, this analysis was restricted to male current smokers. Duration of nonfilter or filter use was calculated separately, based on the history of smoking. Current smokers were categorised into two groups: 'filter-exclusive smokers' comprised men who were lifetime smokers of filter cigarettes; 'mixed or nonfilter smokers' were men who had smoked nonfilter cigarettes at some point. Any history of cigarette use before 1957, when filter cigarettes first became commercially available in Japan, was regarded as nonfilter cigarette use. The mean number of cigarettes per day was defined as the weighted mean of each average number of filter and nonfilter cigarettes smoked per day. Total duration was defined as the sum of durations of filter and nonfilter smoking. Subjects who reported smoking other types of cigarettes were excluded from the analysis.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression analysis in order to estimate the risk of lung cancer by histological type. Statistical adjustment was made for age (continuous variable) and prefecture (three categories). Adjusted ORs in relation to type of cigarettes were presented with and without adjustment for mean number of cigarettes smoked per day (continuous variable). All statistical computations were performed using PC-SAS (SAS Institute Inc., Cary, NC, USA).

RESULTS

Prevalences of SCC, AC, small cell carcinoma, large cell carcinoma, and unknown histology were 34.3, 44.0, 11.3, 3.9 and 6.4% for men and 8.9, 75.6, 7.6, 2.8, and 5.1% for women, respectively.

Current cigarette smoking was associated with increased risk of overall lung cancer, SCC and AC; adjusted ORs of current smokers as compared to nonsmokers were 4.56 (95% CI: 3.00-6.94) for all lung cancers, 24.5 (95% CI: 7.39-80.9) for SCC, and 2.56 (95% CI: 1.61-4.07) for AC, respectively, for men, and 2.29 (95% CI: 1.44-3.64) for all lung cancers, 10.9 (95% CI: 3.99-30.0) for SCC, and 1.48 (95% CI: 0.87-2.51) for AC, respectively, for women.

Adjusted ORs for lung cancer in relation to duration of smoking and number of cigarettes per day are presented by sex in Tables 1 and 2. For men, adjusted ORs among current smokers as compared to lifelong nonsmokers increased with longer duration of smoking and increasing number of cigarettes per day, irrespective of histological type of lung cancer (Table 1). The adjusted OR for SCC was much higher than that for AC. Male former smokers displayed an approximately 14-fold increase in risk of SCC, whereas elevation in the adjusted OR for AC was two-fold.

Similarly, in women, increasing risk regardless of lung cancer histology (as indicated by adjusted OR) with increasing intensity of smoking was observed among current smokers (Table 2). Adjusted ORs for SCC were much greater than those for AC. Female former smokers were only at significant elevated risk for SCC.

Table 1 Adjusted odds ratios (ORs) for lung cancer associated with cigarette smoking by histological type among men

		Cases					
		Squamous cell carcinoma		Adenocarcinoma		All lung cancers	
Smoking status	Controls No.	No.	Adjusted[a] OR (95% CI)	No.	Adjusted[a] OR (95% CI)	No.	Adjusted[a] OR (95% CI)
Nonsmoker	90	3	1.00 (reference)	30	1.00 (reference)	40	1.00 (reference)
Past smoker	161	87	13.9 (3.16-61.0)	120	1.95 (1.09-3.50)	246	2.46 (1.47-4.12)
Current smoker							
Duration of smoking in years							
1-20	13	2	5.65 (0.80-39.9)	6	1.56 (0.53-4.62)	9	1.85 (0.71-4.85)
21-39	137	52	17.4 (5.08-59.9)	94	2.38 (1.42-3.99)	189	3.74 (2.37-5.90)
40+	90	144	29.8 (8.96-89.4)	119	2.89 (1.70-4.90)	355	6.02 (3.76-9.62)
Number of cigarettes per day[b]							
1-20	104	69	3.00 (1.61-5.59)	84	1.67 (1.05-2.65)	197	1.94 (1.31-2.87)
21-39	88	73	7.11 (3.74-13.5)	80	2.23 (1.39-3.59)	210	3.38 (2.67-5.05)
40+	37	43	12.5 (5.88-26.6)	43	3.01 (1.69-5.37)	110	4.61 (2.80-7.57)

[a]Adjusted for age and prefecture. [b]In total, 36 cases and 11 controls for current smokers were not included because of incomplete data. CI = confidence interval.

Table 2 Adjusted odds ratios (ORs) for lung cancer associated with cigarette smoking by histological type among women

Smoking status	Controls No.	Cases: Squamous cell carcinoma No.	Squamous cell carcinoma Adjusted[a] OR (95% CI)	Adenocarcinoma No.	Adenocarcinoma Adjusted[a] OR (95% CI)	All lung cancers No.	All lung cancers Adjusted[a] OR (95% CI)
Nonsmoker	320	10	1.00 (reference)	195	1.00 (reference)	231	1.00 (reference)
Past smoker	28	8	9.56 (2.73–33.4)	14	0.54 (0.23–1.26)	29	0.93 (0.47–1.81)
Current Smoker							
Duration of smoking in years							
1–20	16	1	2.48 (0.28–21.8)	4	0.48 (0.15–1.50)	6	0.63 (0.23–1.68)
21–39	23	6	12.5 (3.77–41.5)	19	1.85 (0.95–3.63)	32	2.61 (1.44–4.74)
40+	2	3	40.2 (5.71–282.7)	7	4.26 (0.87–20.9)	18	9.34 (2.13–41.1)
Number of cigarettes per day[b]							
1–20	33	9	12.3 (4.34–35.0)	22	1.31 (0.72–2.37)	40	1.98 (1.18–3.32)
21+	6	1	7.54 (0.75–75.8)	7	3.09 (0.97–9.86)	13	4.37 (1.57–12.2)

[a]Adjusted for age and prefecture. [b]In total, three case and two controls for current smokers were not included because of incomplete data. CI = confidence interval.

Table 3 Mean age and smoking status by histological type and filter/nonfilter cigarette consumption among male current smokers

	Type of smoking	Cases: Squamous cell carcinoma	Adenocarcinoma	All lung cancers	Controls
Number (%)	Mixed	114 (83.2)	84 (61.3)	259 (72.8)	80 (49.4)
	Filter	23 (16.8)	53 (38.7)	97 (27.2)	82 (50.6)
Mean age	Mixed	67.2	65.5	66.6	63.6
	Filter	56.3	52.3	53.2	51.6
Mean number of cigarettes per day	Mixed	28.3	26.4	27.3	23.9
	Filter	34.5	32.1	32.6	28.6
Mean total duration	Mixed	47.0	45.3	46.5	43.7
	Filter	34.1	30.4	32.0	28.5
Mean duration of filtered cigarettes	Mixed	29.4	29.2	29.5	26.6
	Filter	34.1	30.4	32.0	28.5
Mean duration of nonfiltered cigarettes	Mixed	17.6	16.1	17.0	17.2
	Filter	—	—	—	—

Mixed = nonfilter-exclusive smoker or filter/nonfilter-mixed smoker; Filter = filter-exclusive smoker.

Table 3 shows mean age and smoking status in terms of filter/nonfilter cigarette consumption among current male smokers by histological type. Lifelong nonfilter-exclusive smokers comprised 7.5% (39 of 518 men). Filter-exclusive smokers were much younger and consumed more cigarettes per day. Total duration of smoking among nonfilter or mixed cigarette smokers was substantially longer than that of filter smokers; this difference was largely due to the duration of nonfilter cigarette smoking among nonfilter or mixed smokers. Although duration of filter cigarette smoking showed less variation, smoking duration was slightly longer among filter-exclusive smokers. Men with SCC were older, had smoked for a longer duration and consumed more cigarettes per day than men with AC, for both filter and nonfilter users.

Table 4 shows adjusted ORs for lung cancer according to filter/nonfilter use among male current smokers by histological type. Overall, after adjustment for age and prefecture, OR for all lung cancers tended to be decreased by 30% (not significant) among filter-exclusive smokers as compared to mixed or nonfilter smokers. A nonsignificant tendency towards a reduction in adjusted OR was found for SCC, but not for AC. When we further examined the association between type of cigarettes and lung cancer histology according to age, by dividing participants into age groups of $\leqslant$54-, 55–64-, and $\geqslant$65-year old, ORs were shown to vary according to age and histology. Adjusted ORs in filter-exclusive smokers compared to mixed or nonfilter smokers decreased with increasing age group, regardless of histology. For men $\leqslant$54-year old, a nonsignificant two-fold increase in risk in prefecture-adjusted OR of AC was observed among filter-exclusive smokers, whereas the adjusted OR indicated a nonsignificant 60% reduction in the risk of SCC. For men 55–64-year -old, a reduction in adjusted ORs in filter-exclusive smokers as compared to mixed or nonfilter smokers was observed for SCC, but not for AC. For the oldest group ($\geqslant$65-years), filter-exclusive smoking was associated with decreased risk irrespective of histological type. The reduction in adjusted ORs related to SCC and AC in filter-exclusive smokers was similar. Odds ratios after further controlling for mean number of cigarettes smoked per day were not substantially different, generally displaying a slight decline in adjusted ORs.

DISCUSSION

The present study supports existing evidence of increased risks of both SCC and AC with higher numbers of cigarettes smoked and longer duration of smoking. In current smokers, risks indicated by adjusted ORs were higher for SCC than for AC. Furthermore,

Table 4 Adjusted odds ratios (ORs) for lung cancer by histological type according to filter/nonfilter cigarette consumption and age

	Controls	Cases								
		Squamous cell carcinoma			Adenocarcinoma			All lung cancers		
	No.	No.	OR1[a] (95% CI)	OR2[b] (95% CI)	No.	OR1[a] (95% CI)	OR2[b] (95% CI)	No.	OR1[a](95% CI)	OR2[b] (95% CI)
All subjects										
Mixed	80	114	1.00 (ref.)	1.00 (ref.)	84	1.00 (ref.)	1.00 (ref.)	259	1.00 (ref.)	1.00 (ref.)
Filter	82	23	0.52 (0.27–1.03)	0.55 (0.27–1.15)	53	0.88 (0.47–1.63)	0.83 (0.44–1.59)	97	0.70 (0.40–1.15)	0.70 (0.41–1.21)
Age ⩽54										
Mixed	12	5	1.00 (ref.)	1.00 (ref.)	4	1.00 (ref.)	1.00 (ref.)	13	1.00 (ref.)	1.00 (ref.)
Filter	53	8	0.38 (0.10–1.42)	0.38 (0.10–1.45)	33	2.01 (0.60–6.81)	2.54 (0.66–9.79)	54	1.00 (0.42–2.40)	1.05 (0.43–2.56)
55 ⩽age ⩽64										
Mixed	34	33	1.00 (ref.)	1.00 (ref.)	24	1.00 (ref.)	1.00 (ref.)	72	1.00 (ref.)	1.00 (ref.)
Filter	25	13	0.38 (0.10–1.42)	0.49 (0.18–1.35)	18	1.05 (0.46–2.43)	0.83 (0.33–2.11)	37	0.68 (0.34–1.36)	0.62 (0.29–1.35)
Age ⩾65										
Mixed	34	76	1.00 (ref.)	1.00 (ref.)	56	1.00 (ref.)	1.00 (ref.)	174	1.00 (ref.)	1.00 (ref.)
Filter	4	2	0.36 (0.05–2.24)	0.30 (0.05–1.97)	2	0.30 (0.05–1.74)	0.28 (0.05–1.71)	6	0.31 (0.08–1.21)	0.31 (0.08–1.20)

Mixed = nonfilter-exclusive smoker or filter/nonfilter-mixed smoker; Filter = filter-exclusive smoker. [a]Adjusted ORs were presented after controlling for age and prefecture for all subjects, and for prefecture for each age-specific stratum. [b]Additional control for number of cigarettes smoked per day.

overall, although filter cigarette smokers were at lower risk compared to nonfilter smokers regardless of histology, a greater reduction in adjusted OR was observed for SCC than for AC.

Lower risk of all lung cancers has been observed among filter cigarette smokers compared to nonfilter cigarette smokers in some case-control studies of men (Wynder and Stellman, 1979; Lubin *et al*, 1984; Benhamou *et al*, 1989; Benhamou *et al*, 1994; Armadans *et al*, 1999) and women (Wynder and Stellman, 1979; Lubin *et al*, 1984; Agudo *et al*, 2000). However, the reduction in risk of all lung cancers among filter cigarette smokers compared to nonfilter cigarette smokers has been obscured. This results from the fact that the total incidence of lung cancer has increased in recent years, despite the widespread predominance of filter cigarettes. It is possible that, since this move towards filter cigarettes, insufficient time has elapsed to reflect a reduction in lung cancer incidence. Furthermore, overall lung cancer mortality rates had been increasing, although they have tended to level off in the last 5 years (Yoshimi *et al*, 2003). Separate analysis of an association between type of cigarette and lung cancer should therefore be performed by histological type of lung cancer.

One US case-control study has shown that the effect of filter cigarettes varies depending on the histological type of lung cancer, and revealed that reduced risk of SCC, but not AC, was apparent among filter cigarette smokers compared to nonfilter smokers (Stellman *et al*, 1997). These results are consistent with those of the present study. Another case-control study demonstrated a reduction in risk of Kreyberg I lung cancer, but not of Kreyberg II, among filter smokers (Wynder and Kabat, 1988). Trends towards a relative increase in AC compared to SCC might be partially attributable to a greater reduction in SCC among filter cigarette smokers compared to nonfilter cigarette smokers.

However, we cannot assume that the relative increase in AC observed in Japan is attributable to the same mechanisms seen in Western countries, since smoking has a lower impact on lung cancer risk among Asian populations and overall lung cancer death rates are lower in Japan than in Western countries (Sobue *et al*, 2002). This implies that factors other than smoking, such as lifestyle and diet, particularly the traditional Japanese diet, play important roles in lung cancer development (Wynder and Hoffmann, 1994). Furthermore, the association between certain dietary factors and lung cancer may be histological type specific (De Stefani *et al*, 1997; Kubik *et al*, 2001). The traditional Japanese diet, incorporating elements such as fish and soybean products, was found to be associated with a reduced risk of AC (Takezaki *et al*, 2001), and one study found the protective effects of tofu (a soybean product) appeared more significant for SCC (Wakai *et al*, 1999). In contrast, high levels of fat consumption increase the risk of lung cancer, particularly for AC (Ozasa *et al*, 2001). The Japanese diet has recently undergone substantial Westernisation, and such dietary alterations might represent an alternate explanation for the observed changes in histological types of lung cancer.

It should be noted that the effects of filter cigarettes on lung cancer by histological type varied according to age. Among men aged ⩽54 years, elevation in the adjusted OR for filter cigarettes compared to nonfilter cigarettes was found for AC, but not SCC. For men aged 55–64 years, use of filter cigarettes was associated with a reduction in adjusted ORs for SCC, but not for AC, whereas the magnitude of reduction was similar for SCC and AC in men ⩾65 years. No clear explanation for the age-related effects of filter cigarettes was apparent. Among young smokers, the tendency of filter smokers to inhale deeply to compensate for the low-tar delivery of filter cigarettes (Wynder and Muscat, 1995) might sufficiently affect the more peripheral regions of the lung, where most AC appear, even among short-term filter cigarette smokers. However, for older smokers, and considering long-term smoking, the cumulative exposure to tar contained in smoke might be substantially reduced among filter-exclusive cigarette smokers than among nonfilter or mixed cigarette smokers. The total protective effects for both SCC and AC might therefore be more apparent among older smokers. Indeed, trends in SCC and AC incidence from 1974 to 1997 among Japanese men differed according to age group, and the relative increase of AC compared to SCC was intensified in younger age groups (Yoshimi *et al*, 2003). Any elevation in risk of AC (or a smaller reduction in AC compared to SCC) attributable to filter cigarette use among younger smokers might represent an important issue, as the younger the age group, the more the smokers consume filter cigarettes in preference to nonfilter cigarettes. However, since no studies have addressed age-specific or duration-dependent protective effects of filter cigarettes, further confirmation is needed for other populations.

Reasons other than deep inhalation have been proposed as being responsible for filter cigarettes not providing relative protection against AC. These include reduced tar and nicotine delivery in filter cigarettes. Filter cigarettes remove the larger carcinogenic particles, meaning that smaller particles in the smoke from filter

cigarettes reach the peripheral regions of the lung. Although tar delivery from filter cigarettes is reduced, concentrations of nitrosamines such as NNK (4-(methylnitrosamino)-1-3(pyridil)-1-butanone), which is known to induce the formation of AC, are not decreased in filter smoke (Agudo *et al*, 2000).

When we analysed the association between filter and nonfilter smoking, the most likely confounding factors were age and total duration of smoking. Duration of smoking was strongly associated with both SCC and AC in a dose-dependent manner. As age and total duration of smoking were also well correlated (correlation coefficient = 0.80 ($P<0.0001$)), we avoided simultaneous inclusion of these variables in the logistic regression model. However, residual confounding related to cumulative smoking exposure might be partially responsible for the protective effects of filter cigarettes observed. In our subjects, mean number of cigarettes smoked per day was associated with risk of overall lung cancers and was higher among filter cigarette smokers than among nonfilter or mixed smokers. Comparison of filter/nonfilter cigarette smokers might thus be confounded by daily cigarette consumption. In this regard, the relationship between type of cigarette and lung cancer with adjustment for mean number of cigarettes is interesting. However, controlling for the amount of smoking, as a measure of exposure to lung carcinogens, requires caution when comparing the risks of different types of cigarettes. As low-nicotine low-tar filter cigarette smokers tend to smoke more cigarettes in order to maintain nicotine intake, adjustment by number of cigarettes may not be appropriate in case comparison between low-tar filter smokers and nonfilter or mixed cigarette smokers. These result in a spurious reduction in risk for filter cigarette smokers as compared to nonfilter or mixed cigarette smokers. Indeed, after adjustment for mean number of cigarettes per day, most adjusted ORs for overall lung cancers, SCC, and AC for filter cigarette smokers as compared to nonfilter or mixed cigarette smokers were slightly decreased. However, the increased risk of AC among men $\leqslant$54-year and no reduction in the risk of AC among men aged 55–64 years were not changed even after controlling for this variable.

As controls were patients admitted to hospital, and controls with conditions known to be related to cigarette smoking were excluded, the possibility of underestimating lung cancer risks in smokers due to over-representation of smokers among hospital patients was minimised. However, one limitation of the present study should be considered. Smoking histories were obtained using self-reported questionnaires, and the number of subjects recording complete smoking histories was low; among current smokers, only 65% of the original subjects eligible as cases or controls were used for further analysis of associations between type of cigarette and lung cancer. The present study might therefore lack the power to detect slight to moderate increases (or decreases) in ORs. Finally, we did not obtain data on brand names of cigarettes smoked, which might have led to misclassification of cigarette types.

In conclusion, this study of a Japanese population revealed a type-specific association of filter cigarettes as compared to nonfilter cigarettes, that is, a protective effect against SCC, but no such effect (or, at least, a relatively reduced effect) against AC, particularly among younger smokers. Further confirmation is required to ascertain possible differences in risks of filter cigarettes for lung cancer. However, almost all smokers have now changed to filter cigarettes. The more prevalent smoking of filter cigarettes becomes, the more limited the opportunities for further investigations comparing filter and nonfilter cigarettes.

Epidemiology

ACKNOWLEDGEMENTS

This study was supported in part by a Grant-in-Aid from the Ministry of Health and Welfare of Japan for a Comprehensive 10-year Strategy for Cancer Control. We thank the collaborating hospitals for contributing to the collection and processing of data that made this publication possible, Osaka Medical Center for Cancer & Cardiovascular Diseases, Toneyama National Hospital National Kinki Central Hospital For Chest Diseases, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka Prefectural Habikino Hospital, Osaka Red Cross Hospital, Kitano Hospital, Kansai Denryoku Hospital, Japan Anti-Tuberculosis Association Osaka Hospital, Osaka City Central Hospital, Otemae Hospital, Saiseikai Nakatsu Hospital, Osaka Prefectural General Hospital, Osaka University Hospital, Osaka City University Hospital, Osaka Medical College Hospital, Kansai Medical University Hospital, and Kinki University Hospital in Osaka Prefecture, Saku Central Hospital in Nagano Prefecture, and Okinawa Prefectural Miyako Hospital and National Okinawa Hospital in Okinawa Prefecture. We also thank the hospital staff: K Sawamura, K Furuse, T Mori, M Fukuoka, T Taki, O Doi, M Kuwabara, T Yasumitsu, I Kawase, H Tada, K Bando, Y Saito, Y Tanio, H Tachibana, T Masuno, Y Fujii, N Sagara; further thanks to Y Murai, who managed the study database. TM received a Research Resident Fellowship from the Foundation of Cancer Research (Japan) for the second Term Comprehensive 10-year Strategy for Cancer Control.

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Progression of Focal Pure Ground-Glass Opacity Detected by Low-Dose Helical Computed Tomography Screening for Lung Cancer

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Objective: To clarify the progression of focal pure ground-glass opacity (pGGO) detected by low-dose helical computed tomography (CT) screening for lung cancer.

Methods: A total of 15,938 low-dose helical CT examinations were performed in 2052 participants in the screening project, and 1566 of them were judged to have yielded abnormal findings requiring further examination. Patients with peripheral nodules exhibiting pGGO at the time of the first thin-section CT examination and confirmed histologically by thin-section CT after follow-up of more than 6 months were enrolled in the current study. Progression was classified based on the follow-up thin-section CT findings.

Results: The progression of the 8 cases was classified into 3 types: increasing size (n = 5: bronchioloalveolar carcinoma [BAC]), decreasing size and the appearance of a solid component (n = 2: BAC, n = 1; adenocarcinoma with mixed subtype [Ad], n = 1), and stable size and increasing density (n = 1: BAC). In addition, the decreasing size group was further divided into 2 subtypes: a rapid-decreasing type (Ad: n = 1) and a slow-decreasing type (BAC: n = 1). The mean period between the first thin-section CT and surgery was 18 months (range: 7–38 months). All but one of the follow-up cases of lung cancer were noninvasive whereas the remaining GGO with a solid component was minimally invasive.

Conclusions: The pGGOs of lung cancer nodules do not only increase in size or density, but may also decrease rapidly or slowly with the appearance of solid components. Close follow-up until the appearance of a solid component may be a valid option for the management of pGGO.

Key Words: ground-glass opacity, low-dose helical computed tomography screening, lung cancer

(*J Comput Assist Tomogr* 2004;28:17–23)

Focal pure ground-glass opacities (pGGOs), or nodules of the lungs, has become a major concern as low-dose helical computed tomography (CT) screening for lung cancer becomes more widely available, not only in the field of diagnostic imaging,[1–5] but also in the field of limited surgery.[6–10] GGO is a finding on thin-section CT images of the lung which has been described as a hazy, increased attenuation of the lung tissue with preservation of the bronchial and vascular margins. GGO is usually a nonspecific finding that is found in many types of pulmonary disease.[11] However, some investigators have recently reported that most localized pGGOs or focal GGOs are malignant.[1,2,5] Although a few reports have described the evolution of lung cancer using conventional chest CT,[12–14] thin-section CT[15–17] and low-dose screening CT,[18,19] the natural history of peripheral lung cancers that exhibit as pGGO on thin-section CT images detected using low-dose helical CT screening is still unclear.

The purpose of this retrospective study was to clarify the progression of pGGOs, which were not visible on chest radiographs, detected by low-dose helical CT screening examinations performed every 6 months. We evaluated the progression of pGGOs based on the thin-section CT findings obtained during the follow-up after the first thin-section CT.

PATIENTS AND METHODS

Subjects

Between September 1993 and January 2003, low-dose helical CT screening was conducted semiannually in Tokyo by

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This study was supported in part by a Grant-in-Aid for Cancer Research (13-8) from the Ministry of Health, Labor, and Welfare of Japan and by a Grant-in-Aid from the Second-Term Comprehensive 10-Year Strategy for Cancer Control.

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the Anti–Lung Cancer Association (ALCA), a for-profit organization for lung cancer screening.[20,21] Each screening consisted of a low-dose helical CT examination, chest radiography, and cytologic sputum studies. During this period, a total of 15,938 low-dose helical CT examinations were performed in 2052 ALCA members. Among the low-dose helical CT examinations, a total of 1566 CT examinations were judged as having abnormal findings requiring further examination. Sixty-seven cases of lung cancer (peripheral-type lung cancer, 61; hilar-type lung cancer, 6) were detected during the ALCA lung cancer screening project. Out of these 67 cases, 51 cases (76%) were pathologic stage IA. The treatments used in the 67 cases were as follows: surgery (n = 55), radiotherapy (n = 5), radiotherapy and chemotherapy (n = 2), chemotherapy (n = 4), and photodynamic therapy (n = 1). Among the patients with peripheral nodules detected by the low-dose helical CT examinations performed every 6 months, the patients with histologically diagnosed nodules exhibiting pGGO larger than 5 mm in diameter at the time of the first thin-section CT and followed-up by thin-section CT for more than 6 months were enrolled in the current study.

CT Scanning Conditions

A TCT900S Superhelix CT scanner (Toshiba Medical Inc., Tokyo, Japan) was used for all of the examinations. Low-dose helical CT screening was performed under the following conditions: 120 kV, 50 mA, beam width of 10 mm, 1 rotation of the x-ray tube per second, and a table speed of 20 mm per second (pitch 2:1). Reconstruction was performed at intervals of 10 mm. The CT images were displayed on a monitor with a window width of 2000 HU and a window level of −700 HU. If newly developed nodules were identified, thin-section CT examinations were performed under the following conditions: 120 kV, 250 mA, beam width of 2 mm, 1 rotation of the x-ray tube per second, and a table speed of 2 mm per second (pitch 1:1). Reconstruction was performed at intervals of 2 mm using a thin-section CT algorithm.

Evaluation of pGGO Progression Patterns

The progression patterns were classified based on changes in the size and density of the pGGOs on the thin-section CT images. The study period was divided into 2 phases: the unidentified phase (ie, the period prior to the first thin-section CT scan) and the follow-up phase (ie, the period after the first thin-section CT scan). CT images of the pGGOs in the unidentified phase were reviewed independently by 4 physicians (R.K., M.K., H.O., K.E.), who are diagnostic experts in chest radiology, and by 1 radiologist (M.K.). CT findings were adopted as positive findings if 3 of more of the doctors agreed. After the independent reviews, we decided by consensus as to how many pGGOs were newly developed or had arisen from inconspicuous nodules during the helical CT screening period. In the follow-up phase, the size of the pGGOs was measured with a pair of calipers on the thin-section CT images obtained during the initial scan and the final scan by consensus of 2 diagnostic experts (R.K., M.K.) to assess doubling time. The size of the lesion was evaluated using measurements that passed through the center of the lesion. Size was defined as the average of the length and width of the lesion. Doubling times were calculated using the Schwartz equation.[22] The density of faint opacities was evaluated visually on the thin-section CT images obtained during the follow-up phase. pGGO was defined as a homogeneous GGO, and mixed GGO was defined as a GGO with a solid component.

Pathologic Classification of Adenocarcinomas

The histologic findings of the adenocarcinomas were classified according to the criteria of the World Health Organization (WHO)[23] and the criteria of Noguchi et al.[24] The classification system for replacement growth patterns developed by Noguchi et al is as follows: type A (localized bronchioloalveolar carcinoma; LBAC), type B (LBAC with foci of collapsed alveolar structure), and type C (LBAC with foci of active fibroblastic proliferation).

RESULTS

Patient Characteristics

Eight patients with pGGOs (6 men and 2 women) were enrolled in the current study (Table 1). The patients ranged in age from 49 to 69 years (mean, 64 years). With regard to smoking history, 3 patients were nonsmokers, 4 were ex-smokers, and 1 was a current smoker. Four of these 8 pGGO patients were not apparent during the initial screening and became apparent during the screening period, and 3 of the other 4 pGGO patients with inconspicuous opacities visible in retrospect during the initial screening became apparent later. In 1 other case, a conspicuous opacity and multiple old tuberculosis lesions were observed during the initial CT screening. The locations of the pGGOs were as follows: right upper lobe (n = 4), right lower lobe (n = 1), left upper lobe (n = 1), and left lower lobe (n = 2).

Clinical Course

The period between the first visible nodule of a pGGO on a thin-section CT image and the first visible opacity on a helical CT screening image when viewed retrospectively ranged from 13 to 46 months (mean, 22 months) (Table 1). The period between the first thin-section CT examination and the surgery ranged from 7 to 39 months (mean, 19 months). The interval between the last thin-section CT examination and surgery ranged from 1 to 98 days (mean, 32 days).

Histology of GGOs

Seven patients had bronchioloalveolar carcinoma (BAC), defined as noninvasive by the WHO classification in 1999, and 1 had an adenocarcinoma with mixed subtypes (Table 1). Based on Noguchi's classification for small adeno-

TABLE 1. Clinical Characteristics and Histology of Ground-Glass Opacities

Case No.	Sex	Age at Detection (Years)	Smoking Index	Development	Lobe	Period Between: First Visible and the First TS-CT (Months)*	Period Between: The First TS-CT and Surgery (Months)*	Period Between: The Last TS-CT and Surgery (Days)	Histology: WHO Classification	Histology: Noguchi Type
1	M	69	1300	New	RU	41	13	1	Ad	C
2	M	69	800 (ex)	New	RU	13	39	36	BAC	B
3	F	66	Non	New	LL	13	14	33	BAC	A
4	M	66	450 (ex)	New	LU	18	26	98	BAC	A
5	F	65	Non	ic	LL	46	28	13	BAC	B
6	M	69	800 (ex)	ic	RU	21	12	13	BAC	A
7	M	49	515 (ex)	ic	RU	14	10	6	BAC	A
8	M	63	Non	c	RL	13	7	57	BAC	B

Non, nonsmoker; ex, ex-smoker; ic, inconspicuous; c, conspicuous; RU, right upper lobe; LU, left upper lobe; LL, left lower-lobe; TS-CT, thin-section CT; BAC, bronchioloalveolar carcinoma; Ad, adenocarcinoma.
*Number of months was rounded.

carcinomas, the pGGOs consisted of 4 cases of type A and 2 cases of type B while the mixed GGOs consisted of 1 case of type B and 1 case of type C (Tables 1, 2). All the lung cancers were diagnosed at pathologic stage IA.

Progression of pGGOs

The period between the first thin-section CT and the final thin-section CT examinations ranged from 6 to 37 months (mean, 17 months) (Table 3). The opacities ranged in size from 6.5 mm to 17 mm (mean, 10 mm) at the time of the first thin-section CT examination and from 7 mm to 16.5 mm (mean, 10.5 mm) at the time of the final thin-section CT examination. The progressions of 8 opacities in the follow-up phase were classified into 3 types: increasing in size (Increasing type, n = 5), decreasing in size and the appearance of a solid component (decreasing type, n = 2), and stable in size and increasing in density (density type, n = 1). In addition, the decreasing type was classified into 2 subtypes: a rapid-decreasing type (case 1, Fig. 1; decrease in size at the time of the 6-month follow-up) and a slow-decreasing type (case 2, Fig. 2; decrease after follow-up for more than 1 year). All but 1 of the follow-up cases were noninvasive, and the remaining GGO with a solid component was judged to be minimally invasive adenocarcinoma because the size of the collapse fibrosis was only 2 mm in diameter (Fig. 1F).

TABLE 2. Thin-Section CT Findings, Progression Types, and Doubling Time of Ground-Glass Opacities

Case No.	Follow-Up Phase with Thin-Section CT: GGO Size (mm) First	GGO Size (mm) Final	Final TS-CT of GGO: Density	Solid	Finding	Progression Type	Period of Follow-Up with TS-CT (Months)*	GGO Doubling Time (Days)
1	17	12	Increasing	+	Mixed	Dec	12	−214
2	14	12	Increasing	+	Mixed	Dec	37	−1680
3	6.5	7.5	Stable	−	Pure	Inc	13	617
4	7	10.5	Stable	−	Pure	Inc	22	383
5	7	7	Increasing	−	Pure	Den	27	—
6	8.5	9.5	Stable	−	Pure	Inc	12	669
7	6.5	9	Stable	−	Pure	Inc	10	216
8	13.5	16.5	Stable	−	Pure	Inc	6	198

CT, computed tomography; GGO, ground-glass opacity; TS-CT, thin-section computed tomography; Inc, increasing; Dec, decreasing; Den, density.
*Number of months was rounded.

TABLE 3. Evolution of Solid Components in Ground-Glass Opacities

Case No.	Follow-Up Phase with TS-CT Solid Size (mm)					Doubling Time (Days)
	First TS-CT	Months After the First TS-CT				
		6	11	23	36	
1	0*	8				14*
2	0	—	2	3	7.5	130†

TS-CT, thin-section computed tomography.

*Doubling time of solid component in case 1 was calculated on the assumption that the first size was 0.5 mm.

†Doubling time of solid component in case 2 was calculated based on the sizes between 11 months and 36 months after the first TS-CT.

Doubling Time

The doubling times of the increasing-type opacities ranged from 198 to 669 days (mean ± SD, 417 ± 220 days). The doubling time of the density-type opacity could not be calculated because it did not change in size. For the decreasing-type opacities, the doubling times were calculated based on the sizes of the pGGOs and the solid components, individually. In case 1, the doubling times of the pGGO and the solid component were −214 and 14 days, respectively. In case 2, the doubling times of the pGGO and the solid component were 1680 and 130 days, respectively.

Correlation of Thin-Section CT Images and Pathologic Findings

The pGGO corresponded to the lepidic growth of cancer cells (Fig. 1E), the thickening of the alveolar wall (Fig. 1E), and the collapse of the alveolar space (Fig. 1E). Solid components corresponded not only to the collapse of the alveolar space and fibrosis (Fig. 1F and Fig. 2G), but also to a severe narrowing of the alveolar space (Fig. 1F). With the development of a solid component in case 2, the distance between the surrounding pulmonary veins and the bronchus gradually narrowed (Figs. 2C–F). The same finding was observed in case 1 (Figs. 1C, D).

DISCUSSION

To our knowledge, this study is the first report to describe the progression of pGGOs in minute lung cancers that appeared as new pGGOs during the screening process or arose from inconspicuous minute nodules on low-dose helical CT screening images obtained at 6-month intervals. In addition, the progressions of the pGGOs on the thin-section CT images were classified into 3 types for the first time. Although a few papers have described the natural history of GGOs in pulmonary adenocarcinoma,[4,7,12,15–17] only 1 researcher[15] reported 2 GGOs that decreased in size, but the size reduction occurred in mixed GGOs, not in pGGOs. The rapid decreasing of a pGGO and the appearance of a solid component has not previously been reported.

Radiologic-pathologic correlations revealed that pGGOs on thin-section CT images mainly represent the lepidic growth of adenocarcinomas.[1,3,4,12,15–17] Solid components in the mixed GGOs were caused by the collapse of alveolar spaces or regions of fibrosis[12] and by a severe narrowing of the alveolar space (case 1). The narrowing of the distance between the surrounding pulmonary vessels and the bronchus was caused not only by the collapse of the alveolar space (cases 1 and 2), but also by the development of fibrosis (case 1) in the pGGO lesions. This finding has been termed "vessel convergence."[12,15,17] Based on our observations of the progression from a pure GGO to a mixed GGO in cases 1 and 2, our results also support the stepwise progression of replacement-type adenocarcinoma.[12,15,17]

Although 1 researcher raised serious questions about the concept of 2-year stability implying benignity,[25] pulmonary nodules are generally considered to be benign if they remain the same size or decrease in size over a 2-year observation period.[26,27] However, our results show that stability or reduction in size over a 2-year period does not necessarily indicate benignity. In the case of a pGGO that decreases in size, can the Schwartz equation be applied to a change from a pGGO to a mixed GGO if the area of the GGO decreases? Usually, the Schwartz equation is based on the assumption that constant exponential tumor growth is the basic pattern of neoplastic proliferation.[22] The doubling time for mixed GGOs has been reported to be 457 ± 260 days.[28] However, progression to a mixed GGO in a case where the pGGO decreases in size and a solid component simultaneously appears has not previously been reported. Moreover, the calculation of doubling times for each component in a mixed GGO has never, to the best of our knowledge, been performed prior to the current study. The doubling time for the solid component in case 1 was calculated based on the assumption that the initial size of the solid component was 0.5 mm, this because the thin-section CT images were taken not only by the single-slice CT scanner described above, but by a multislice CT scanner with the imaging parameters set at 0.5 mm × 4 rows and image reconstruction performed at 1-mm intervals.

Whether pGGOs should be resected or followed up is controversial. Definite evidence of the natural history of pGGOs does not exist at present. However, based on the indirect corroboration described below, we suggest that close follow-up until the appearance of a solid component may be a valid option for the management of pGGO. First, most pGGOs are either atypical adenomatous hyperplasia (preinvasive lesions according to the 1999 WHO criteria), BAC (a noninvasive lesion), or minimally invasive adenocarcinoma.[1,8,29] Second, 1 researcher[7] has previously reported information concerning

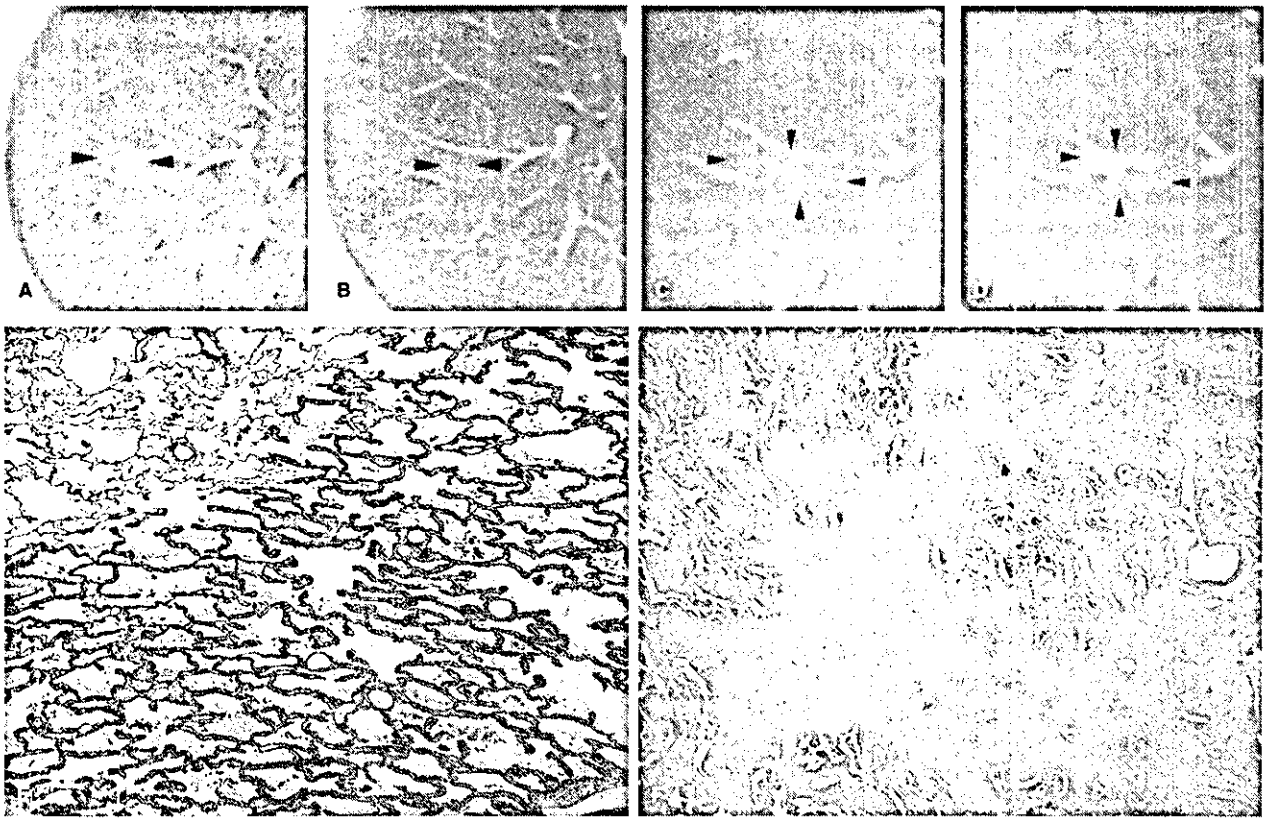

FIGURE 1. Case 1: Adenocarcinoma in a 69-year-old man. A, A faint localized increase in density was identified in segment 1 of the right upper lobe of the lung on a CT screening image obtained in December 2001. B, In retrospect, the opacity was also present on a CT screening image obtained in June 1998. C, Thin-section CT image obtained in December 2001 showing a pGGO in segment 1 of the right upper lobe of the lung. D, Thin-section CT image obtained in June 2002 shows a decrease in the size of the pGGO and the appearance of a solid component. E, Medium-magnification image of the pathologic specimen (H&E staining, ×40). Thickening of the alveolar walls as a result of the tumor cells is visible. F, Medium-magnification image of the pathologic specimen (H&E staining, ×40). Severe narrowing of the alveolar space from the thickening of the alveolar walls and an area of collapse-fibrosis with active fibroblastic proliferation are visible. A right upper lobectomy was performed in January 2003. The lesion was diagnosed as an adenocarcinoma, 17 mm in diameter (Noguchi type C). The size of collapse- fibrosis was 2 mm in diameter.

the natural history of pGGOs after conducting a long-term follow-up study lasting more than 2 years. Five of the 19 cases of pGGOs were diagnosed as lung cancers, that is, 5 BACs (1 case had 2 BACs) and 1 adenocarcinoma, after a mean follow-up of 61 months. Although the patient with adenocarcinoma was followed up for 124 months, personal communication with the author revealed that his lung cancer was of pathologic stage IA and that the size of the central fibrosis of the adenocarcinoma was less than 3 mm in diameter. We have also experienced 2 other pGGOs that developed into mixed GGOs after a 1-year and a 3-year follow-up period, respectively (unpublished data). These lesions were diagnosed as pathologic stage IA adenocarcinomas, and the size of the central fibrosis was 1.5 mm and 2 mm in diameter, respectively. Regarding the relationship between central fibrosis and prognosis, our research team[30] previously reported that 21 out of 100 patients with a lung adenocarcinoma that was 3 cm or less in diameter and which had a central fibrosis of 5 mm or less in diameter had a 5-year survival rate of 100%. Therefore, the adenocarcinoma follow-up cases described above and in this study were thought to be minimally invasive, allowing the possibility of a cure. Third, the adenocarcinoma cases with mixed GGOs did not experience any relapses or deaths, even though the solid components of the GGOs became larger but remained less than 50% of the mixed GGO nodule, this from the standpoint of the GGO's length,[31] the vanishing ratio of GGO[10] ("air-containing type"), and the volume of the GGO.[9] Finally, adenocarcinoma pGGOs tend to grow slowly, as the mean doubling time of pGGOs has been reported to be 813 days[28] or 880 days.[12] In addition, one-fourth of the GGOs in 1 study were

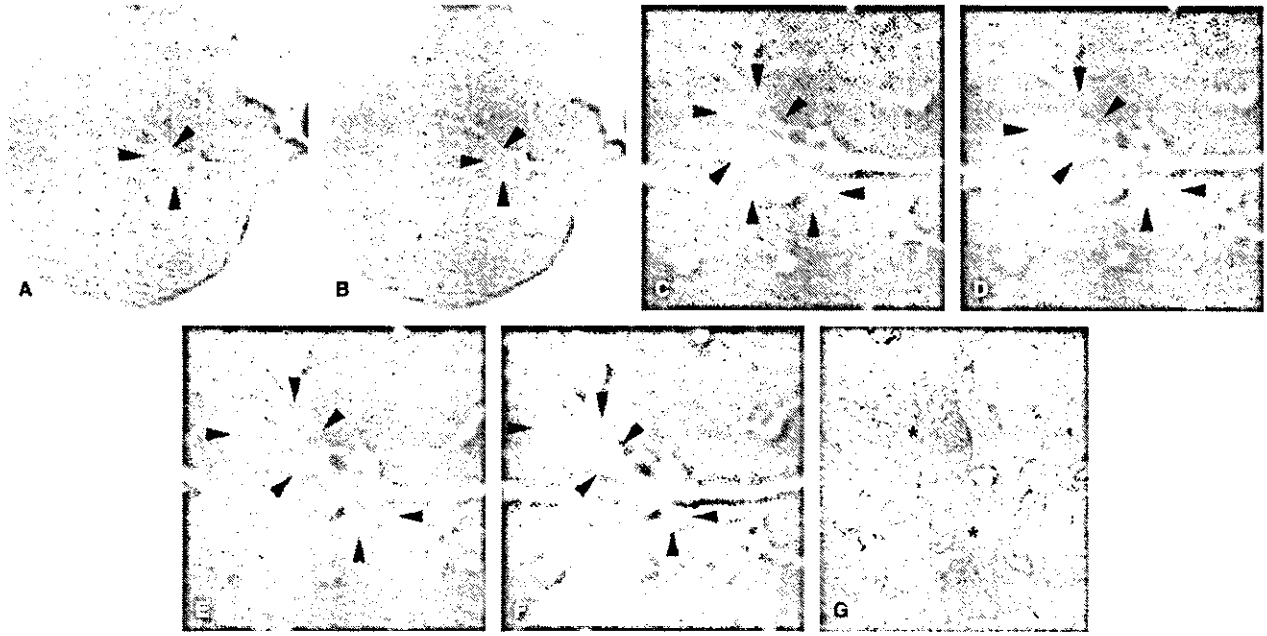

FIGURE 2. Case 2: Bronchioloalveolar carcinoma in a 69-year-old man. A, A faint localized increase in density was identified in segment 1 of the right upper lobe of the lung on a CT screening image obtained in February 1999. B, In retrospect, the opacity was also visible on a CT screening image obtained in February 1998. C, Thin-section CT revealed a pGGO in segment 1 of the right upper lobe of the lung in March 1999. D, Thin-section CT image obtained in February 2000 showing a pGGO with a small solid component. E, Thin-section CT image obtained in February 2001 showing a decrease in the size of the pGGO and a slight increase in the size of the solid component. F, Thin-section CT image obtained in February 2002 showing a larger decrease in the size of the pGGO and an increase in the size of the solid component. G, Low-magnification image of the pathologic specimen (H&E staining, ×5). The foci of alveolar collapse (asterisks) are shown. A right upper lobectomy was performed in May 2002. The lesion was diagnosed as a bronchioloalveolar carcinoma, 15 mm in diameter (Noguchi type B).

stable after a mean follow-up period of 16 months,[17] whereas half of the pGGOs in another study showed no change in size after a median follow-up period of 32 months.[7] Therefore, the classification of some pGGOs may be affected by an overdiagnosis bias.

This study has some limitations. First, the period of pGGO development was not accurately assessed because only thick-sectioned screening CT images were available for the unidentified phase. Therefore, the partial volume effect affected the detectability of small faint opacities on screening CT images. Multislice CT imaging using a narrow collimation and thinner reconstruction images may reveal the natural history of pGGOs more precisely. Second, measurements made with a pair of calipers to calculate doubling times may lead to measurement errors. Although technical advances have been reported,[32,33] we did not have any commercial software for volume measurements. Third, our study cohort was very small. At the start of the helical CT screening project, surgery without follow-up tended to be recommended in cases with pGGO. After knowledge of pGGOs had accumulated (ie, that most pGGOs consisted of preinvasive, noninvasive, or minimally invasive lesions), our treatment procedure changed.[8] Now, resection is only 1 option, not the only option, as in the past. Because of this, resection data cannot always be obtained, and the number of cases was small as a result.

In conclusion, the natural history of pGGOs detected by helical CT screening for lung cancer was partially revealed. A classification for pGGO progression was proposed based on thin-section CT images obtained during the follow-up phase. The pGGOs of lung cancer nodules do not only increase in size or density, but may also decrease rapidly or slowly with the appearance of solid components. Close follow-up until the appearance of a solid component may be a valid option for the management of pGGO.

ACKNOWLEDGMENTS

The authors thank Fumio Shishido, MD, PhD (Department of Radiology, School of Medicine, Fukushima Medical University) for his encouragement. We also wish to thank the pathologists who assisted in this study: Yoshihiro Matsuno, MD (National Cancer Center Research Institute), Tomoyuki Yokose, MD, and Genichiro Ishii, MD (National Cancer Center Research Institute East). We also thank the physicians, the

technical staff, and the administrative staff of the Anti–Lung Cancer Association in Tokyo.

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Gastric Cancer (2004) 7: 140–148
DOI 10.1007/s10120-004-0282-7

Review article

TNM and Japanese staging systems for gastric cancer: how do they coexist?

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Abstract

Two staging systems for gastric cancer, International Union Against Cancer (UICC)/TNM and the Japanese classification, have been used widely for clinical practice and research. The two systems started independently in the 1960s, and underwent several revisions and amendments in order to approach each other, but have become more divergent in the latest editions because of characteristics based on different philosophies. The TNM system adopted a number-based system for N-staging that provides easy and accurate prognostic stratification. Comparative studies have shown that the TNM system has greater prognostic power than the Japanese classification. It contains, however, no treatment guidance and should primarily be used as a guide to prognosis. In contrast, the Japanese classification has been designed as a comprehensive guide to treatment, originally for surgeons and pathologists, and today for oncologists and endoscopists as well. Its anatomical-based N-staging was established based on analysis of lymphadenectomy effectiveness, and naturally provides direct surgical guidance. Clinicians should understand the roles of each system and must not mix the systems or terminology when they report their study results.

Key words Stomach neoplasms · Classification · TNM · Japanese classification · Stage

Introduction

Gastric cancer is the world's second commonest cancer, superseded only by lung cancer in this undesirable world ranking. While the incidence of gastric cancer continues to decline steadily in the West, it is still the commonest malignancy in Japan. However, the chance of cure from the disease remains highest in Japan, where there has been a steady improvement in survival rate over the past three decades. Much of this is due to increased diagnosis of early gastric cancer, which accounts for half of all cases, as well as more radical intervention for advanced disease. By contrast, the majority of the cases in the West present late with advanced disease, and there has not been a significant improvement in the overall survival, despite improvements in surgical technique.

Narrowing the gap between Western and Japanese outcomes will probably require changes at many levels. However, attempts to compare gastric cancer outcomes have been hampered by differences in both the philosophy and practicality of staging the disease in Japan and the West [1].

The two main staging systems for gastric cancer are the TNM staging system of the International Union Against Cancer (UICC), and the Japanese Classification of Gastric Carcinoma by the Japanese Gastric Cancer Association (JGCA). Similarities between these two staging systems exist; namely, that staging is dependent on the extent of the primary tumor, the extent of lymph node involvement, and the presence or absence of distant metastasis. However, there still remain fundamental differences between the two staging systems. The most recognizable difference lies with the classification of regional lymph node spread. The UICC/TNM staging system divides N stage on the basis of the number of metastatic lymph nodes, while the Japanese classification stresses the location of involved nodes.

Staging has a variety of functions, which should be reflected in the staging systems used. In addition to providing an indication of prognosis, staging should ideally be able to provide a framework for treatment decisions, and should allow for evaluation of treatment with meaningful comparisons between different treatments or the same treatment modalities by different groups.

The purpose of this review is to outline the philosophy, background, and major features of the current staging systems and to assess their suitability to serve the above functions.

Offprint requests to: T. Sano
Received: January 26, 2004 / Accepted: March 23, 2004

Two main classifications

The current main classification systems for gastric cancer are the sixth edition of the UICC/TNM classification (2002) [2] and the thirteenth edition of the *Japanese classification of gastric carcinoma* (second English edition [3] (1998), downloadable from http://www.jgca.jp/PDFfiles/JCGC-2E.PDF), herein referred to as the JGCA classification. Other systems have been proposed, which will be discussed briefly later in the text.

UICC/TNM classification

In 1954, the UICC appointed a Committee on Tumor Nomenclature and Statistics, which subsequently agreed on a technique for classification of cancer according to the anatomical extent of the disease. Gastric cancer was first included in the TNM staging system in 1966. There have been relatively few revisions to the UICC classification, which is now still only in its sixth edition.

The UICC/TNM system was originally a purely clinical classification, so that a disease stage could be decided before any treatment. In gastric cancer, however, surgical findings were indispensable for classification, because the principal prognostic factors were diagnosed only after surgical exploration. The American Joint Committee on Cancer Staging and End Results Reporting (AJCC) was organized in 1959 to develop a staging system acceptable to the American medical profession, basically using the UICC/TNM format. In 1970, the AJCC published a TNM-based staging system, using clinical, surgical, and histological information [4]. The background database was from 1241 patients with gastric cancer, which had been analyzed by a task force from seven American institutions. The system used penetration of stomach wall (T), proximity to the primary cancer of metastatic perigastric lymph nodes (N), and presence or absence of distant metastases (M), including nodes not in the perigastric area, as these criteria had the greatest impact on outcome in the above cohort.

The third edition of the UICC/TNM in 1978 contained a unified classification with the AJCC. The T stage was defined by stomach-wall invasion, but the "clinical T" and "pathological T" had different definitions. The N stage was defined by anatomic location of nodes from N0 to N3. N1 nodes were defined as metastatic perigastric nodes within 3 cm of the primary, and N2 nodes were nodes beyond 3 cm from the primary, or along the celiac, splenic, left gastric, or hepatic arteries. N3 nodes were paraaortic and hepatoduodenal nodes. In the fourth of the TNM classification edition (1987), T stage was unified to the style of the current edition, and the N3 category was dropped and reclassified as M1 (Table 1).

Table 1. TNM classification, 4th edition; 1987

		M0			M1
		N0	N1	N2	
M0	T1	IA	IB	II	
	T2	IB	II	IIIA	
	T3	II	IIIA	IIIB	
	T4	IIIA	IIIB		
M1					IV

N1, perigastric nodes within 3 cm of the primary tumor; N2, nodes beyond 3 cm from the primary, or along the celiac, splenic, left gastric or hepatic arteries

Table 2. TNM classification, 5th edition; 1997

		M0				M1
		N0	N1	N2	N3	
M0	T1	IA	IB	II		
	T2	IB	II	IIIA		
	T3	II	IIIA	IIIB		
	T4	IIIA				IV
M1						

N1, 1–6 involved nodes; N2, 7–15 involved nodes; N3, >15 nodes

The fifth edition (1997) of the TNM classification contains several amendments from the previous edition. The greatest change was that, whereas previously N status was determined by the anatomical site of involved lymph nodes, in the new classification, N stage is determined by the number of metastatic lymph nodes from a minimum yield of 15 lymph nodes in total (N1, 1–6 involved nodes; N2, 7–15 involved nodes; and N3, >15 nodes; Table 2). This had been explored as an option for some time and a proposal to add the number of involved lymph nodes to the anatomical-based N stage was published by the UICC in 1993 [5]. The idea of adopting a number-based N-staging for gastric cancer had also been proposed by some Japanese surgeons [6,7]. Data from a German multicenter gastric cancer study showed the effectiveness of the new proposal in providing better prognostic stratification than previous systems [8].

The new classification was developed, with four N categories (N0 to N3) instead of three as was initially proposed, and was presented in Seoul, Korea, at the 12th International Seminar of the WHO Collaborating Centre for Gastric Cancer in 1996 [9].

In addition to the change in N status, hepatoduodenal nodes are now once again regarded as regional nodal metastases rather than distant metastases, and the stage grouping has been altered, with all N3 patients now classified as stage IV (Table 2). T4N1 disease has also been changed to stage IV, having previously been classified as stage IIIb in 1987.

The latest edition of the TNM classification (sixth edition; 2002) amends pT2 into the subgroups pT2a and pT2b, which represent invasion confined to the muscularis propria and subserosa, respectively. This equates to T2 MP and T2 SS in the JGCA classification.

Japanese classification

The first edition of the General Rules for Gastric Cancer Study was published by the Japanese Research Society for Gastric Cancer in 1962. Stage groups were defined by the extent of serosal involvement (S stage), the location of involved lymph nodes depending on the site of the primary tumor (N stage), and the extent and sites of distant metastases (M, H, and P stages for distant metastasis, and hepatic and peritoneal disease, respectively). In its twelfth edition, the General Rules changed from the S-stage to a T-stage system, which was equivalent to the T-staging of the UICC system.

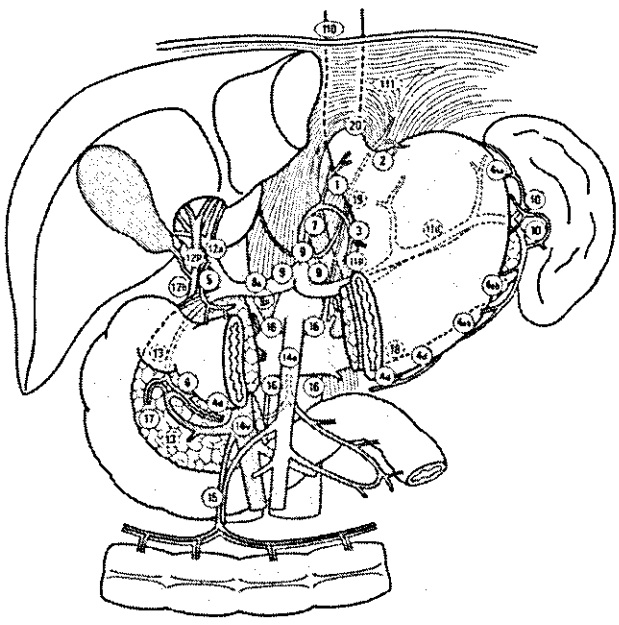

Fig. 1. Lymph node station numbers (*circled*) in the Japanese classification of gastric carcinoma [3]. These stations are further classified into N1/N2/N3 according the location of the primary tumor

The JGCA classification gives a number to all of the regional lymph node stations (Fig. 1), which are classified into three tiers according to the location of the primary tumor. Radical lymphadenectomy in gastric cancer surgery has long been commonplace in Japan and large databases of the incidence and sites of lymph node involvement exist, depending on the site of the tumor and its T stage. The purpose of the meticulous lymph node classification in the General Rules was therefore to guide surgeons to decide the extent and location of lymphadenectomy, so that any potentially involved nodes could be removed according to the site and depth of penetration of the primary gastric cancer.

Lymph node staging was characterized on the basis that gastric cancer metastasizes to groups of lymph nodes arranged radially around the stomach in tiers. The nomination of different lymph node groups to their respective tier was based upon the results of anatomical and physiological studies on lymph flow with different tumor sites.

Various amendments to the original classification followed, and the most recent classification is aimed at surgeons, pathologists, oncologists, and endoscopists who carry out endoscopic mucosal resection (EMR).

English versions were published in the *Japanese Journal of Surgery* in 1973 [10] and 1981 [11] and were referred to in Western studies. However, they were only a digest and could not fully convey the concept or details of the General Rules. The first comprehensive English edition was published in 1995 [12], based on the twelfth Japanese edition, and was named *Japanese classification of gastric carcinoma* (Table 3). The second English edition was based on the thirteenth Japanese edition, and was published in *Gastric Cancer* in 1998 [3].

There were a variety of changes in the most recent edition of the JGCA classification [13], such as rules for EMR and for staging carcinoma of the remnant stomach, and peritoneal cytology has been included in staging.

The most important changes in the current edition from a surgical point of view are the revision of lymph node staging and the consequent limitation of dissection level. Lymph node groups were reallocated from four tiers (N1 to N4) to three tiers (N1 to N3) on the basis of a detailed study of the effectiveness of dissection of different lymph node stations for tumors in the various locations within the stomach. Some lymph node groups, even some perigastric nodes for specific tumor locations, are no longer regarded as regional nodes if involved, but are regarded as sites of distant metastasis (M). This follows because their involvement is rare, and if it occurs, it invariably reflects a very bad prognosis [14]. One example would be the involvement of no. 2