LETTER

Title:

Incidental detection of malignant lymphoma in subjects in a cancer surveillance programme

Authors:

Y. Kamiyama[1,4], Y. Kobayashi[1], S, Fukuhara[1], N. Morikawa[1,4], W. Munakata[1], A. M. Maeshima[2], D. Maruyama[1], S.-W. Kim[1], T. Watanabe[1,5], T. Terauchi[3], Y. Muramatsu[3], K. Tobinai[1]

Departments of [1]Hematology and Hematopoietic Stem Cell Transplantation, [2]Pathology, and [3]Research Center for Cancer Prevention and Screening, National Cancer Center Hospital, Tokyo, Japan

Current addresses: [4]Department of Clinical Oncology and Hematology, Tokyo Jikei University, Tokyo, Japan; [5]Komaki City Hospital, Aichi, Japan

Correspondence to:

Yukio Kobayashi, Department of Hematology, National Cancer Center Hospital, 5-1-1 Tsukiji Chuo-ku, Tokyo 104-0045, Japan. Phone: +81-3-3542-2511; Fax: +81-3-3542-3815; E-mail: ykkobaya@ncc.go.jp

Running title: Lymphoma detection in cancer surveillance programme

Key words:

cancer screening, cancer surveillance, PET, malignant lymphoma, mortality rate

Cancer surveillance programmes have recently been introduced in Japan. The usefulness of [^{18}F] fluoro-deoxyglucose positron emission tomography/computed tomography (PET/CT) has been established for the diagnosis/treatment monitoring of various types of cancer. The superiority of PET/CT over conventional scintigraphy for diagnosing malignant lymphoma (ML) has been demonstrated; PET/CT has also been used to evaluate treatment responses in ML (Moog et al, 1997; Moog et al, 1998). However, the diagnostic value of this modality for each histopathological type continues to be debated; in particular, its value for diagnosing low-grade lymphoma is controversial (Karam et al, 2006).

We analysed data of 10,659 individuals who participated in a cancer surveillance programme that included PET/CT at the Research Center for Cancer Prevention, National Cancer Center from 2004 to 2011. The subjects were healthy individuals over the age of 40 with no history of cancer who had elected to participate in this programme. Written informed consent was obtained from all participants.

The median age of participants was 59; the oldest was 89 years old. For 4 consecutive years after the screening, all participants were surveyed annually about their health by questionnaires that included questions about development of cancer. The participants could opt for repeated screening. The screening included blood tests, urinalysis, sputum cytology, abdominal ultrasonography, thoracic CT, upper gastrointestinal endoscopy and either colonoscopy or colon X-ray examination. Cervical cytology, mammography, breast ultrasonography and pelvic magnetic resonance imaging (MRI) were also performed on women.

PET/CT was performed optionally. Blood tests included a complete blood count, biochemical tests, hepatitis virus screening and serum concentrations of the tumour markers carcinoembryonic antigen, cancer antigen (CA)19-9, prostate specific antigen in men, and CA125 in women. Histopathological subtype, examination(s) that contributed to making the diagnosis, survival and the cause of death were collected for the subjects who had been diagnosed as having ML.

ML was detected in the initial screening of 18 participants, representing a prevalence of 0.16%, which is higher than the estimated incidence (0.012%) in the general Japanese population (Matsuda et al, 2012). ML was diagnosed in subsequent optional screening in another seven subjects who had not been found to have ML in their initial screening (Fig 1). The questionnaire survey yielded another two cases who had been found by other institutions to have diffuse large B-cell lymphoma (DLBCL).

This cancer screening programme detected 25 cases of ML including 12 of marginal zone lymphoma, five of follicular lymphoma, four of DLBCL, two of small lymphocytic lymphoma/chronic lymphocytic leukaemia, and two of unspecified low-grade B-cell lymphoma (Table 1).

The most commonly diagnosed lymphoma was mucosa-associated lymphoid tissue (MALT) lymphoma of the gastrointestinal tract: its detection rate by upper gastrointestinal endoscopy was high; total 9 cases were detected. In the Japanese population, the expected *Helicobacter pylori* positivity rate is as high as 80% (Haruma, 2000), in contrast to reported rates of 30–40% in Caucasian populations (Stone et al, 1998; Senra-Varela et al, 1998). Thus, the high incidence of MALT lymphoma in our study may be attributable to the high

prevalence of *H. pylori*.

The next most frequently found subtypes were follicular lymphoma (FL) and small lymphocytic lymphoma/chronic lymphocytic leukaemia (SLL/CLL). Again, that these subtypes were detected more frequently by screening than more aggressive lymphomas may be attributable to the indolent nature of these lymphomas, which may never have manifested clinically throughout the subjects' lives.

No increase in 2-deoxy-2-[F-18]fluoro-D-glucose (FDG) uptake was observed on PET/CT in the cases of SLL/CLL and low-grade B-cell lymphoma not otherwise specified, as previously reported (Karam et al, 2006). In addition, only half the cases of FL diagnosed as low-grade lymphoma showed increased uptake of FDG. In contrast, all cases of DLBCL had increased FDG uptake on PET/CT, which confirms the usefulness of PET/CT for diagnosing aggressive lymphomas (Schöder et al, 2005). Thus, 18 % of cases of ML would have been missed without PET/CT.

Eighteen of the 25 cases (72%) diagnosed as having ML underwent anti-lymphoma therapy, whereas the remaining seven (28%) were followed up without treatment. The prognosis was excellent; 22/25 patients (88%) were alive at the time of the last follow-up in March 2011, after a median follow-up of 3.3 years. When stratified according to histopathological type, all patients who had been diagnosed as having FL, SLL/CLL and low-grade B-cell lymphoma were alive. Survival data were obtained for 11/12 cases of MALT lymphoma, and 2/4 cases of DLBCL. In all, three of the 25 patients died; two of ML progression 14 and 37 months after diagnosis, and one of a disease unrelated to ML.

Of the 25 cases found to have ML among the 10,659 participants, only two died of ML, which was less than the estimated mortalities of 2.57. This reduction in mortality is not significant. (Supplementary Table 1).

The screening examinations that contributed to detecting the ML were upper gastrointestinal endoscopy in 40%, thoracic CT in 20%, PET/CT in 20%, blood tests in 18%, ultrasonography in 20%, and pelvic MRI in 4%. It has been suggested that inclusion of PET/CT in cancer screening protocols increases the power of the screening to detect lesions of the extremities and bones, which are located out of the range of detection or difficult to detect by CT. Thus, more cases of ML are detected when PET/CT is combined with modalities like ultrasound, CT and MRI. However, there are still limitations because many subjects with low grade lymphomas have negative PET/CT scans.

This is the first report to examine the prevalence of ML in an apparently healthy population; however, the increased detection rate did not translate into early intervention and a reduction in ML-associated mortality. The significance of reducing cancer mortality through early detection should also be evaluated for other types of cancer screening protocols.

Acknowledgements:

This work was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan (Clinical Cancer Research 22-014, 22-031, and 23-004) and the National Cancer Center Research and Development Fund (21-6-3, 20-1, 23-A-17, 23-A-23, and 23-C-7).

Author contributions:

Y. Kamiyama designed the research, analysed data and wrote the manuscript. S.F., N.M., W.M., D.M., S-W.K. and T.W collected data. Y. Kobayashi and Y.M. analysed data. Y. Kobayashi assisted with preparation of figures. A.M.M. performed pathological reviews. T.T reviewed radiological examinations. K.T. oversaw all analyses, and revised the manuscript.

Conflict of interest:

The authors have no conflicts of interest in connection with this research.

References:

Haruma K. (2000) Trend toward a reduced prevalence of Helicobacter pylori infection, chronic gastritis, and gastric cancer in Japan. Gastroenterol Clin North Am, 29, 623-631.

Karam M., Novak L., Cyriac J., All A., Nazeer T., Nugent F. (2006) Role of fluorine-18 fluoro-deoxyglucose positron emission tomography scan in the evaluation and follow-up of patients with low-grade lymphomas. Cancer, 107, 175-183.

Matsuda T., Marugame T., Kamo K., Katanoda K., Ajiki W., Sobue T.; Japan Cancer Surveillance Reseach Group. (2012) Cancer incidence and incidence rates in Japan in 2006: based on data from 15 population-based cancer registries in the monitoring of cancer incidence in Japan (MCIJ) project. Jpn J Clin Oncol, 42, 139-147.

Moog F., Bangerter M., Diederichs C.G., Guhimann A., Kotzerke J., Merkle E., Kolokythas O., Herrmann F., Reske S.N. (1997) Lymphoma: role of whole-body 2-deoxy-2-[F-18]fluoro-D-glucose (FDG) PET in nodal staging. Radiology, 203, 795-800.

Moog F., Bangerter M., Diederichs C.G., Guhimann A., Merkle E., Frickhofen N., Reske S.N. (1998) Extranodal malignant lymphoma: detection with FDG PET versus CT. Radiology, 206, 475-481.

Schöder H., Noy A., Gönen M., Weng L., Green D., Erdi Y.E., Larson S.M., Yeung H.W. (2005) Intensity of 18fluorodeoxyglucose uptake in positron emission tomography distinguishes between indolent and aggressive non-Hodgkin's lymphoma. J Clin Oncol, 23, 4643-4651.

Senra-Varela A., Lopez-Saez J.B., Gomez-Biondi V. (1998) Prevalence of Helicobacter pylori infection in two Spanish regions with different incidence of gastric cancer. Eur J Epidemiol, 14, 491-494.

Stone M.A., Barnett D.B., Mayberry J.F. (1998) Lack of correlation between self-reported symptoms of dyspepsia and infection with Helicobacter pylori, in a general population sample. Eur J Gastroenterol Hepatol, 10, 301-304.

Supplementary Table 1. Mortality of malignant lymphoma compared with that in the general population

Age	Mortality in Japan (a)	Participants (b)	Mortal cases	Expected number of mortalities (a)x(b)	
40-44	0.0000096702	902	0	902×0.0000096702=	0.008
45-49	0.0000198189	1003	0	1003×0.0000198189=	0.020
50-54	0.0000301432	1561	0	1561×0.0000301432=	0.047
55-59	0.0000501979	2112	0	2112×0.0000501979=	0.106
60-64	0.0000768500	2304	0	2304×0.0000768500=	0.177
65-69	0.0001079903	1838	1	1838×0.0001079903=	0.198
70-74	0.0001951255	639	0	639×0.0001951255=	0.124
75-79	0.0003067628	237	1	237×0.0003067628=	0.072
80-84	0.0004424825	55	0	55×0.0004424825=	0.024
85-	0.0005511956	8	0	8×0.0005511956=	0.004
Total		10,659	2		0.780

The longest duration of observation of participants was 6.6 years; thus, the median duration of observation of this cohort was approximately 3.3 years. The mortality rate in this cohort was calculated as 2.57 (=0.78 × 3.3). Thus, the SMR was 2 divided by 2.57, that is 0.778. Because the number of events, represented here by the mortality, was less than 20, the LL (ISR) and UL (ISR) were obtained from the Poisson table. The 95% confidence interval factor for the Poisson distribution with two events was 0.12 to 3.61. Because the expected mortality was LL, and UL of ISR was calculated as 0.778 multiplied by 0.12 and 3.61, respectively. Thus LL and UL was 0.0934 and 2.81. The occurrence of two events was neither increased nor decreased. The data of mortality in Japanese was accorded from Cancer Statics 2013 by Center for Cancer Control and Information Center [cited 2013 August 30]; Available from: http://ganjoho.jp/professional/statistics/monita.html.

Table 1. ML cases detected in this programme, including those that developed during follow up. (Left, continues to Right)

Timing of detection	WHO histology	Grade	Age	Sex	Stage	Site	Pointed abnormal finding
Initial screening (N=18)	MALT lymphoma		57	M	N/A	Stomach	Gastric lesion
			60	F	N/A	Stomach	Gastric lesion
			61	F	N/A	Stomach	Gastric lesion
			62	F	N/A	Stomach	Gastric lesion
			63	M	N/A	Stomach	Gastric lesion
			64	M	N/A	Stomach	Gastric lesion
			71	M	N/A	Stomach	Gastric lesion
			62	F	IV	Lung	Multiple lung lesion
			64	F	IE	Lung	Lung nodule
			66	F	IE	Thymus	Mediastinal tumor
	FL	G1	60	M	N/A	Para-aorta LN	Duodenal tumor
		G2	62	M	IV	Systemic LN	Enlarged axillary and mesenteric LN, adrenal tumor
		G2	54	F	III	Systemic LN	Enlarged axillary LN
	SLL/CLL		77	M	IV	Peripheral blood	Leukocytosis
	Low-grade B-cell lymphoma, not otherwise specified		72	F	IV	Systemic LN	Enlarged LN in the axilla and abdominal cavity
	DLBCL		53	F	N/A	Soft tissue	Soft tissue tumor of thigh
			68	M	IE	Bone	Tumor of the thoracic spine
			78	F	IV	Uterus, ovary, para-aortic LN	Enlarged uterus, ovary and para-aortic LN

Subsequent screening (N=7)	MALT lymphoma		45	F	N/A	Stomach	Gastric lesion
			57	M	N/A	Stomach	Gastric lesion
	FL	G1	58	F	IE	Intestinal tumor	Intestinal lesion
		G2	77	F	IV	Systemic LN	Enlarged LN in cavity
	SLL/CLL		67	M	IV	Peripheral blood, systemic LN	Enlarged LN in the cervix, axilla and inguinal, leukocytosis
	Low-grade B-cell lymphoma, not otherwise specified		72	M	IV	Peripheral blood	Leukocytosis
	DLBCL		59	M	II	Axillary LN	Enlarged axillary LN
Disease manifestation (N=2)	DLBCL		48	M	II	Cervical LN	
			55	M	II	Cervical LN	

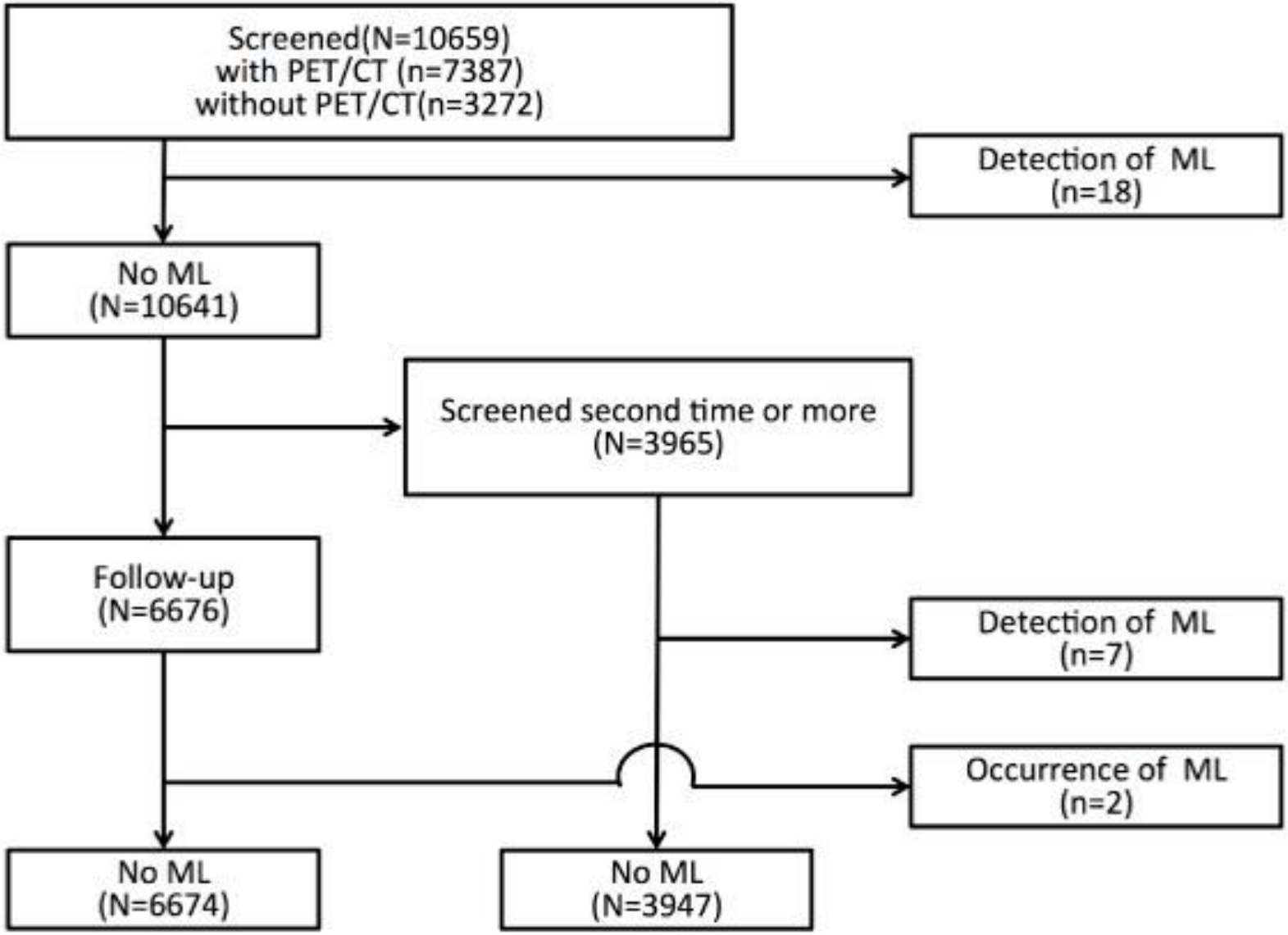
(a): dyed, but not from ML. (b): dyed from ML.
Abbreviations: CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IFRT, involved-field radiotherapy; LN, lymph node; MALT, mucosa-associated lymphoid tissue; ML, malignant lymphoma; MRI, magnetic resonance imaging; N/A, not available; PET/CT, positron emission tomography; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukaemia; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-C-MOPP, rituximab, cyclophosphamide, vincristine, procarbazine, prednisolone; US, ultrasonography.

Table 1. ML cases detected in this programme, including those that developed during follow up. (Right, continues from Left)

Screening test that contributed to detection	PET/CT performed	FDG uptake	Therapy	Follow-up (months)
Gastrointestinal endoscopy	Yes	No	Eradication of H.pylori	80+
Gastrointestinal endoscopy	Yes	No	Eradication of H.pylori	66+
Gastrointestinal endoscopy	No	-	Eradication of H.pylori	3+
Gastrointestinal endoscopy	Yes	No	Eradication of H.pylori	55+
Gastrointestinal endoscopy	Yes	No	Eradication of H.pylori	54+
Gastrointestinal endoscopy	Yes	No	Eradication of H.pylori	55+
Gastrointestinal endoscopy	Yes	No	Eradication of H.pylori	47+
Thoracic CT	Yes	No	Watch and wait	69+
Thoracic CT	No	-	Watch and wait	64+
Thoracic CT	No	-	Watch and wait	32(a)
PET/CT	Yes	Yes	Surgery followed by chemotherapy	81+
Thoracic CT, abdominal US	No	-	R-CHOP	17+
PET/CT	Yes	Yes	Watch and wait	5+
Blood test	No	-	Watch and wait	51+
Thoracic CT, abdominal US	Yes	No	R-C-MOPP	40+
PET/CT	Yes	Yes	N/A	63+
PET/CT	Yes	Yes	R-CHOP followed by IFRT	37(b)
Pelvic MRI	No	-	R-CHOP	13(b)
Gastrointestinal endoscopy	No	-	Eradication of H.pylori	11+
Gastrointestinal endoscopy	Yes	No	Eradication of H.pylori	33+

Gastrointestinal endoscopy	Yes	No	Rituximab	49+
US	Yes	No	Watch and wait	6+
Breast and abdominal US, blood test	Yes	No	Oral fludarabine	57+
Blood test	Yes	No	Watch and wait	32+
PET/CT	Yes	Yes	R-CHOP followed by IFRT	9+
			Chemotherapy	
			Chemotherapy	

Figure 1


Screened(N=10659)
with PET/CT (n=7387)
without PET/CT(n=3272)
Detection of ML
(n=18)
No ML
(N=10641)
Screened second time or more
(N=3965)
Follow-up
(N=6676)
Detection of ML
(n=7)
Occurrence of ML
(n=2)
No ML
(N=6674)
No ML
(N=3947)