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The International Prognostic Index predicts outcome in aggressive adult T-cell leukemia/lymphoma: analysis of 126 patients from the International Peripheral T-cell Lymphoma Project

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Background: The International Peripheral T-cell Lymphoma Project was organized to better understand the T-cell and natural killer (NK) cell lymphomas, and our task is to present the clinicopathologic correlations and therapeutic results for adult T-cell leukemia/lymphoma (ATL).

Patients and methods: Among 1153 patients with T-cell or NK cell lymphomas, 126 patients (9.6%) with ATL were represented in this project. All were categorized as aggressive ATL, i.e. acute or lymphoma type, and 87% fell into the lymphoma type.

Results: The median age was 62 years and the male to female ratio was 1.2 : 1. Significant prognostic factors for overall survival (OS) by univariate analysis were the presence of B symptoms ($P = 0.018$), platelet count $<150 \times 10^9$/l ($P = 0.065$), and the International Prognostic Index (IPI; $P = 0.019$). However, multivariate analysis indicated that only the IPI was an independent predictor of OS. Combination chemotherapy including anthracyclines was given as the initial therapy in 109 of the 116 patients (94%) who received treatment, and the overall and complete response rates were 70% and 34%, respectively. However, there was no survival benefit for those receiving an anthracycline-containing regimen.

Conclusion: Patients with aggressive ATL have a poor clinical outcome and the IPI is a useful model for predicting outcome in ATL of the lymphoma type.

Key words: ATL, leukemia, lymphoma, T-cell, prognostic index, international

introduction

Adult T-cell leukemia/lymphoma (ATL) is a peripheral T-cell malignancy caused by a retrovirus, human T-cell lymphotropic virus type I (HTLV-1) [1, 2], and is now regarded as a tumor derived from regulatory T cells which express FoxP3 [3, 4]. ATL is diagnosed based on its characteristic clinicopathologic features and the presence of integrated HTLV-1 provirus in the DNA of the tumor cells. ATL has characteristic cytological features with atypical 'flower cells' in the peripheral blood and pleomorphic lymphoma cells in tissue sections [1, 2, 5] and can be divided into four clinical subtypes, i.e. smoldering, chronic, acute, and lymphoma types. The acute type is the most common variant, presenting with disseminated disease and having a highly aggressive clinical course. In contrast, the smoldering type has an indolent clinical course with only a small percentage of leukemic cells and occasional skin involvement. The chronic type also has an indolent clinical course, but with a higher percentage of leukemic cells, slowly progressive skin disease, mild lymphadenopathy, and hepatosplenomegaly. The lymphoma type usually presents with disseminated disease including prominent lymph node enlargement, but with few leukemic cells [1, 2, 5]. The aggressive forms of ATL, including the acute and lymphoma types, are usually treated with combination chemotherapy, but the prognosis is poor with a median survival of <1 year

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compared with other forms of peripheral T-cell lymphoma (PTCL) [6–9].

In the past decade, there have been significant advances in our understanding of the biology of malignant lymphoma and some progress in treatment as well. However, our understanding of PTCL in general is far behind that of the B-cell lymphomas. Therefore, the International Peripheral T-cell Lymphoma Project was organized to assess the clinical applicability and reproducibility of the World Health Organization classification of peripheral T-cell and natural killer (NK) cell lymphomas, as well as to evaluate therapeutic outcomes and identify prognostic factors [10]. This report describes the clinicopathologic correlations and therapeutic results for patients with ATL from the International Peripheral T-cell Lymphoma Project.

patients and methods

We collected previously untreated patients with *de novo* peripheral T-cell or NK/T-cell lymphoma, excluding mycosis fungoides and Sézary syndrome, who were diagnosed from 1 January 1990 to 31 December 2002, in 22 centers in 13 countries around the world (Appendix 1) [10]. The diagnosis of ATL was based on histologic features and the presence of either positive HTLV-1 serology or monoclonal integration of HTLV-1 provirus [2, 9]. All cases were reviewed by four expert hematopathologists, and a consensus diagnosis was made by the agreement of three or four experts. We collected clinical data and laboratory findings including HTLV-1 serology, leukocyte count, and absolute lymphocyte count, as well as initial treatment and subsequent therapy. Treatment outcome was determined by overall survival (OS) and failure-free survival (FFS). OS was defined as the time from diagnosis to death from any cause, with surviving patient follow-up being censored at the last contact date. FFS was defined as the time from diagnosis to first progression, relapse after response, or death from any cause. Follow-up of patients not experiencing any of these events was censored at the date of last contact. OS and FFS were calculated by the method of Kaplan and Meier, and time to event distributions were compared using the log-rank test. Comparisons of clinical and prognostic factors were carried out using the chi-square or Fisher's exact test. Multivariate analysis was carried out with a Cox hazards regression model using stepwise selection.

Table 1. Clinical characteristics of 126 patients with aggressive ATL

Age (years)		
Median (range)	62	(20–92)
Sex		
Male/female	69/57	1.2 : 1
Stage		
I/II	12	9.6%
III	22	17.6%
IV	91	72.8%
B symptoms		
No	87	69.0%
Yes	39	31.0%
Performance status		
Ambulatory	97	77.0%
Nonambulatory	29	23.0%
Largest mass		
<5 cm	74	65.5%
≥5 cm	39	34.5%
Bone marrow involvement		
No	87	71.9%
Yes	34	28.1%
Nodal/extranodal disease		
Nodal only	37	31.4%
Nodal and extranodal	72	61.0%
Extranodal only	9	7.6%
Extranodal sites		
0–1	83	65.9%
≥2	43	34.1%
Serum LDH		
≤Normal	74	59.7%
>Normal	50	40.3%
Absolute lymphocyte count		
<4000/μl	104	86.7%
≥4000/μl	16	13.3%
IPI scores		
0/1	23	18.5%
2	41	33.1%
3	40	32.3%
4/5	20	16.1%

ATL, adult T-cell leukemia/lymphoma; LDH, lactate dehydrogenase; IPI, International Prognostic Index.

results

In this project, 1314 cases were collected from North America, Europe, and Asia, and a diagnosis of PTCL or NK/T-cell lymphoma was confirmed in 1153 cases. ATL was diagnosed in 126 patients (9.6%) and was rare in North America (2.0%) and Europe (1.0%), but frequent in Asia (25%) among all PTCL patients. All the Asian cases were from Japan.

There are four clinical subtypes of ATL, i.e. smoldering, chronic, acute, and lymphoma types, in Shimoyama's classification [5]. In this study, smoldering and chronic ATL were excluded. The lymphoma type of ATL is defined by a lymphocyte count of <4000/μl in Shimoyama's classification [5]. Thus, 104 patients (87%) were classified as the lymphoma type and the rest as acute type (13%).

The clinical characteristics of the 126 ATL patients are shown in Table 1. There were 69 males and 57 females, with a median age of 62 years. Major signs and symptoms included lymphadenopathy (77%), fatigue (32%), anorexia (26%), skin eruption (23%), abdominal pain (23%), splenomegaly (13%), and hepatomegaly (10%). Overall, 90% of the patients had advanced stage disease by the Ann Arbor classification, 31% had B symptoms, and 23% were nonambulatory. Bone marrow infiltration and two or more sites of extranodal involvement were seen in 28% and 34% of the cases, respectively. In addition, 20 patients (17%) had a platelet count of $<150 \times 10^9$/l. We were able to evaluate 124 patients according to the International Prognostic Index (IPI) [11] and only 18.5% were in the good prognosis category (IPI = 0/1).

Chemotherapy was given to 116 patients, and combination chemotherapy including an anthracycline was given as an initial therapy to 109 patients (94.0%). Autologous or allogeneic hematopoietic stem-cell transplantation (HSCT) was carried out in 17 patients, including 10 patients as initial therapy and

seven in first relapse. The response to initial therapy is shown in Table 2. The overall and complete response rates were 70% and 34%, respectively. However, majority of the patients (82%) have died, mostly from lymphoma or the complications of therapy. Only 5% of the patients were in complete remission at the time of death, and the median FFS and OS were only 0.6 and 0.8 years, respectively (Figure 1).

Table 3 shows the significant prognostic factors by the univariate analysis. Adverse prognostic factors for OS were the presence of B symptoms ($P = 0.018$), a platelet count $<150 \times 10^9$/l ($P = 0.065$), and a high (≥3) IPI score ($P = 0.019$; Figure 2A). Unexpectedly, bone marrow involvement, an elevated absolute lymphocyte count (≥4000/μl; Figure 3), elevated serum lactate dehydrogenase (LDH), hypercalcemia, and combination chemotherapy without an anthracycline (Figure 4) had no influence on OS. The IPI score was the only significant predictor of survival in multivariate analysis. Figure 5 shows OS according to the IPI in the lymphoma type of ATL (lymphocytes < 4000/μl). The IPI predicted for OS in the lymphoma type of ATL ($P = 0.04$), but not in the acute type (not shown; $P = 0.24$). Based on these results, the IPI is a useful model for predicting outcome in ATL of the lymphoma type.

Table 2. Response to initial therapy and clinical course in aggressive ATL

Treatment response	CR	32 (28%)		
	CRu	7 (6%)	CR + PR	81 (70%)
	PR	42 (36%)		
	NR	35 (30%)		
Recurrence of disease				71 (88%)
Alive 23 (18%)/dead 103 (82%)				
Causes of death	Lymphoma			74 (75%)
	Toxicity			10 (10%)
	Infection			2 (2%)
	Myelodysplasia			1 (1%)
	Other			8 (8%)
	Unknown			8 (8%)
Remission at death				5 (5%)

ATL, adult T-cell leukemia/lymphoma; CR, complete response; CRu, complete response unconfirmed; PR, partial response; NR, no response.

discussion

The International Peripheral T-cell Lymphoma Project was organized to better understand the T-cell and NK cell lymphomas [10]. ATL is endemic in southwest Japan, the Caribbean Islands, countries surrounding the Caribbean Basin, and parts of Central Africa and South America [12]. In the present study, one half of the patients were registered from Fukuoka, located in southwest Japan, and 30% from the rest of Japan, but none from the rest of Asia. Also, 20% of the patients were registered from Europe or North America including two patients from the Vancouver site and highlighting a previously unknown HTLV-1 endemic region. Both of these patients were indigenous American Indians [13].

The present study reveals that the IPI has predictive value for patients with aggressive ATL, particularly those with the lymphoma type. A previous nationwide study in Japan revealed five adverse prognostic factors for ATL by multivariate analysis: (i) age over 40 years; (ii) low performance score; (iii) hypercalcemia; (iv) elevated serum LDH level; and (v) the number of lesions [14]. These prognostic factors are similar to those in the IPI. This previous study in Japan reported on 818 ATL patients diagnosed from 1984 to 1987 [5, 14], with 56.5% having the acute type, 19.1% the lymphoma type, 18.6% the chronic type, and 5.5% with the smoldering type of ATL. Thus, the acute type is the most common subtype of ATL in Japan [5, 7, 8, 14]. However, in the present study, 87% of the patients had the lymphoma type and the rest had the acute type. The IPI has been shown to predict outcome in patients with PTCL [15], but cases of ATL were not included in that study. Although the IPI was developed for patients with aggressive B-cell lymphoma treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens [11], our study shows that the IPI is also useful for predicting outcome in aggressive ATL, especially the lymphoma type.

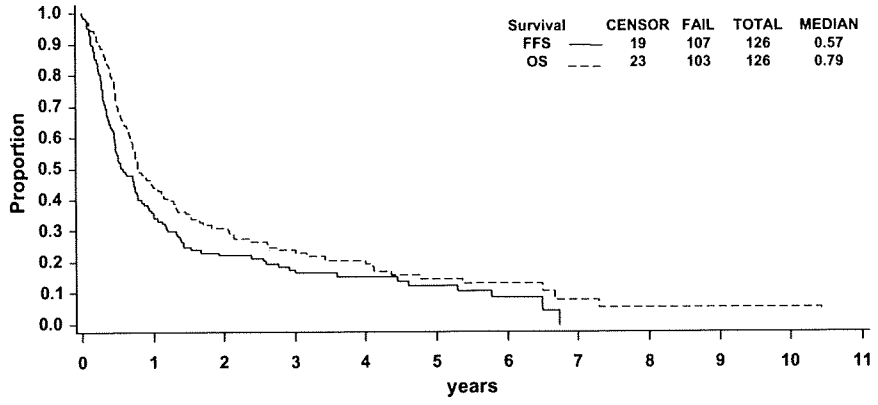

Figure 1. Overall survival (OS) and failure-free survival (FFS) of 124 patients with the aggressive adult T-cell leukemia/lymphoma.

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The frequency of bone marrow involvement was only 28% in the present study, but was 85% in the previous Japanese report [14]. This difference is most likely due to the differences in ATL subtypes in the two studies. Although few reports have described the frequency of bone marrow involvement in the various subtypes of ATL, Kinoshita [16] reported that 60 of 65 patients (92.3%) with the acute type, but only 7 of 40 patients (17.5%) with the lymphoma type, had bone marrow involvement. Recently, Takasaki et al. [17] reported that visceral organ involvement, including the bone marrow, was a prognostic factor in ATL. Thrombocytopenia ($<100 \times 10^9$/l) and monocytosis ($\geq 0.8 \times 10^9$/l) were also found to be significant adverse prognostic factors by multivariate analysis. In contrast, we could identify no significant prognostic factors other than the IPI by multivariate analysis. However, Takasaki et al. [17] analyzed 168 ATL patients consisting of 75% with the acute type, 9% with the lymphoma type, 15% with the chronic type, and 4% with the smoldering type. Therefore, the proportions of the various subtypes in that paper were quite different from those in the present study, making meaningful comparisons difficult. Furthermore, in a recent report, the acute and the lymphoma types of ATL were found to be genomically different [18]. Thus, future studies of ATL should include separate analyses of prognostic factors for each of the ATL subtypes.

Table 3. Prognostic factors in aggressive ATL by univariate analysis

Factors	*n*	Median OS (years)	
B symptoms			
No	87	1.12	$P = 0.018$
Yes	39	0.66	
Platelet count ($\times 10^9$/l)			
≥150	101	0.85	$P = 0.065$
<150	20	0.67	
IPI score			
0/1	23	2.07	$P = 0.019$
2	41	1.32	
3	40	0.71	
4/5	20	0.73	

ATL, adult T-cell leukemia/lymphoma; OS, overall survival; IPI, International Prognostic Index

The clinical outcome in our series of aggressive ATL was extremely poor, with a median OS of only 0.8 years. Combination chemotherapy including an anthracycline was given to most of our patients, but did not improve the survival significantly. These data confirm that CHOP and CHOP-like regimens are not effective in aggressive ATL [19, 20]. Tsukasaki et al. [21] recently reported the results of a phase III trial (JCOG 9801) comparing the safety and efficacy of vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP); doxorubicin, ranimustine, and prednisone (AMP); and vindesine, etoposide, carboplatin, and prednisone (VECP) (VCAP–AMP–VECP) versus biweekly CHOP in the aggressive types of ATL. The 3-year OS of those receiving VCAP–AMP–VECP therapy was only 24%, which was similar to our study. Allogeneic HSCT for ATL appears to be effective in some patients [22, 23], but there are inherent problems including

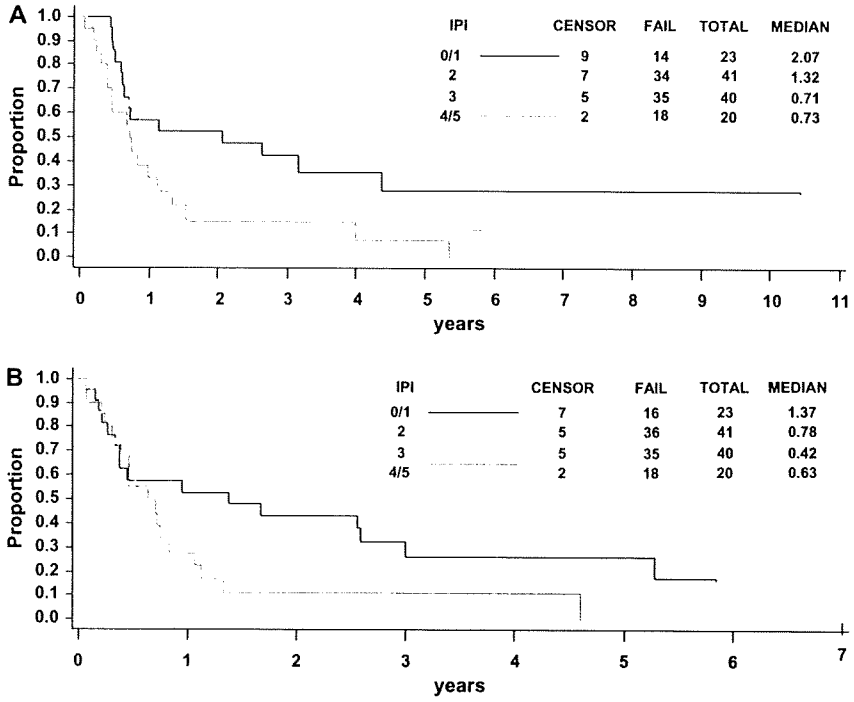

Figure 2. Overall survival (A) and failure-free survival (B) of patients with aggressive adult T-cell leukemia/lymphoma according to the International Prognostic Index (A, $P = 0.019$; B, $P = 0.14$).

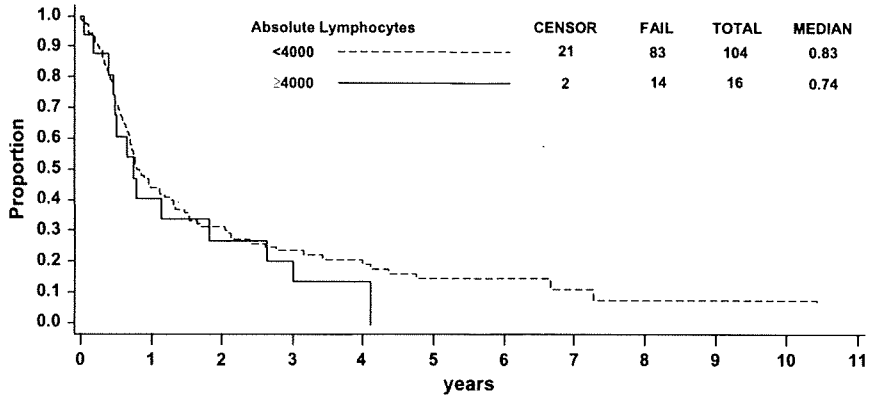

Figure 3. Overall survival of patients with aggressive adult T-cell leukemia/lymphoma according to the absolute lymphocyte count ($P = 0.44$).

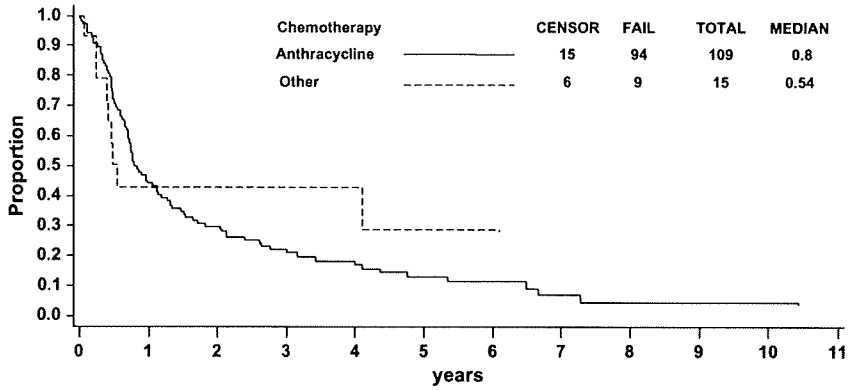

Figure 4. Overall survival of patients with aggressive adult T-cell leukemia/lymphoma according to treatment with or without an anthracycline ($P = 0.63$).

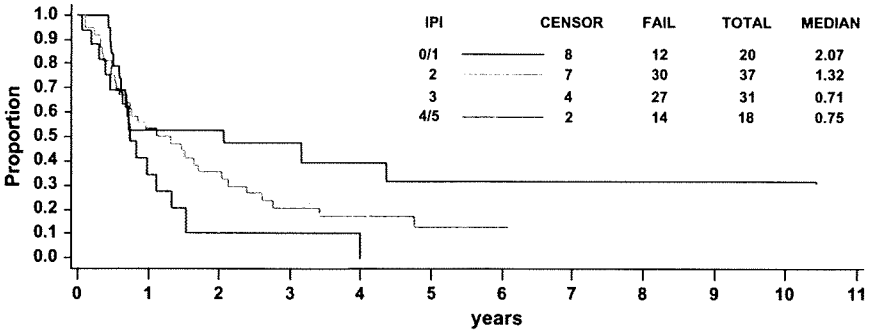

Figure 5. Overall survival of patients with the lymphoma type of adult T-cell leukemia/lymphoma according to the International Prognostic Index ($P = 0.04$).

high transplantation-related mortality, the use of HTLV-1-seropositive donors, and, most importantly, the proper selection of patients who will benefit from this therapy.

Unfortunately, we found no clues that might improve the treatment of ATL from this study. Nonetheless, further international collaboration using novel strategies is necessary to develop better therapies for this difficult disease. This study from the International Peripheral T-cell Lymphoma Project is the first report describing the results of an international cooperative study of ATL and thus represents an important first step in the international effort to improve the treatment and outcome of patients with ATL and other forms of PTCL.

Appendix 1 Participating sites and physicians

British Columbia Cancer Agency	Vancouver, Canada	Kerry Savage, MD; Joseph Connors, MD; Randy Gascoyne, MD; Mukesh Chhanabhai, MD
National Cancer Institute	Bethesda, MD	Wyndham Wilson, MD; Elaine Jaffe, MD
University of Nebraska Medical Center	Omaha, NE	James Armitage, MD; Julie Vose, MD; Dennis Weisenburger, MD; James Anderson, PhD; Fred Ullrich, MS; Martin Bast, BS
Massachusetts General Hospital	Boston, MA	Ephraim Hochberg, MD; Nancy Harris, MD
Los Angeles County Hospital, University of Southern California	Los Angeles, CA	Alexandra Levine, MD; Bharat Nathwani, MD
Arizona Cancer Center	Tucson, AZ	Thomas Miller, MD; Lisa Rimsza, MD
University of Barcelona Hospital	Barcelona, Spain	Emili Montserrat, MD; Armando Lopez-Guillermo, MD; Elias Campo, MD
Spanish National Cancer Center	Madrid, Spain	Marta Cuadros, MD; Javier Alvarez Ferreira, MD; Beatriz Martinez Delgado, MD
Norwegian Radium Hospital	Oslo, Norway	Harold Holte, MD; Jan Delabie, MD
University of Würzburg Hospital	Würzburg, Germany	Thomas Rüdiger, MD; Konrad Müller-Hermelink, MD; Peter Reimer, MD; Patrick Adam, MD
	Nurnberg, Germany	Martin Wilhelm, MD
	Hamburg, Germany	Norbert Schmitz, MD
	Munich, Germany	Christoph Nerl, MD
St James Hospital	Leeds, UK	Kenneth A. MacLennan, MD
University of Bologna Hospital	Bologna, Italy	Pier Luigi Zinzani, MD; Stefano Pileri, MD
Intergruppo Italiano Linfomi and the University of Modena Hospital	Modena, Italy	Massimo Federico, MD; Monica Bellei, PhD
Centre Hospitalier Lyon-Sud	Lyon, France	Bertrand Coiffier, MD; Francoise Berger, MD
King Chulalongkorn Hospital	Bangkok, Thailand	Intragumtornchai Tanin, MD; Pongsak Wannakrairot, MD
Queen Mary Hospital	Hong Kong, China	Wing Au, MD; Raymond Liang, MD; Florence Loong, MD
Singapore General Hospital	Singapore	Sandeep Rajan, MD; Ivy Sng, MD
National Cancer Center Hospital of Japan	Tokyo, Japan	Kensei Tobinai, MD; Yoshihiro Matsuno, MD
Aichi Cancer Center	Nagoya, Japan	Yasuo Morishima, MD; Shigeo Nakamura, MD; Masao Seto, MD, PhD
Okayama University Hospital	Okayama, Japan	Mitsune Tanimoto, MD; Tadashi Yoshino, MD
Fukuoka University Hospital	Fukuoka, Japan	Junji Suzumiya, MD; Koichi Ohshima, MD
Samsung Medical Center	Seoul, Korea	Won-Seog Kim, MD; Young-Hyeh Ko, MD

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