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Original Article

Clinical management and outcomes of completely resected stage I follicular lymphoma

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Recent studies have revealed the clinical and biological features of stage I follicular lymphoma (FL), but information about patients with stage I FL who underwent total resection after tissue biopsy is limited. Among 305 FL patients diagnosed between 2001 and 2013, clinical stage I disease was observed in 36 patients. Of these, 18 patients underwent total resection after diagnostic tissue biopsy. We used ^{18}F-fluorodeoxyglucose positron emission CT for staging assessment in 13 of 18 patients (72.2%). The median age was 56.5 years. Six patients (33.3%) were male. The soluble interleukin-2 receptor alpha concentration was significantly lower than in patients with residual disease. Among these 18 patients, 7 patients (38.9%) were treated with a "watch-and-wait" (WW) policy, 7 (38.9%) were treated with involved-field irradiation, and 4 (22.2%) received systemic chemotherapy. Patients with resected disease were treated with significantly different strategies from those with residual disease ($p = 0.0026$). Five patients experienced relapse during follow-up (median follow-up: 48.2 months). All relapses were distant from the primary site, irrespective of treatment strategy. Among all stage I patients, disease resection was not a significant factor for survival ($p = 0.9294$). Collectively, the choice of treatment strategy was significantly influenced by patient status. Resection status was not significantly associated with survival after several treatment strategies.

Keywords: follicular lymphoma; resected; ^{18}F-fluorodeoxyglucose PET; irradiation

INTRODUCTION

Follicular lymphoma (FL) is the second-most common type of non-Hodgkin lymphoma in the United States and Europe,[1,2] and is increasing in frequency even in Japan.[3] FL is characterized by indolent clinical behavior and subsequent histological transformation linked with an aggressive clinical course and poor outcomes. A substantial number of patients exhibit no clinical symptoms and do not need immediate treatment irrespective of clinical stage, although FL is recognized as an incurable malignant disease.

The treatment modality for patients with malignant lymphoma is generally selected based on clinical stage being early or advanced.[4] For early-stage FL, involved-field irradiation therapy is recommended by published guidelines.[5,6] Moreover, irradiation is the only treatment strategy to demonstrate any advantage in terms of overall survival, although the evidence for this was obtained from retrospective studies.[7,8] However, the reality is that several treatment strategies have been applied for patients with early-stage FL, including combined-modality therapy (CMT), irradiation alone, watch-and-wait (WW), and more recently, rituximab (R)-containing chemotherapy or R monotherapy,[9-11] probably because recommendations have been based on relatively small, retrospective studies from a single center.[5,6] Disease-free survival rates for patients with early-stage disease were

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44 - 54% at 10 years when treated with involved-field irradiation.[12,13] CMT resulted in 76% of patients being free from treatment failure at 10 years.[14] In comparison, even patients treated with a WW policy reportedly had excellent overall survival.[15] The best treatment strategy for early-stage FL thus remains controversial in the absence of evidence from prospective, randomized trials.

One specific characteristic of early-stage FL, particularly stage I disease, is that a substantial proportion of patients undergo total resection after diagnostic surgical biopsy. Such patients presumably have minimal disease compared with other early-stage FL patients, and successful local control by surgical removal may obviate the need for irradiation. However, little clinical information is available regarding patients in this setting, especially since the emergence of modern technologies such as ^{18}F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) and Rituximab. Therefore, this study examined the clinical characteristics of patients who underwent total resection of FL after diagnosis and clinical outcomes after different treatment strategies.

MATERIAL AND METHODS

Among four participating institutes in Japan, a total of 305 patients were diagnosed with FL between January 2001 and July 2013. Duodenal FL and cutaneous FL were excluded from this study because they are distinct clinical entities. Histological diagnosis was made according to the classification criteria of the World Health Organization,[16] and patients with grade 3b were also excluded. Among 305 patients, 36 were defined as having clinical stage I disease based on the Ann Arbor Staging system after rigorous staging procedures,[17] which required pathological and flow cytometric diagnosis of bone marrow aspirates, and diagnostic imaging using whole-body CT and/or 18F-FDG-PET/CT. When residual tumor after diagnostic tissue biopsy was not apparent from imaging or physical examination, the patient was assigned to the "resected tumor group". If residual disease was apparent, the patient was assigned to the "residual tumor group". Laboratory data, including concentrations of soluble interleukin-2 receptor α (sIL2Rα), were evaluated at diagnosis. Treatment strategies for each patient, categorized as chemotherapy with R, R monotherapy, WW or involved-field irradiation, were determined at the discretion of the physician. Complete response (CR) was defined as disappearance of tumor, and partial response (PR) as a decrease of ≥50% in maximum tumor diameter on whole-body CT. When tumor growth was determined by tissue biopsy or other appropriate imaging modality after response, the patient was considered to have disease relapse. The study protocols were approved by the institutional review board at each participating institute.

Statistical analysis: Progression-free survival (PFS) was calculated from the day of diagnosis to the day of event (death from any cause, relapse or progressive disease), and analyses were performed using Kaplan-Meier methods. Survival was compared using the log-rank test. All statistical analyses were performed using JMP version 12 software (SAS, Cary, NC).

RESULTS

Clinical characteristics of the 36 patients with stage I FL are shown according to patient group in Table 1. In the resected tumor group, the median age was 56.5 years, and 6 patients (33.3%) were male. The histological grade was 1 - 2 in 16 patients (88.9%). Cytogenetic analysis of tumor tissue was performed for 7 patients; t(14;18)(q32;q21) was detected in 2 patients and t(3;14)(q27;q32) was detected in 1 patient. FISH analysis for bcl2-IgH fusion gene was performed for one patient among them. FDG-PET/CT was performed for 13 of the 18 patients (72.2%). None of these characteristics were significantly different between the resected and residual tumor groups, with the exception of sIL-2Rα concentration.

As initial treatments, WW (38.9%) and irradiation (38.9%) were the most frequent in the resected tumor group, whereas irradiation (50.0%) and systemic therapy (50.0%) were the most frequent in the residual tumor group (Table 2). The median irradiation dose was 30 Gy (range, 30-40 Gy) in the resected tumor group and 40 Gy (range, 30-50 Gy) in the residual tumor group. With regard to systemic therapy in the resected tumor group, 2 patients were treated with R monotherapy, 1 patient with R-CHOP and the remaining patient with CMT. In the residual tumor group, 4 patients were treated with R-CHOP, 4 patients received CMT and 1 patient received R monotherapy. All patients in the residual tumor group received some form of invasive treatment. The selected treatment strategies differed significantly between groups (Table 2; chi-squared test, $p = 0.0026$). To evaluate the influence of extranodal presentation on treatment choice, the same analysis was performed for patients with nodal disease only. We confirmed similar results (data not shown, $p = 0.0091$).

Treatment Response: For the entire stage I cohort, CR was achieved in 35 of the 36 patients (97.3%) after initial treatment, with PR in the remaining patient. The median follow-up was 62.4 months, and 5-year PFS was 73.1% (95% confidence interval (CI), 55.5-85.5%). All 11 patients who relapsed had nodal disease at diagnosis. No patients developed secondary primary malignancy (SPM) or died of disease.

In the resected tumor group, the median duration of follow-up was 48.2 months. All 18 patients achieved CR after initial therapy. The 5-year PFS was 77.8% (95%CI, 53.5-91.4%). All 5 patients exhibited relapse distant from the primary site, and all had nodal disease at diagnosis (Table 3). The 5-year PFS was 71.4% for all patients with nodal FL with resected disease. Among the 5 patients with relapse, 2 patients were treated with R-CHOP, one with R monotherapy, one with irradiation and one with WW after relapse. By the end of the study, 3 patients remained alive with relapsed disease and the remaining two were alive without disease. One patient exhibited histological transformation 47 months after

Table 1. Patient characteristics

Parameter		Resected tumor group (n = 18)	Residual tumor group (n = 18)	
Age, median (range)		56.5 (28 - 76)	64 (38 - 85)	
	<= 60	8 (44.4)	11 (61.1)	$p = 0.5051$
	> 60	10 (55.6)	7 (38.9)	
Sex				
	Male	6 (33.3)	11 (61.1)	$p = 0.1811$
	Female	12 (66.7)	7 (38.9)	
Performans Status	> 1	1 (5.6)	0 (0)	$p = 0.2245$
Histological Grade				
	Grade 1-2	16 (88.9)	16 (88.9)	$p = 1.0000$
	Grade 3a	1 (5.6)	2 (11.1)	
	ND	1 (5.6)	0 (0)	
PET	(%)	13 (72.2)	13 (72.2)	$p = 1.0000$
Bulky Disease (> 5 cm)	(%)	2 (11.1)	4 (22.2)	$p = 0.3644$
Extranodal disease	(%)	3 (16.7)	4 (22.2)	$p = 1.0000$
	stomach	1	1	
	conjunctiva	1		
	breast	1		
	uterus		1	
	vertebra		1	
	parotid grand		1	
Hb (mg/dl), median (range)		13.4 (9.6 - 17.0)	13.7 (10.6 - 16.6)	$p = 0.5794$
LDH (IU/L) median (range)		170 (88 - 254)	179 (138 - 351)	$p = 0.2415$
sIL-2R (U/ml), median (range)		291 (127 - 677)	476 (224 - 2,150)	$p = 0.0183$*
FLIPI				$p = 0.7001$
	Low	14 (77.8)	13 (72.2)	
	Int	4 (22.2)	5 (27.8)	

ND, not described

Table 2. Treatment choice according to patient status

		Patients' status	
Initial Treatment	n (%)	Resected tumor group (%)	Residual tumor group (%)
Irradiation	16 (44.4)	7 (38.9)	9 (50.0)
Systemic Therapy	13 (36.1)	4 (22.2)	9 (50.0)
	R monotherapy	2	1
	R-CHOP	1	4
	Irradiation + R-CHOP	1	4
WW	7(19.4)	7 (38.9)	0

$p = 0.0026$

WW Watch and Wait, R rituximab

initial diagnosis.

In the residual tumor group, the median follow-up was 79.0 months. The 5-year PFS was 67.3% (95%CI, 40.0-86.4%). One patient with PR in the residual tumor group had nodal lymphoma and achieved PR after 8 doses of R, and has remained in CR after receiving additional irradiation therapy. Six patients developed relapse, and treatment after relapse was R monotherapy in two, R-CHOP and surgical resection in one each, and WW in two. Four patients remained alive without disease and the remaining two were alive with disease.

As patients who had undergone total resection had extremely small residual lymphoma cells, resection status may favorably influence survival. However, comparison of PFS between the resected and residual tumor groups demonstrated no influence of resection status on survival (Fig.1).

DISCUSSION

As a special characteristic of stage I FL, lymphoma lesions are able to be completely resected after diagnostic tissue biopsy. Seymour *et al*. reported that 24 of 102 patients with early-stage indolent lymphoma (23.5%) were without residual disease at initial treatment.[14] Likewise, 27 of 85 early-stage FLs (31.8%) demonstrated total resection status in the MabThera and IF RT (MIR) trial.[18] In our study, 18 of 36 patients with stage I FL (50%) had undergone resection. Patients with this status are probably not rare among cases of early-stage FL, especially at stage I, but clinical information regarding these patients is limited.

Even in this small observational study, treatment choice differed according to patient status in the resected or residual tumor group ($p = 0.0026$), although all patients had the same stage I disease after a rigorous staging procedure. Physicians selected systemic therapy more often for those in the residual tumor group and WW more often for those in the resected tumor group. In the United States, treatment choice has been reported to change depending on age, race, marital status and year of diagnosis, as well as income or health insurance coverage even among patients limited to early-stage disease.[19,20] As such socioeconomic characteristics were not collected in the present study, we cannot rule out the possibility that other factors influenced our results. Thus, it is possible that nodal or extranodal presentation influenced treatment choice. To examine the relationship between primary site and treatment choice, we performed statistical analysis only for patients with nodal disease. Results were similar among all patients ($p = 0.0091$). In additional analyses, we found no significant difference in PFS between resected and residual tumor patients with nodal disease only. These results revealed that extranodal presentation did not influence treatment choice or PFS in this study. Considering the racial homogeneity and universal health care system in Japan, we believe that treatment choice in this study was simply a

Table 3. Clinical course of totally resected tumor patients

Age / Sex	FDG-PET at staging	Initial treatment	Primary site	Relapse (mo)	Relapse site	2nd line Treatment	Survival (mo)	Outcome
58 / M	No	WW	Lt neck	No			74	AWOD
69 / F	Yes	WW	Lt neck	47 (transfomation)	Small intestine	R-CHOP	52	AWD
52 / F	No	WW	Rt inguinal	No			35	AWOD
39 / F	Yes	WW	Lt inguinal	No			65	AWOD
74 / F	Yes	WW	Rt breast	No			25	AWOD
28 / F	Yes	WW	Lt inguinal	No			37	AWOD
76 / F	No	WW	Rt inguinal	15	Lt inguinal	R monotherapy	29	AWD
48 / F	No	WW	Rt inguinal	7	Lt neck	WW	90	AWD
54 / M	Yes	Irradiation	Rt inguinal	21	Lt inguinal	R-CHOP	29	AWOD
49 / F	No	Irradiation	Mesentery	27	Bilateral axilla	Irradiation	164	AWOD
48 / M	No	Irradiation	Rt Orbita	No			91	AWOD
67 / F	Yes	Irradiation	Rt inguinal	No			86	AWOD
47 / M	Yes	Irradiation	Lt neck	No			49	AWOD
55 / M	Yes	Irradiation	Lt inguinal	No			60	AWOD
64 / F	Yes	R monotherapy	Spleen	No			38	AWOD
71 / M	Yes	R monotherapy	Rt inguinal	No			47	AWOD
62 / F	Yes	R-CHOP	Lt iliac bone	No			22	AWOD
69 / F	Yes	R-CHOP	Stomach	No			42	AWOD

WW Watch and Wait, AWD alive with disease, AWOD alive without disease

reflection of disease status. WW is a conceivable selection for patients with no treatment target in the resected tumor group, and physicians may add additional treatments for patients with residual disease. As this was a retrospective, regional study on a small number, the observed treatment trends may not be able to be generalized. Our basic treatment policy for stage I FL is irradiation, and irradiation was the most frequent for all stage I FLs. This policy may have influenced the treatment choice.

Soubeyran *et al*. examined survival status among 43 patients with "stage I_0" FL who underwent total resection after tissue biopsy.[21] A WW policy was adopted for 26 patients and 17 received involved-field irradiation up to 40 Gy, with or without chemotherapy. In the WW group, 13 patients relapsed. Six developed local relapse after a median follow-up of 4.2 years, whereas no local relapse was observed in the irradiated group. In general, the local relapse rate after irradiation for early-stage FL is less than 10%,[22-24] demonstrating the effectiveness of irradiation for local control. Furthermore, considering irradiation as the only strategy with benefits in terms of overall survival for early-stage FL,[7,19,20] irradiation is one of the most important treatment strategies, as reflected in several guidelines and review articles for early-stage FL.[5,6,25,26] On the other hand, 7 of 13 patients in the WW group experienced distal relapse shortly after diagnosis in their report (median, 1 year; range, 0.5-5 years).[21] This suggests that the staging assessment applied was insufficient for stringent determination of clinical stage. In several studies conducted prior to the advent of new imaging modalities, such as ^{18}F-FDG-PET, the PFS or Freedom From Relapse curve often dropped within the first 1-2 years after diagnosis in low grade lymphoma, including FL, of stage 1 or 2.[12,22] This supports the importance of rigorous staging protocols. Although the 7 patients in the resected tumor group observed under WW never exhibited local relapse, sensitive FDG-PET imaging may have allowed for strict segregation of resected patients, as 5 of these 7 patients had been evaluated using FDG-PET/CT. If so, sparing irradiation for the resected tumor group may be a suitable strategy after FDG-PET staging. FL is now considered an FDG-"avid" disease.[27,28] Considering that 23.9-29% of early FL cases were upstaged to advanced stage based on FDG-PET and 0-5.1% were downstaged,[29,30] FDG-PET staging procedures may be important for clinical evaluation of FL, particularly for early-stage cases.

In this study, all relapses occurred distant to the primary site irrespective of disease status or treatment strategy. Prevention of distal relapse remains an important clinical problem for early-stage FL. To overcome this problem, systemic therapy may be warranted. Indeed, some studies have reported that PFS or disease-specific survival improved more after systemic chemotherapy than after irradiation alone or with a WW strategy.[11,31] However, other studies have not found such improvements;[21,24] therefore, the importance of systemic therapy remains debatable. Recently, R has become the preferred candidate for systemic therapy in terms of adverse events such as SPM. A recent observational study demonstrated excellent survival for patients treated with R with or without irradiation,[11,32,33] although the follow-up period was not long enough to estimate clinical outcome. As most of these studies were retrospective in nature, prospective trials are needed to clarify future directions of treatment for early-stage FL.

In conclusion, different treatment strategies were selected for stage I FL patients depending on disease status. However, as this was a small, retrospective series, it is

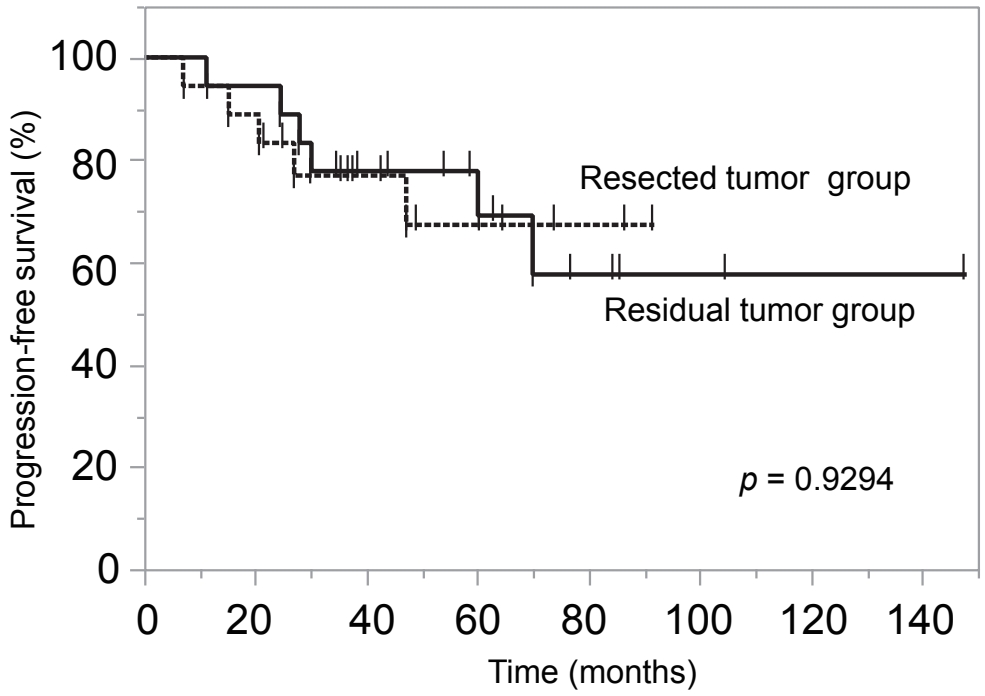

Fig. 1. Progression-free survival in the resected and residual tumor groups.

difficult to draw a conclusion in terms of the best treatment choice for stage I FL. Considering that resection status had no benefit for PFS after these treatment strategies, patients who underwent resection are not special among stage I FL patients, although a WW strategy may be possible if a rigorous staging assessment is applied.

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CONFLICT OF INTEREST

The authors have no competing financial interests to declare.

REFERENCES

1 Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol. 1998; 16 : 2780-2795.
2 Fisher SG, Fisher RI. The epidemiology of non-Hodgkin's lymphoma. Oncogene. 2004; 23 : 6524-6534.
3 Takata K, Miyata-Takata T, Sato Y, *et al*. Pathology of Follicular Lymphoma. J Clin Exp Hematop. 2014; 54 : 3-9.
4 Cheson BD, Fisher RI, Barrington SF, *et al*. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014; 32 : 3059-3068.
5 Zelenetz AD, Abramson JS, Advani RH, *et al*. NCCN Clinical Practice Guidelines in Oncology: non-Hodgkin's lymphomas. J Natl Compr Canc Netw. 2010; 8 : 288-334.
6 Dreyling M, Ghielmini M, Rule S, *et al*. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016; 27 : 83-90.
7 Pugh TJ, Ballonoff A, Newman F, *et al*. Improved survival in patients with early stage low-grade follicular lymphoma treated with radiation: a Surveillance, Epidemiology, and End Results database analysis. Cancer. 2010; 116 : 3843-3851.
8 Shah BK, Ghimire KB. Survival in adult stage I follicular lymphoma treated with and without radiotherapy - a population-based study. Acta Oncol. 2015; 54 : 951-953.
9 Friedberg JW, Byrtek M, Link BK, *et al*. Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the National LymphoCare Study. J Clin Oncol. 2012; 30 : 3368-3375.
10 Michallet AS, Lebras LL, Bauwens DD, *et al*. Early stage follicular lymphoma: what is the clinical impact of the first-line treatment strategy? J Hematol Oncol. 2013; 6 : 45.
11 Janikova A, Bortlicek Z, Campr V, *et al*. Radiotherapy with rituximab may be better than radiotherapy alone in first-line treatment of early-stage follicular lymphoma: is it time to change the standard strategy? Leuk Lymphoma. 2015; 56 : 2350-2356.
12 Mac Manus MP, Hoppe RT. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. J Clin Oncol. 1996; 14 : 1282-1290.
13 Ahmed N, Owen TE, Rubinger M, *et al*. Early stage W.H.O. grade I and II follicular lymphoma treated with radiation therapy alone. PLoS One. 2013; 8 : e65156.
14 Seymour JF, Pro B, Fuller LM, *et al*. Long-term follow-up of a prospective study of combined modality therapy for stage I-II indolent non-Hodgkin's lymphoma. J Clin Oncol. 2003; 21 : 2115-2122.
15 Advani R, Rosenberg SA, Horning SJ. Stage I and II follicular non-Hodgkin's lymphoma: long-term follow-up of no initial therapy. J Clin Oncol. 2004; 22 : 1454-1459.
16 Harris N, Swerdlow S, Jaffe E, *et al*. Follicular lymphoma. 4th ed, Lyon, International Agency for Reseach on Cancer. 2008; pp. 220-226.
17 Rosenberg SA. Validity of the Ann Arbor staging classification for the non-Hodgkin's lymphomas. Cancer Treat Rep. 1977; 61 : 1023-1027.
18 Herfarth K, Schnaidt S. Early stage nodal follicular lymphoma using IF radiotherapy and Rituximab: Results of the MIR trial of the GLSG and ARO. Radiother Oncol. 2014; 111 : S204.
19 Vargo JA, Gill BS, Balasubramani GK, *et al*. What is the optimal management of early-stage low-grade follicular lymphoma in the modern era? Cancer. 2015; 121 : 3325-3334.
20 Bista A, Sharma S, Shah BK. Disparities in Receipt of Radiotherapy and Survival by Age, Sex, and Ethnicity among Patient with Stage I Follicular Lymphoma. Front Oncol. 2016; 6 : 101.
21 Soubeyran P, Eghbali H, Trojani M, *et al*. Is there any place for a wait-and-see policy in stage I0 follicular lymphoma? A study of 43 consecutive patients in a single center. Ann Oncol. 1996; 7 : 713-718.
22 Pendlebury S, el Awadi M, Ashley S, *et al*. Radiotherapy results in early stage low grade nodal non-Hodgkin's lymphoma. Radiother Oncol. 1995; 36 : 167-171.
23 Wilder RB, Jones D, Tucker SL, *et al*. Long-term results with radiotherapy for Stage I-II follicular lymphomas. Int J Radiat Oncol Biol Phys.2001; 51 : 1219-1227.
24 Guadagnolo BA, Li S, Neuberg D, *et al*. Longterm outcome and mortality trends in early-stage, Grade 1-2 follicular lymphoma treated with radiation therapy. Int J Radiat Oncol Biol Phys. 2006; 64 : 928-934.
25 Hiddemann W, Cheson BD. How we manage follicular lymphoma. Leukemia. 2014; 28 : 1388-1395.
26 Izutsu K. Treatment of follicular lymphoma. J Clin Exp Hematop. 2014; 54 : 31-37.
27 Jerusalem G, Beguin Y, Najjar F, *et al*. Positron emission tomography (PET) with 18F-fluorodeoxyglucose (18F-FDG) for the staging of lowgrade non-Hodgkin's lymphoma (NHL). Ann Oncol. 2001; 12 : 825-830.
28 Weiler-Sagie M, Bushelev O, Epelbaum R, *et al*. (18)F-FDG avidity in lymphoma readdressed: a study of 766 patients. J Nucl Med. 2010; 51 : 25-30.
29 Wirth A, Foo M, Seymour JF, *et al*. Impact of [18F]

fluorodeoxyglucose positron emission tomography on staging and management of early-stage follicular non-hodgkin lymphoma. Int J Radiat Oncol Biol Phys. 2008; 71 : 213-219.

30 Metser U, Dudebout J, Baetz T, *et al*. [18F]-FDG PET/CT in the staging and management of indolent lymphoma: A prospective multicenter PET registry 7 Resected follicular lymphoma study. Cancer. 2017; 123 : 2860-2866.

31 Sancho JM, Garcia O, Mercadal S, *et al*. The long term follow-up of early stage follicular lymphoma treated with radiotherapy, chemotherapy or combined modality treatment. Leuk Res. 2015; 39 : 853-858.

32 Cencini E, Fabbri A, Schiattone L, *et al*. Radiotherapy with rituximab as first-line treatment for earlystage follicular lymphoma. Leuk Lymphoma. 2015; 56 : 2997-2998.

33 Ruella M, Filippi AR, Bruna R, *et al*. Addition of Rituximab to Involved-Field Radiation Therapy Prolongs Progression-free Survival in Stage I-II Follicular Lymphoma: Results of a Multicenter Study. Int J Radiat Oncol Biol Phys. 2016; 94 : 783-791.