

# Non-Hodgkin's Lymphomas of Follicular Center Cell Type in Osaka, Japan

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**Abstract**—Five hundred and nineteen patients with follicular center cell (FCC) tumors in Osaka, Japan were selected for study from 1000 patients with non-Hodgkin's lymphoma (NHL). They were admitted to hospital during 1964–1987, which was divided into three periods 1964–1972 (I), 1973–1979 (II), and 1980–1987 (III) to examine the time trend of FCC tumors. The median age of patients rose from 51 to 55 years of age with an increase in female and extranodal disease patients. The frequency of nodal FCC tumors among all nodal NHL increased from 37.5 to 51.5% ( $P < 0.05$ ), but that of extranodal types decreased from 82.9 to 56.8% ( $P < 0.01$ ), although the total number showed little change. When the cases were categorized as diffuse type and follicular type, the diffuse type predominated through the period in both nodal and extranodal sites. The frequencies of follicular type among all NHL were 10.2, 6.3, and 8.4% during the periods I, II and III, respectively. These results showed that follicular lymphoma was a minor constituent of NHL in Japan compared to Western countries, and the frequency did not increase from 1964 to 1987. The frequency of FCC tumors in the present series was rather higher than that in Western countries, therefore it is concluded that FCC tumors in Japanese have much less potential for forming a follicular structure than those in patients from Western countries.

## INTRODUCTION

ONE of the main differences in non-Hodgkin's lymphoma (NHL) in Japan from that in Western countries is a lower frequency of nodular lymphomas [1, 2]. The diagnosis of nodular lymphomas in the past was defined as proliferation of medium to large lymphoid cells forming nodular structures. Recent investigations have shown that the proliferating cells in the nodular lymphomas derived from follicular center cells (FCCs), thus it has been recommended that the term follicular is more appropriate than the term nodular for this disease [3, 4]. Because tumors of FCCs may be of a diffuse pattern, follicular lymphoma has been regarded as a follicular variant of FCC tumors. Whether FCC tumors in Japan are a minor component among NHLs thus resulting in the low frequency of follicular lymphoma or whether

they have a follicular pattern less frequently compared to those in Western countries remains unclear at present.

Epidemiological studies have shown that the incidence rates for cancer at selected primary sites in patients in Osaka, Japan are becoming closer to those observed in North America [5]. This time trend of cancer incidence might be due to the change of the Japanese life style to a Western style [6]. Recently, our investigation of Hodgkin's disease in Osaka, Japan [7] revealed that the frequency of Hodgkin's disease did not increase but the distribution of histologic subtypes became closer to that in Western countries.

In the present study, we examined the frequencies of follicular lymphomas among all NHLs and FCC tumors in Osaka, Japan and, subsequently, the chronological change in ratio of FCC tumors showing follicular to diffuse proliferation, during the period 1964–1987, was studied to examine the time trend of follicular NHL in Japan.

## MATERIALS AND METHODS

Biopsy specimens obtained from 15 hospitals in Osaka and Hyogo prefectures, Japan were reviewed,

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a total of 1637 cases were diagnosed histologically as malignant lymphoma and related diseases during the period 1964–1987. Paraffin blocks were obtained in all cases and sectioned at 4  $\mu$ m for hematoxylin and eosin staining or, if necessary, additional stains (periodic acid–Schiff reaction, silver impregnation etc.). The slides were reviewed by one of us (K.A.). Five hundred and fifteen cases were diagnosed as non-lymphoid malignancy, reactive diseases, or undefined diseases; they were eliminated. Numbers and ratios of cases diagnosed as non-lymphomatous diseases were 132/285 cases (46.3%), 204/594 cases (34.3%), and 179/758 cases (23.6%) in the periods 1964–1972, 1973–1979, and 1980–1987, respectively. The remaining 1122 cases were confirmed to be malignant lymphomas, of which 1000 cases (89.1%) were non-Hodgkin's lymphoma (NHL) and 122 cases (10.9%) were Hodgkin's disease (HD). The general features of NHL and HD, in a part of these cases, have been previously reported [1, 7]. Based on the criteria proposed by Lennert [3] and Lukes *et al.* [4], 519 out of 1000 cases of NHL showing proliferation of centrocytes (cleaved cells) and/or centroblasts (non-cleaved cells) were regarded as the tumors derived from the FCCs and selected for the present study. They were classified as centrocytic, centroblastic/centrocytic, or centroblastic types by the Kiel classification [3]. Each type of tumor was subdivided into five groups according to the extent of follicular area in the tumors as follows: nil, less than 25%, 50%, 75% or over 75%. To examine the chronological change of histologic types, the cases were divided into three time periods: 1964–1972, 1973–1979, and 1980–1987. Brief clinical information including age, sex, and sites of the tumors was available. The primary site of tumor was nodal in 553 patients, extranodal in 416, and unknown in 31. The extranodal tumors were situated in the gastrointestinal tract in 119 cases, Waldeyer's ring in 111, skin in 34, nose and paranasal sinuses in 27, thyroid in 18, and elsewhere in 67. The intervals from the appearance of the tumors to biopsy or operation was identified in 29 cases of follicular lymphoma and 54 of diffuse lymphoma of FCC type selected at random.

## RESULTS

The numbers of patients with NHL during the periods 1964–1972 (I), 1973–1979 (II), and 1980–1987 (III) were 127, 350, and 523, respectively. The age of patients in groups I, II, and III ranged from 2 to 79 years (median 51 years), 1 to 88 years (median 57 years), and 4 to 91 years (median 55 years) with male to female ratios of 2.9, 1.4, and 1.7, respectively. This showed an increase in the proportion of female patients (Table 1). The ratios of nodal to extranodal NHL were 2.5, 1.4, and 1.1, respectively, showing a gradual increase in extranodal NHL.

The histologic distribution of NHL according to the Kiel classification is shown in Table 2. The frequencies of FCC tumors among all NHLs in nodal, extranodal, and both sites are given in Table 3. The frequency of nodal FCC tumors gradually increased from 37.5 to 51.5% ( $P < 0.05$ ), but that in extranodal sites decreased from 82.9 to 56.8% ( $P < 0.01$ ) without a significant change in the frequency of FCC tumors. The frequencies of FCC tumors with varying degrees of follicularity among nodal, extranodal, and all NHLs are given in Table 4. Group 1 with no follicular areas was the most prevalent through periods I (35.4%), II (34.9%), and III (40.2%). The percentages of Group 5, that is cases of showing over 75% of follicular area, were 10.2%, 6.3%, and 8.4% during periods I, II, and III, respectively. When these five subgroups were reclassified as diffuse type (Groups 1 + 2) and follicular type (Groups 3 + 4 + 5), the diffuse type increased with time from 23.8 to 33.9% among the cases with nodal FCC tumors. But this change was not statistically significant. Meanwhile, the cases with follicular type decreased among the cases with extranodal FCC tumors from 11.4 to 7.1%. This change also was not significant. As a result, the frequency of total FCC tumors with the follicular pattern showed a slight decrease among all NHL. The frequencies of the patients over 70 years of age in the various sub-groups of lymphomas are given in Table 5. Intervals from the appearance of tumors to biopsy or operation ranged from 1 week to 12 months (median 2.8 months) and 2 days to 18 months (median 2.8 months) in the patients with

Table 1. Site, age and sex ratio of non-Hodgkin's lymphomas

Period	Number of cases			Age (years)	Sex ratio (M:F)
	Nodal	Extranodal	Total	Range (median)	
1964–1972	88	35	127	2–79 (51)	2.9:1
1973–1979	197	138	350	1–88 (57)	1.4:1
1980–1987	268	243	523	4–91 (55)	1.7:1
1964–1987	553	416	1000	1–91 (55)	1.6:1

Table 2. Results of Kiel classification in 1000 cases with non-Hodgkin's lymphomas

Histologic type	Number of cases (%)
Lymphocytic	22 (2.2%)
Lymphoplasmacytic/lymphoplasmacytoid	47 (4.7%)
Centrocytic	47 (4.7%)
Centroblastic/centrocytic, follicular	99 (9.9%)
Centroblastic/centrocytic, diffuse	247 (24.7%)
Centroblastic	126 (12.6%)
Lymphoblastic	64 (6.4%)
Immunoblastic	149 (14.9%)
Undefined	199 (19.9%)

Table 3. The frequencies of follicular center cell tumors among non-Hodgkin's lymphomas

Period	Number of cases with FCC tumors (% among all NHL in each site)		
	Nodal	Extranodal	Total
1964-1972	33 (37.5)	29 (82.9)	64 (50.4)
1973-1979	87 (44.2)	80 (58.0)	172 (49.1)
1980-1987	138 (51.5)	138 (56.8)	283 (54.1)
1964-1987	254 (46.7)	247 (59.4)	519 (51.9)

FCC: follicular center cell; NHL: non-Hodgkin's lymphoma.

follicular type (Groups 1 + 2) and diffuse type (Groups 3 + 4 + 5), respectively.

## DISCUSSION

Follicular lymphoma is categorized as one of the FCC tumors, therefore its characterization should be made in consideration of their relationship. The present study showed that the frequencies of FCC tumors in the nodal and extranodal NHLs were 46.7 and 59.4%, respectively, both of them were about 10% higher than that reported from the West Germany (38.3%) [3] and North America (41.2%) [4]. NHL in Japanese comprised more FCC tumors than in Western countries.

Previous study has revealed that NHL in Japan has a much lower frequency of follicular type [1]. Even when the cases with a small amount of follicular formation were accepted as follicular type, the present series had a low incidence of follicular types, 15.7% in nodal cases and 7.5% of extranodal cases, compared to 31-44% [2, 8] in Western countries. The frequency of follicular type among FCC tumors in our series (22.9%) was much lower than the 77% reported by Lennert from West Germany [3] and 65% by Nobholz *et al.* from France [8]. These findings indicated that the proliferating cells of FCC tumors in indigenous Japanese more frequently showed a diffuse pattern than patients living Western countries.

Table 4. The frequencies of follicular center cell tumors divided into five groups\* among all non-Hodgkin's lymphomas

	Number of cases with follicular center cell tumors (% among all NHL in each site)								
	1964-1972			1973-1979			1980-1987		
	Nodal	Extranodal	Total	Nodal	Extranodal	Total	Nodal	Extranodal	Total
Group 1	20 (22.7)	24 (68.6)	45 (35.4)	48 (22.4)	69 (50.0)	122 (34.9)	85 (31.7)	118 (48.6)	210 (40.2)
Group 2	1 (1.1)	1 (2.9)	2 (1.6)	11 (5.6)	1 (0.7)	12 (3.4)	6 (2.2)	3 (1.2)	9 (1.7)
Group 3	1 (1.1)	0 (0)	1 (0.8)	6 (3.0)	5 (3.6)	11 (3.1)	7 (2.6)	8 (3.3)	15 (2.9)
Group 4	3 (3.4)	0 (0)	3 (3.1)	5 (2.5)	0 (0)	5 (1.4)	4 (1.5)	1 (0.4)	5 (1.0)
Group 5	8 (3.4)	4 (11.4)	13 (10.2)	17 (8.6)	5 (3.6)	22 (6.3)	36 (13.4)	8 (3.3)	44 (8.4)

\*Extent of follicular area was 0% (Group 1), <25% (Group 2), ~50% (Group 3), ~75% (Group 4), >75% (Group 5).  
NHL: non-Hodgkin's lymphoma.

Table 5. The number and frequencies of patients older than 70 years among all non-Hodgkin's lymphomas and follicular center cell tumors

Period	Number of cases (% among all NHL)			Number of cases (% among FCC tumors)		
	Nodal	Extranodal	Total	Nodal	Extranodal	Total
1964-1972	11 (12.5)	2 (5.7)	13 (10.2)	7 (21.2)	2 (6.9)	9 (14.1)
1973-1979	36 (18.3)	37 (26.8)	73 (20.9)	23 (26.4)	24 (30.0)	47 (27.3)
1980-1987	70 (26.1)	56 (23.0)	128 (24.5)	30 (21.7)	30 (21.7)	62 (21.9)

NHL: non-Hodgkin's lymphoma; FCC: follicular center cell.

The chronological change of histological forms in our cases was reflected in the ratio of nodal to extranodal NHL, with the extranodal rising from 27.6 to 46.5% during the period 1964–1987. A previous study revealed that the frequency of extranodal NHL among all NHL was higher in Japan (37.6%) than in the Western countries (24–36%) [2], thus the present study seemed to suggest that the pattern of NHL in Japan has become distinct from that in Western countries. However, the present result might be influenced by the increase in elderly female patients who frequently showed extranodal tumors (Table 4).

The relative frequency of FCC tumors among all NHL was increased in the nodal site (from 37.5 to 51.5%) but decreased in the extranodal site (from 82.9 to 56.8%), resulting in no remarkable change in total FCC tumors. The frequency of FCC tumors with follicular structure among all FCC tumors slightly increased in the nodal site (13.6 to 17.5%) but decreased in the extranodal site (from 11.4 to 7.6%).

The marked lower frequency of the follicular lymphoma among FCC tumors in the present survey of Japanese cases could result from the proliferating cells in FCC tumors less frequently forming a follicular pattern or the Japanese patients with FCC tumors being admitted to hospital in a more advanced stage than Western patients. It is well known that diffuse lymphoma could evolve from

follicular lymphoma, i.e. a diffuse lymphoma of FCC type might be an advanced stage of a follicular lymphoma [9]. There were no significant differences in the intervals between the appearance of tumors and biopsy or operation among the patients with follicular type and diffuse type, indicating that the preponderance of diffuse type was not caused by a delay in the diagnosis of patients originally having a follicular tumor.

In conclusion, this study has shown that follicular lymphoma is a minor constituent of NHL in Japan, and its frequency did not increase from 1964–1987. The recent change of cancer in Japan to resemble that in Western countries is thought to be due to the change of Japanese life style to a Western style [6]. However, the current study indicates that lymphoid malignancies, at least follicular center cell tumors, are less influenced by life style than epithelial malignancies such as cancers in the stomach, colon, mammary gland, and lung. Also, it is suggested that follicular center cell tumors in Japanese have a lower potential for forming a follicular structure than those seen in Western countries. Factors affecting the formation of follicular structure could be investigated by comparing follicular center cell tumors in Japan and Western countries.

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