Close association between IgG4-related disease and malignancy within 12 years after diagnosis: an analysis of 158 patients after long-term follow-up

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Abstract

***Objectives*:** As it is controversial whether IgG4-related disease (IgG4-RD) is associated with malignancy, we evaluated the incidence of cancer development in a large cohort of IgG4-RD patients.

***Methods*:** A total of 158 patients diagnosed as having IgG4-RD between 1992 and 2012 were enrolled. We calculated the standardized incidence ratio (SIR) and cumulative rate of malignancies in this group and searched for risk factors associated with the occurrence of tumors.

***Results*:** A total of 34 malignancies were observed in the IgG4-RD patients over a mean follow-up period of 5.95±4.48 years. The overall SIR of malignancies was 2.01 (95% confidence interval [CI] 1.34-2.69). The SIR of patients who exhibited a tumor within 1 year after IgG4-RD diagnosis was 3.53 (95% CI 1.23-5.83), while that of subjects forming a malignancy in subsequent years was 1.48 (95% CI 0.99-1.98). The cumulative rate of malignancy development was significantly higher in patients with IgG4-RD within 12 years after diagnosis than that in the Japanese general population. Comparable results were obtained for an AIP subgroup. The serum concentrations of several disease activity markers at diagnosis were significantly higher in patients with malignancies than in those without.

***Conclusion*:** We identified a close association between IgG4-RD and malignancy formation within 12 years after diagnosis, particularly during the first year. An active IgG4-RD state is presumed to be a strong risk factor for malignancy development.

Key Indexing Terms:

IgG4-related disease (IgG4-RD), autoimmune pancreatitis (AIP), malignancies, activity marker

Introduction

IgG4-related disease (IgG4-RD) is a systemic condition characterized by high serum IgG4 concentration and IgG4-bearing plasma cell infiltration in affected organs (1-3). The concept of IgG4-RD was established through extensive evaluation of extra-pancreatic lesions complicating autoimmune pancreatitis (AIP) (2). IgG4-RD characteristically involves multiple organs, and is believed to manifest as Mikulicz's disease (4), respiratory disorders (5), sclerosing cholangitis (6), retroperitoneal fibrosis (3), tubulointerstitial nephritis (7), and prostatitis (8). Although corticosteroid therapy is effective for IgG4-RD, relapses sometimes occur during dose tapering and maintenance phases (9-11).

Recently, the long-term outcome of this new disease entity has been described to include the complication of malignancy development (12-14). Yamamoto et al. reported that patients with IgG4-RD were significantly more prone to malignancies than the general population in a follow-up study of 105 patients (15). Shiokawa et al. uncovered similar results in 108 patients with AIP (16). Since the occurrence of malignancies in the first year after diagnosis was significantly higher than that in subsequent years, the authors proposed that AIP may feature aspects of a paraneoplastic syndrome and that the fate of AIP patients was closely influenced by the occurrence and treatment of malignancies. On the other hand, Hirano et al. reported that IgG4-RD was not significantly associated with malignancy after evaluating 113 patients with IgG4-RD (17). This may have been due to the fact that whereas Hirano excluded cases of malignancies that were diagnosed

concomitantly with IgG4-RD, Yamamoto and Shiokawa did not. Hart et al. also noted that 116 patients with type 1 AIP were not significantly complicated with malignancies when compared with 344 control subjects from a primary care clinic (18). Accordingly, the issue of whether an association exists between IgG4-RD and malignancy remains controversial.

Close relationships have been identified between chronic inflammation and malignancy, including one between gastric cancer and gastritis from Helicobacter pylori (19, 20) and another between hepatocellular carcinoma and viral hepatitis (21, 22). Similarly, the chronic inflammatory state of IgG4-RD may be related to malignancies in systemic organs in which IgG4-RD is found. Furthermore, because IgG4-RD is recognized as an autoimmune disease that occurs predominantly in the elderly, a deficiency in immune surveillance may trigger the occurrence of this disease, which in turn induces associated malignancies (23). Elevated patient age also appears to be a major contributing factor to the occurrence of malignancies in general (24). It will be necessary to precisely identify the time of IgG4-RD onset, affected lesions, and various other risk factors in a large number of patients following long-term observation to clarify whether IgG4-RD is related to malignancy. The aim of the present study is to determine the key relationships between IgG4-RD and malignancy, such as if IgG4-RD is significantly complicated by malignancy.

Materials and Methods

1. Patients

We enrolled 158 patients with IgG4-RD (119 men and 39 women, median age at IgG4-RD onset: 72 years) who had been diagnosed based on the Japanese Comprehensive Diagnostic Criteria for IgG4-RD (25) between 1992 and 2012 at our clinic or affiliated hospitals. The cohort included 109 patients with type 1 AIP (84 men and 25 women, median age at AIP onset: 66 years), among whom 103 patients possessed extra-pancreatic lesions. AIP was diagnosed according to the International Consensus Diagnostic Criteria 2011 (ICDC 2011) that were based mainly on characteristic imaging findings, high serum IgG4 concentration, the presence of extra-pancreatic lesions (other IgG4-RDs), and steroid responsiveness, and less on pathological findings since pancreatic biopsy samples have been difficult to obtain in sufficient sample sizes for correct diagnosis (26). One hundred and eleven patients received steroid therapy when involved vital organs exhibited a risk of serious organ dysfunction or failure, such as obstructive jaundice due to pancreatic head swelling or urethral stenosis from retroperitoneal fibrosis, or when severe symptoms, including unbearable abdominal pain, were evident. Steroid treatment was carried out at our institute according to the Japanese consensus guidelines for AIP, which recommended a minimum of 3 years of maintenance therapy (27).

2. Methods

2-1. Survey for complication of malignancy

Of the 158 patients, we searched for the complication of malignancy in 142 subjects by examining medical records dated until December 2013. For the 16 patients who discontinued treatment at our institutions during the study period, we sent questionnaires for the clinical survey of malignancy and obtained replies from 8 individuals. We screened for the occurrence of malignancy up until the time of last contact for the remaining 8 patients with whom we had lost contact during the survey period. Malignancies before IgG4-RD diagnosis were not analyzed in the present study.

2-2. Analysis for correlation between IgG4-RD and malignancy

The standardized incidence ratio (SIR) of malignancy in our cohort was calculated to evaluate whether IgG4-RD was significantly complicated with malignancy by adopting the cancer incidence rates for the Japanese general population as stratified by sex, 5-year age groups, and calendar year (28). The SIR was calculated by dividing the actual number of malignancies by the expected one if the cohort exhibited malignancies at the same age-stratified rate as the Japanese general population. Furthermore, we determined the 95% confidence interval (CI) using normal approximation based on Poisson's distribution. The occurrence of malignancy in IgG4-RD was considered to be significantly elevated when the lower value in this interval exceeded 1.00. We analyzed 2 patient groups in the present study: one that included patients who were diagnosed as having IgG4-RD and

malignancy concurrently and another that excluded such patients. A concurrent diagnosis of IgG4-RD and malignancy meant that a malignancy was diagnosed during the period of intensive examination using CT and MRI for the detection of IgG4-RD, which usually lasted approximately 1-3 months after the suspicion of IgG4-RD. However, in most cases, intensive examination using these image tests continued about 3 months after diagnosis because of the evaluation for steroid effects and the check for relapse occurrence, suggesting that malignancies may be easily found in these periods of 3 months after IgG4-RD diagnosis. Accordingly, we defined the period of a concurrent diagnosis as within 3 months after IgG4-RD diagnosis.

To evaluate the possibility of paraneoplastic syndrome manifesting in IgG4-RD, we calculated and compared the SIRs of patients in whom malignancies were found to complicate IgG4-RD within 1 year and 1 year or more after diagnosis.

Identical procedures were performed for the AIP subgroup in our cohort since several previous studies were restricted to AIP patients only.

The Kaplan-Meier method was used to estimate the cumulative rate of malignancy development. Cancer incidence rate curves were calculated using the data per 100,000 people according to year, age, and gender as reported by the Ministry of Health, Labor, and Welfare of Japan. The log-rank test was adopted to test hypotheses concerning the differences in malignancy development between the IgG4-RD group and the Japanese general population. Information on the

Japanese general population was obtained with regard to sex, cancer site, 5-year age groups, and calendar year during the period of 1975-2008 (28, 29). Since the general population sample size was very large, the widths of its 95% confidence intervals (CIs) were nearly zero.

2-3. Risk factors for the occurrence of malignancy in IgG4-RD

We searched for risk factors of malignancy complications by comparing clinical parameters between all patient groups with and without malignancies, including IgG4-RD onset age, gender, serum levels of various activity markers, such as IgG4, IgG, complement proteins, soluble interleukin-2 receptor (sIL-2R), and circulating immune complex (CIC), number of lesions, experience of corticosteroid therapy, and occurrence of relapse. We defined relapse as a reappearance of IgG4-RD symptoms, elevation of disease activity markers, and identification of active lesions in diagnostic imaging. Since alcohol intake, smoking, and diabetes mellitus (DM) are also considered to be major risk factors for the development of malignancies, we evaluated the effects of these factors as well. Alcohol intake and smoking were defined as daily consumption of >20 g of alcohol and >10 cigarettes, respectively, at the diagnosis of IgG4-RD. DM was assessed before or around IgG4-RD diagnosis, whereby a fasting glucose level of >126 mg/dl and/or hemoglobin A1c (HbA1c) level of >6.5% was judged as indicative of DM (30). The same procedures were done for the AIP subgroup.

3. Statistics

Differences between groups were analyzed using the Mann-Whitney test for continuous data and the $\chi 2$ test or Fisher's exact test for categorical data. Statistical analyses were performed using Stat Flex ver. 6 software (Artech Co., Ltd.). All tests for Kaplan-Meier analysis were calculated with the IBM SPSS Statistics Desktop for Japan (version 19.0; IBM Japan Inc., Tokyo, Japan). A p value of <0.05 was considered to be statistically significant.

4. Ethics

The present study was approved by the ethics committee of our institute (Approval Code 2602).

Results

1. Malignancies complicating IgG4-RD

Among the 158 patients with IgG4-RD who were followed for a mean period of 5.95±4.48 years, we identified 36 malignancies in 34 patients, which included 5 cases each of lung, colon, and prostate cancer and 4 cases each of gastric and pancreatic cancer (Table 1). Among the 109 patients with AIP, we detected 30 malignancies in 28 patients, which included 5 cases of prostate cancer and 4 cases each of lung and pancreatic cancer (Table 1). When malignancies other than those occurring concurrently with IgG4-RD diagnosis were analyzed in our cohort, a total of 29 malignancies were found in 27 patients. When the period for developing malignancies after IgG4-RD diagnosis was set

at before and after 5 years, 26 patients demonstrated the occurrence of malignancies before 5 years versus 8 patients afterwards. Consequently, the occurrence of malignancies tended to be most frequent within 5 years after IgG4-RD diagnosis (Fig. 1).

In the present study, the malignancies found in 11 patients were successfully treated by surgery, chemotherapy, or radiotherapy, after which 8 patients experienced no relapse during or after subsequent corticosteroid therapy. The remaining 3 patients did not receive corticosteroid therapy. We encountered no cases of genuine paraneoplastic syndrome that were apparently improved following surgery and/or chemotherapy alone.

We observed that 12 patients experienced malignancy in the same organ affected by IgG4-RD, namely, pancreas and lung in 4 patients each, prostate in 2 patients, and bile duct and kidney in 1 patient each.

2. Is IgG4-RD associated with the occurrence of malignancy?

2-1. Overall analysis

The expected incidence of cancer in our IgG4-RD cohort according to rates for the Japanese general population during an overall follow-up of 940 person-years was 16.9. Based on this, we first calculated the overall SIR of malignancies after IgG4-RD diagnosis, which was 2.01 (95% CI 1.34-2.69) and indicative that IgG4-RD was significantly complicated with malignancy (Table 2). Next, we selected the patients whose malignancies were not diagnosed concurrently with IgG4-RD

and witnessed an SIR of 1.60 (95% CI 1.07-2.13), which also represented a significant result.

2-2. Comparison of SIR of malignancies found within one year after IgG4-RD diagnosis with that of tumors detected in subsequent years

The SIR of malignancies identified within 1 year after IgG4-RD diagnosis was 3.53 (95% CI 1.23-5.83), whereas that for subsequent years was 1.48 (95% CI 0.99-1.98), indicating a significant occurrence of malignancies in the first year after IgG4-RD diagnosis that became less frequent afterwards (Table 2).

2-3. Analysis of type 1 AIP in IgG4-RD

The expected incidence of cancer in our AIP cohort according to rates for the Japanese general population during an overall follow-up of 740 person-years was 13.4. Based on this, the calculated SIR restricted to type 1 AIP was 2.08 (95% CI 1.32-2.85), indicating that type 1 AIP was significantly associated with malignancy as well. Moreover, the SIR of malignancies within 1 year after type 1 AIP diagnosis was 3.91 (95% CI 1.02-6.80), whereas that for subsequent years was 1.57 (95% CI 0.90-2.23), which suggested that the occurrence of malignancies in type 1 AIP was also significantly more frequent within the first year and less frequent afterwards (Table 2). Next, we selected the patients whose malignancies were not diagnosed concurrently with AIP and witnessed an SIR of 1.71 (95% CI 1.01-2.41), which also represented a significant result.

2-4. Kaplan-Meier analysis of cumulative malignancy rate between the IgG4-RD group and the

Japanese general population

In Kaplan-Meier testing, the lower limit of the 95% CI for cumulative malignancy rate for the IgG4-RD group was higher than that for the Japanese general population during the first 12 years after diagnosis according to log-rank testing (Fig. 2).

2-5. Analysis of malignancy type

SIR calculations for each malignancy type uncovered no significant results. Pancreatic cancer demonstrated an SIR of 5.48 (95% CI 0.11-10.85), which suggested a non-significant association with IgG4-RD. Comparable results were obtained for each malignancy type for the AIP group, in which the SIR for pancreatic cancer was markedly higher (Table 3).

3. Risk factors associated with malignancy development

To identify the risk factors associated with the formation of malignancies, we compared several clinical parameters between IgG4-RD patients with malignancies and those without (Table 4). Serum concentrations of IgG, IgG4, sIL-2R, and CIC were significantly higher in patients with malignancies (p = 0.002, 0.005, 0.005, and 0.019, respectively). In contrast, a history of corticosteroid treatment, number of recurrences, alcohol intake, smoking, and DM all showed no significant associations with risk (Table 4-a). Similar results were obtained for the AIP group apart from a negative result for CIC (Table 4-b).

Discussion

1. Are IgG4-RD and AIP significantly associated with the occurrence of malignancies?

The present study showed that IgG4-RD and AIP were significantly associated with the occurrence of malignancies, which was consistent with Yamamoto's and Shiokawa's reports (15, 16). However, Hirano et al. described that the incidence of total malignancies in IgG4-RD was similar to that of the Japanese general population (17). This discrepancy may be attributed to differences in study protocol; whereas Hirano excluded patients who were concomitantly diagnosed as having IgG4-RD and malignancies to avoid selection bias, Yamamoto and Shiokawa included these subjects. Here, we were able to confirm that IgG4-RD (AIP) was significantly associated with malignancy even in patients without a concurrent diagnosis of malignancy. In Kaplan-Meier testing, the cumulative malignancy rate for the IgG4-RD group was significantly higher than that for the Japanese general population up to 12 years after diagnosis according to log-rank testing. These results indicated that IgG4-RD was significantly associated with the occurrence of malignancies within this period. This significant association disappeared afterwards, likely due to a higher malignancy rate attributed to older age.

There may have been detection bias in the present study for the diagnosis of malignancy because patients with IgG4-RD were likely followed more closely than the general population, which could have resulted in a more timely and frequent detection of malignancy. In addition, many

patients were referred to a tertiary care center that promptly made the diagnosis of malignancy using intensive imaging examination. To mitigate this selection bias, we also examined subjects after excluding those with a concurrent diagnosis of malignancy. This group showed a significant association with malignancy as well. On the other hand, Hart et al. compared the occurrence of malignancies between type 1 AIP and control subjects from a primary care clinic, in which the risk of detection bias could be ignored, and found no significant association of malignancy occurrence between the groups (18). However, the control subjects from the primary care clinic likely carried the risk of more frequent complications of malignancies than the general population since their visit may have been due to malignancy-related complaints.

2. *Should some cases of IgG4-RD and AIP be regarded as a type of paraneoplastic syndrome?*

The occurrence of malignancies was significantly more frequent within the first year after IgG4-RD diagnosis compared with that of subsequent years. This was in agreement with Shiokawa's study showing that IgG4-RD may be considered as a type of paraneoplastic syndrome, which was recently found to be the case for AIP (16). Paraneoplastic syndrome is described as systemic inflammatory diseases provoked by inflammatory mediators generated by malignancies (31). If IgG4-RD is indeed a paraneoplastic syndrome, treatment of the underlying malignancy may result in amelioration of IgG4-RD (32). In the present study, 8 patients whose malignancies were successfully treated by surgery, chemotherapy, or radiotherapy experienced no relapse during or

after subsequent corticosteroid therapy, thus strengthening the hypothesis that IgG4-RD can be regarded as a type of paraneoplastic syndrome, although we have encountered no cases of genuine paraneoplastic syndrome that were apparently improved following surgery and/or chemotherapy alone. Several cases of pancreatic cancer complicated with AIP have been described to show abundant IgG4-bearing plasma cell infiltration, suggesting that pancreatic cancer could initiate an immune response with subsequent plasma cell infiltration in pancreatic and peripancreatic tissue, which is a hallmark of AIP (33-35). However, because not all of the cases of IgG4-RD were associated with malignancies, another mechanism apart from paraneoplastic syndrome, such as a failure in immune surveillance, might lead to a loss in inflammation control or tumor growth suppression and subsequent systemic inflammation and malignancy (36, 37).

3. Which malignancies complicate IgG4-RD?

The present study uncovered 36 malignancies in 158 patients with IgG4-RD, among which 5 cases each of lung, colon, and prostate cancer and 4 cases each of gastric and pancreatic cancer were noted. In Shiokawa's analysis of 18 malignancies of 108 AIP patients, gastric (7 cases) and lung (5 cases) cancers were most commonly seen, but pancreatic cancer was not observed (16). In Hirano's study of 14 malignancies of 113 IgG4-RD patients, lung cancers were most frequently detected (5 cases), followed by pancreatic and gastric cancers (2 cases each) (17). Similarly to these reports, our results revealed a higher prevalence of gastric and lung cancers, both of which are also

more common in the Japanese general population. Pancreatic malignancies are considerably rare among the Japanese. However, their relatively high occurrence in Hirano's study and ours suggests that pancreatic cancer may be closely associated with IgG4-RD or AIP (17).

The high prevalence of pancreatic cancer in IgG4-RD patients may have been due to the large proportion of AIP (109 of 158 patients) in our cohort. Four cases of pancreatic cancer were found in the AIP cohort at 3, 5, 5, and 9 years after IgG4-RD diagnosis, suggesting that an inflammatory state of pancreatic tissue induced malignancy and possibly accounted for the association between AIP and pancreatic cancer. As IgG4 values are generally not measured for typical pancreatic cancer cases, instances of pancreatic cancer with an AIP background may have largely been ignored (16).

4. Does the chronic inflammatory state of IgG4-RD cause malignancies?

It is well known that chronic inflammation induces malignancies under some circumstances (38). Mediators of the inflammatory response, such as cytokines, free radicals, prostaglandins, and growth factors, can induce genetic and epigenetic changes, including point mutations in tumor suppressor genes, DNA methylation, and post-translational modifications, and lead to the development of cancer (39). Chronic pancreatitis was reported to be a significant risk factor for pancreatic cancer (40), and some cases of AIP were prone to transformation into chronic pancreatitis after calcification (41). Furthermore, Kamisawa et al. found that *K-ras* mutations occurred significantly more frequently in the pancreatobiliary regions of patients with AIP,

suggesting a close association between AIP and pancreatic cancer (42). The present study showed that the SIR of malignancies occurring after 1 year following IgG4-RD diagnosis was 1.48 (95% CI 0.99-1.98), indicating a possible association between a chronic inflammatory state of IgG4-RD and malignancy. Considering that a period of more than a decade is often needed for chronic inflammation to lead to carcinogenesis, we cannot conclude with certainty that a chronic inflammatory state in IgG4-RD induces malignancies since most of the tumors in our cohort were detected within 5 years after IgG4-RD diagnosis. In addition, the fact that the majority of malignancies occurred in organs different from those affected by IgG4-RD inflammation indicated a weak correlation between chronic inflammatory state and malignancy in IgG4-RD, although pancreatic cancer demonstrated a high SIR in the AIP subgroup.

5. What are the risk factors for developing malignancies in IgG4-RD patients?

The present study showed that among various clinical parameters, serum concentrations of IgG, IgG4, sIL-2R, and CIC were significantly higher in patients with malignancies than in those without, indicating that such activity markers may be associated with the development of tumors. Shiokawa et al. found a similar result, in which serum IgG4 was significantly higher in patients with a malignancy compared with patients without (16). Such findings imply that IgG4-RD patients may harbor a weakened defense system, such as an immunodeficient state, or a paraneoplastic condition in affected organs, such as deranged oncogenes, and that a highly active disease state may

exacerbate weakened immune defenses to result in the development of cancer. Accordingly, IgG4-RD patients with high serum concentrations of activity markers should be carefully followed for early detection of complicating malignancies.

In conclusion, IgG4-RD is believed to have a close association with the development of malignancy within 12 years after diagnosis, most notably during the first year. High concentrations of activity markers are a risk factor for cancer onset and should be monitored closely.

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Table 1. Number of malignancies in patients with IgG4-RD and AIP

Type of malignancy	Total number of malignancies in patients with IgG4-RD	Total number of malignancies in patients with AIP
Total	36	30
Lung	5	4
Colon	5	3
Prostate	5	5
Stomach	4	3
Pancreas	4	4
Kidney	2	1
Lymphoma	2	2
Biliary tract	1	1
Liver	1	1
Esophagus	1	0
Breast	1	1
Ovary	1	1
Thyroid	1	1
Skin	1	1
Tongue	1	1
Myelodysplastic syndrome	1	1

Table 2. SIR of malignancies in IgG4-RD and AIP

	IgG4-RD		AIP	
	SIR	95% CI	SIR	95% CI
Overall	2.01	1.34-2.69	2.08	1.32-2.85
Without concurrent diagnosis	1.60	1.07-2.13	1.71	1.01-2.41
Years after IgG4-RD diagnosis				
＜1	3.53	1.23-5.83	3.91	1.02-6.80
≧1	1.48	0.99-1.98	1.57	0.90-2.23

Table 3. SIR for each malignancy in IgG4-RD and AIP

	IgG4-RD		AIP	
Type of malignancy	SIR	95% CI	SIR	95% CI
Lung	2.09	0.26-3.93	2.10	0.26-3.94
Colon	1.75	0.22-3.29	1.33	0.17-2.48
Prostate	2.05	0.25-3.85	2.07	0.26-3.88
Stomach	1.43	0.03-2.83	1.35	0.03-2.66
Pancreas	5.48	0.11-10.8	6.81	0.13-13.5

Table 4. Comparison of clinical parameters

a. Between IgG4-RD patients with malignancies and those without

Parameter	Malignancies (+)	Malignancies (-)	*p* value
Onset age of IgG4-RD (mean)	67.6	65.0	0.211
Sex (male/female)	29/5	90/34	0.194
Number of involved organs (mean)	3.03	2.56	0.054
Corticosteroid use (+/-)	26/8	85/39	0.467
Recurrence of IgG4-RD (+/-)	7/26	20/58	0.799
Alcohol intake (+/-)	10/22	36/79	0.834
Smoking (+/-)	20/14	69/46	0.939
Diabetes mellitus (+/-)	8/26	31/93	0.860
IgG (mg/dl) (median)	2420	1986	0.002
IgG4 (mg/dl) (median)	749	430	0.005
C3 (mg/dl) (median)	100	107	0.638
C4 (mg/dl) (median)	19.3	22.8	0.229
CIC (μ g/ml) (median)	8	5.1	0.019
sIL-2R (U/ml) (median)	1250	755	0.005

b. Between AIP patients with malignancies and those without

Parameter	Malignancies (+)	Malignancies (-)	*p* value
Onset age of AIP (mean)	67.0	64.1	0.226
Sex (male/female)	24/4	60/21	0.316
Number of involved organs (mean)	3.14	2.95	0.404
Corticosteroid use (+/-)	22/6	62/19	0.968
Recurrence of IgG4-RD (+/-)	6/21	23/57	0.682
Alcohol intake (+/-)	7/19	26/48	0.601
Smoking (+/-)	17/11	45/31	0.931
Diabetes mellitus (+/-)	7/21	24/57	0.640
IgG (mg/dl) (median)	2419	1997	0.019
IgG4 (mg/dl) (median)	749	442	0.027
C3 (mg/dl) (median)	99.5	103	0.705
C4 (mg/dl) (median)	20.6	22.2	0.451
CIC (μ g/ml) (median)	7.7	5.35	0.097
sIL-2R (U/ml) (median)	1233	755	0.011

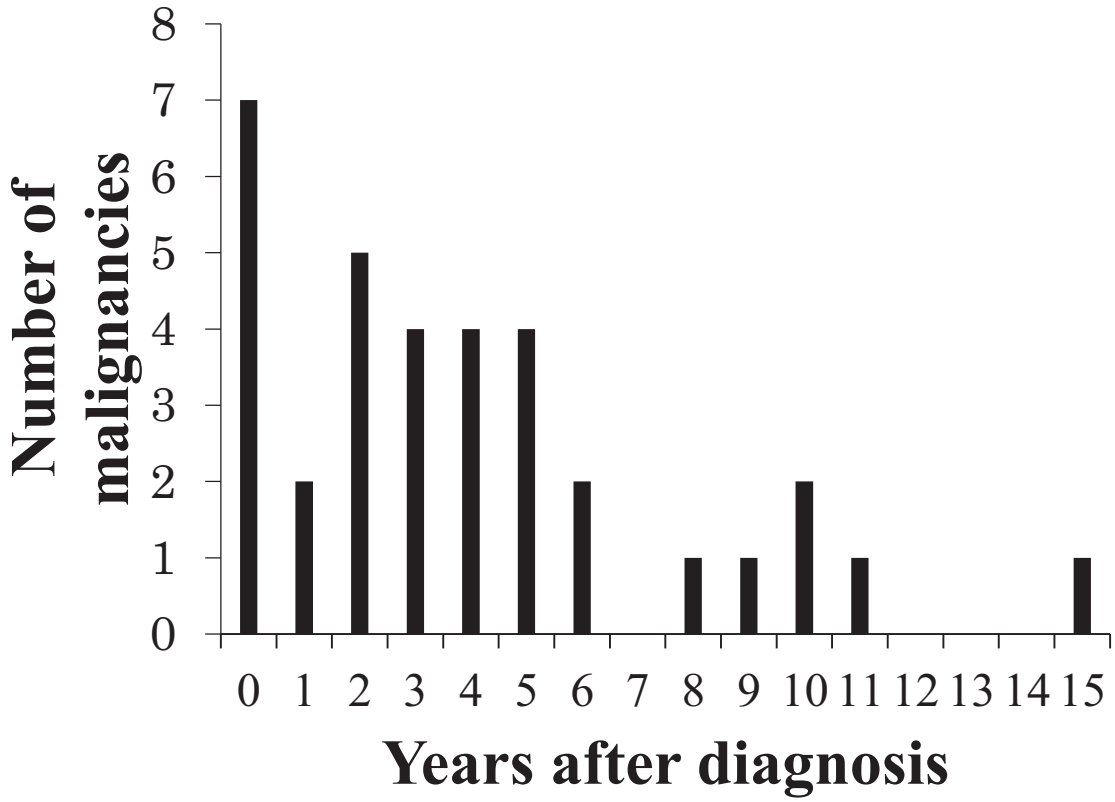

Figure 1. Incidence of malignancies according to time after IgG4-RD diagnosis. Twenty-six patients experienced malignancies within the first 5 years after diagnosis versus 8 patients afterwards, indicating that the occurrence of malignancies tended to be most frequent within 5 years after IgG4-RD diagnosis.

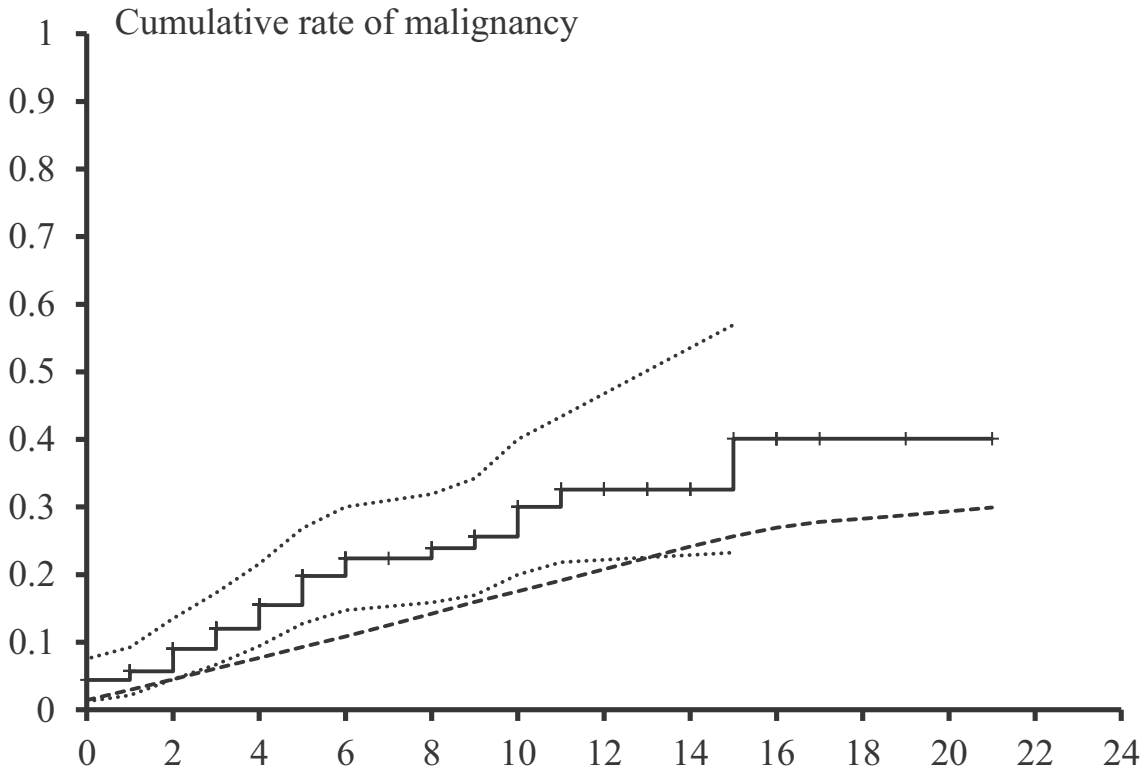

Figure 2. Cumulative malignancy rate for patients with IgG4-RD (solid line) and for the Japanese general population (broken line). The development rate of malignancy was higher for patients with IgG4-RD until 12 years after IgG4-RD diagnosis according to log-rank testing.