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The role of surveillance computed tomography in patients with follicular lymphoma

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Abstract

Introduction: Surveillance computed tomography (CT) is performed during the follow-up of patients with lymphoma who have completed initial therapy. However, studies on the clinical benefit of surveillance CT for patients with incurable subtypes, such as follicular lymphoma (FL), are limited. This study aimed to evaluate the value of surveillance CT for patients with FL after achieving the first complete response (CR) or CR unconfirmed in the rituximab era.

Methods: We retrospectively reviewed the medical records of patients with FL who achieved CR with first-line treatment between 2000 and 2016 at our institution. In patients who experienced first relapse, we examined the patient's clinical characteristics at the time of relapse, subsequent therapies, and post-relapse survival, based on the method of relapse detection.

Results: Of the 248 patients who achieved CR after initial therapy, 109 had a relapse, with a median follow-up of 11 years; 100 were enrolled into this study. Relapse was detected by surveillance CT in 61 patients (surveillance CT group) and by means other than surveillance CT, such as the presence of patient-reported symptoms, physical findings, and blood work-up abnormalities (non-surveillance CT group), in 39 patients. There was no significant difference in the patients' characteristics at the time of relapse between the two groups, except for a higher incidence of extranodal involvement in the non-surveillance CT group. The method of relapse detection did not affect therapeutic selection after relapse and post-relapse survival. In this study, 86.8% of the 38 patients who relapsed with only deep lesions, such as mesenteric or retroperitoneal lymph nodes, had surveillance CT-detected relapse.

Conclusion: Surveillance CT did not show any clinical benefit for patients with FL in CR; however, it might lead to early detection of relapse in cases of deep lesions that cannot be identified without imaging.

Keywords: B-cell non-Hodgkin lymphoma, follicular lymphoma, surveillance computed tomography

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Introduction

Surveillance computed tomography (CT) is a traditional follow-up practice for patients with lymphoma who have achieved the first complete response (CR). The rationale is based on the hypothesis that surveillance CT can detect relapse at an early stage and therefore lead to a favorable clinical outcome. However, previous studies of patients with curable lymphoma subtypes, such as diffuse large B-cell lymphoma (DLBCL) and Hodgkin lymphoma (HL), have reported that routine surveillance imaging with CT or positron

emission tomography (PET) detects relapse in only few cases; most relapse cases are detected clinically, based on patient-reported symptoms, abnormal physical findings, and blood workup abnormalities.[1–10] Moreover, most previous studies have revealed that surveillance imaging offers no survival benefit for patients with curable lymphoma subtypes, mainly DLBCL and HL.[2,5–7,10,11] Given the excessive radiation exposure, medical costs, and unclear survival benefit associated with surveillance imaging, the 2014 Lugano classification discouraged its use for curable lymphoma subtypes, and the American Society of Hematology Choosing Wisely Campaign recommended limiting the use of surveillance CT for curable non-Hodgkin lymphoma (NHL).[12,13]

Follicular lymphoma (FL) is the second commonest subtype of NHL, accounting for 7–20% of NHL cases.[14,15] Since the introduction of rituximab, a chimeric anti-CD20 monoclonal antibody, the prognosis of patients with FL has improved dramatically, with a median survival of >20 years.[16,17] However, patients with FL experience incurable relapse after treatment with rituximab-containing regimens.

There are few studies on the clinical benefit of surveillance CT in patients with FL,[18–20] compared to studies on DLBCL and HL. These studies have not supported routine surveillance imaging, and the 2014 Lugano classification also describes that judicious use of follow-up scans may be considered in indolent lymphomas with residual intra-abdominal or retroperitoneal disease in the follow-up evaluations section.[12] This study aimed to evaluate the value of surveillance CT for patients with FL after achieving the first CR or CR unconfirmed (CR/CRu) in the rituximab era.

Methods

Patients

We retrospectively reviewed the medical records of patients with FL grades 1–3a, who achieved CR/CRu with first-line treatment between 2000 and 2016 at the National Cancer Center Hospital (NCCH). Patients with disease refractory to first-line treatment and achieved CR after receiving second-line treatment were excluded from this study. The 2008 World Health Organization criteria were used for diagnosis.[21] The International Working Group criteria published in 1999 and subsequently revised in 2007 were used to assess response.[22,23] This study was approved by the institutional review board of the NCCH on 13 October 2017, and informed consent was waived because of the retrospective nature of the study. Written informed consent to treatment was obtained from all patients. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[24]

Follow-up

In accordance with the practice policy at our institution, during each follow-up, patients underwent a symptom assessment, physical examination, and blood workup. Follow-ups were scheduled every 1–3 months during the first 2 years after treatment completion, then every 3–6 months from the third to fifth year, and every 3–12 months thereafter. The blood workup included a complete blood count, serum lactate dehydrogenase, liver function tests, renal function tests, and C-reactive protein; meanwhile, soluble interleukin-2 receptor was not routinely measured. Surveillance CT was generally performed every 6 months for the first 5 years, and then at least once annually. Cervical, thoracic, abdominal, and pelvic CT was used routinely for response assessment and surveillance; however, in the presence of clinical signs giving suspicion of relapse (based on clinical signs), PET-CT was used for confirmation.

Outcome

Patients who relapsed after achieving the first CR/CRu were divided into two groups, based on the method of relapse detection: patients with relapse detected by surveillance CT (surveillance CT group) and those with relapse detected by means other than surveillance CT, such as patient-reported symptoms, abnormal physical findings, and blood workup abnormalities (non-surveillance CT group). The clinical characteristics at relapse and outcome after relapse were evaluated according to the method of relapse detection. Progression of disease within 24 months (POD24) was defined as occurrence of relapse within 24 months after diagnosis. Moreover, patients were categorized into two groups, based on the detected

lesions at the time of relapse: the group wherein patients had only impalpable and deep-seated lesions, such as intracranial, intrathoracic, and intraabdominal masses (only deep lesions); and the group wherein patients had at least one palpable and superficial lesion (superficial lesions with or without deep lesions). We examined the relationship between the lesion detected at the time of relapse and relapse detection methods.

Statistical analysis

Categorical data were compared using the chi-square tests. Continuous data were compared using the Welch's *t*-test and Mann–Whitney *U*-test, depending on the data distribution. The overall survival (OS) after relapse was calculated from the date of relapse to the date of death from any cause or the last follow-up date. Patients were censored at the last follow-up date on which they were known to be alive. Survival curves were plotted using the Kaplan–Meier method and compared using the log-rank test between different groups. All comparisons were considered significant if the p value was <0.05. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for *R* (The R Foundation for Statistical Computing, Vienna, Austria). Specifically, it is a modified version of *R* commander with added statistical functions that are frequently used in biostatistics.[25]

Results

Patient characteristics at the time of relapse

A total of 248 patients were identified. Five patients died before relapse. The median follow-up duration was 11.0 (range: 1.74–16.0) years. Of those who had relapse (109 patients), nine patients were excluded from the analysis (underwent surveillance PET-CT instead of CT, $n=4$; underwent surveillance esophagogastroduodenoscopy, $n=2$; irregular follow-up because of concurrent breast cancer, $n=1$; relapse detected by screening colonoscopy, $n=1$; attending physician's discretion, $n=1$; Figure 1). Finally, 100 patients were enrolled in the study: 61 in surveillance CT group and 39 in non-surveillance CT group. There was no significant difference in the median time from the end of initial treatment to relapse between surveillance CT group (2.79 (interquartile range, IQR: 1.88–5.15) years) and non-surveillance CT group (2.36 (IQR: 1.20–5.11) years; $p=0.178$). During the study period, relapse occurred at a constant rate, and the cumulative incidence curve did not reach a plateau in either group (Supplemental Figure 1). The patients underwent a total of 672 CT scans during the first CR (approximately 6.7 scans per patient), and there was no significant difference in the median number of surveillance CT sessions between surveillance CT group (5 (range: 1–17)) and non-surveillance CT group (5 (range: 1–21); $p=0.226$). There was a significant difference in

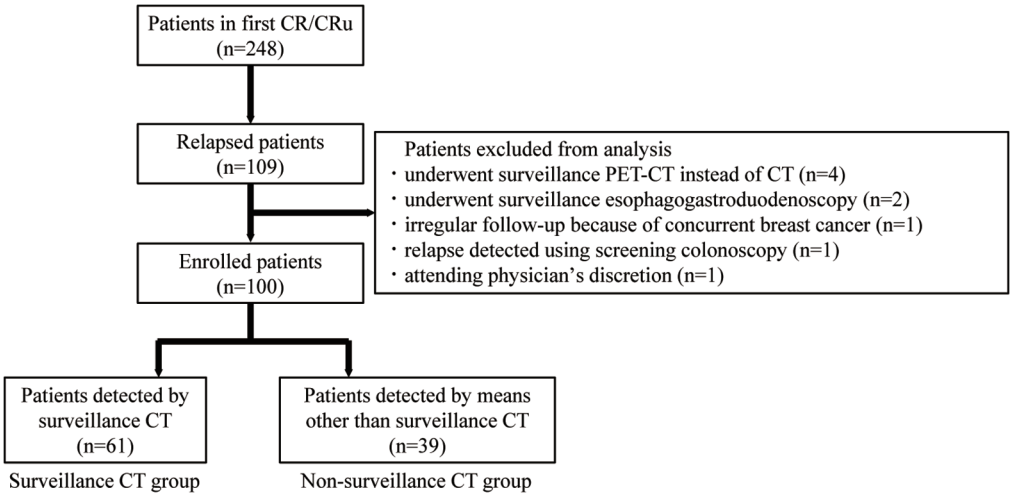

Figure 1. Flow diagram of patients in this study.

Table 1. Symptoms at the time of relapse.

	Non-surveillance CT group ($n=39$)
Symptoms, *n* (%)	
Enlarged lymph node	23 (59.0)
Extranodal mass[a]	9 (23.1)
Pain	5 (12.8)
Fever	1 (2.6)
Weight loss	1 (2.6)
Abnormal blood test[b]	1 (2.6)
Abducent paralysis	1 (2.6)

CT: computed tomography.
Two patients presented with multiple symptoms at the time of relapse.
[a]Subcutaneous ($n=5$), parotid gland ($n=2$), and palate ($n=2$).
[b]Abnormal elevation of lactate dehydrogenase levels and thrombocytopenia ($n=1$).

the median time from the last follow-up CT to relapse detection between surveillance CT group (187 (IQR: 181–206) days) and non-surveillance CT group (175 (IQR: 112–189) days; $p<0.001$).

The most common signs of relapse and patients' characteristics at the time of relapse are summarized in Tables 1 and 2. The most common sign of relapse was enlarged lymph nodes ($n=23$), followed by extranodal masses ($n=9$); both were palpable masses. Despite routine blood tests, relapse was detected by blood abnormalities (elevated lactate dehydrogenase levels and thrombocytopenia) in only one patient. There were no significant differences in the patients' characteristics at the time of relapse between the two groups, except for a higher incidence of extranodal involvement in non-surveillance CT group. Histological transformation (HT) at relapse was clinically suspected in seven (11.4%) patients in surveillance CT group and eight (20.5%) in non-surveillance CT group; the difference was not significant ($p=0.343$). Eleven of the 15 patients with a suspected transformation at the time of relapse underwent biopsy. Transformation of HT to DLBCL was pathologically confirmed in five (8.2%) patients in surveillance CT group and three (7.7%) patients in non-surveillance CT group; the difference was not significant ($p=1.00$).

Outcome after relapse

There was no significant difference in OS after relapse between surveillance CT group (OS at 10 years: 70.5%; 95% confidence interval (CI), 37.6–88.2%) and non-surveillance CT group (OS at 10 years: 81.5%; 95% CI, 59.1–92.4%; $p=0.837$; Figure 2). Of those who had relapse, seven patients died from progressive disease, and five died from other causes: myelodysplastic syndrome (MDS, $n=2$), colon cancer ($n=2$), and an unknown cause ($n=1$). Six patients were referred to other hospitals, and the remaining patients were followed up at our hospital.

According to the attending physician's discretion, 49 (80.3%) patients in surveillance CT group and 32 (82.1%) in non-surveillance CT group received the next anti-lymphoma treatment, including systemic chemotherapy (24 in surveillance CT group and 12 in non-surveillance CT group), rituximab monotherapy (11 in surveillance CT group and 10 in non-surveillance CT group), ibritumomab tiuxetan (2 in surveillance CT group and 2 in non-surveillance CT group), radiotherapy (RT) only (1 in surveillance CT group), and investigational agents (11 in surveillance CT group and 8 in non-surveillance CT group); there was no significant difference between the two groups ($p=1.00$). In addition, there was no significant difference in the time from relapse to the initiation of next anti-lymphoma treatment between surveillance CT group (median, 0.68 years; 95% CI, 0.479–1.34 years) and non-surveillance CT group (median, 0.56 years; 95% CI, 0.153–1.26 years; $p=0.778$; Figure 3(a)).

The proportion of patients who received cytotoxic chemotherapy after relapse was 50.8% ($n=31$) in surveillance CT group and 61.5% ($n=24$) in non-surveillance CT group; the difference was not significant ($p=0.398$). There was also no significant difference in the time from relapse to cytotoxic chemotherapy initiation after relapse between the two groups (median, 4.49 years; 95% CI, 2.48–6.94 years *vs* 2.42 years; 95% CI, 1.08–9.36 years; $p=0.414$; Figure 3(b)).

Lesions at relapse

At the time of relapse, 62/100 patients had superficial lesions with/without deep lesions and 38/100

Table 2. Characteristics of patients at the time of relapse.

	At the time of relapse		
	Surveillance CT group (*n* = 61)	**Non-surveillance CT group (*n* = 39)**	***p***
Median age, (range, years)	62 (36–84)	61 (29–77)	0.316
Age > 60 years, *n* (%)	32 (52.5)	21 (53.8)	1
Male sex, *n* (%)	24 (41.0)	12 (30.8)	0.412
Stage III/IV, *n* (%)	20 (32.8)	19 (48.7)	0.167
ECOG PS 2>, *n* (%)	0	0	NA
LDH > ULN, *n* (%)	10 (16.4)	4 (10.3)	0.571
Extranodal involvement, *n* (%)	11 (18.0)	15 (38.5)	0.042
BM involvement, *n* (%)[a]	6 (9.8)	3 (7.7)	0.884
Not done	28 (45.9)	16 (41.0)	
Bulky disease (>7 cm), *n* (%)	4 (6.6)	2 (5.1)	1
B symptoms, *n*(%)	0	1 (2.6)	0.821
GELF HTB, *n* (%)	12 (19.7)	10 (25.6)	0.649
FLIPI, *n* (%)			
Low	39 (63.9)	21 (53.8)	0.105
Intermediate	19 (31.1)	11 (28.2)	
High	3 (4.9)	7 (17.9)	
Histological transformation, *n* (%)[b,c]			
Clinically suspected	7 (11.4)	8 (20.5)	0.343
Pathologically confirmed	5 (8.2)	3 (7.7)	1
First-line treatment, *n* (%)			
Systemic therapy[d]	51 (83.6)	34 (87.2)	0.841
RT alone	10 (16.4)	5 (12.8)	

BM: bone marrow; BR: bendamustine and rituximab; CT: computed tomography; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; FL: follicular lymphoma; FLIPI: follicular lymphoma international prognostic index; GELF: Groupe d'Etude des Lymphomes Folliculaires; HTB: high tumor burden; LDH: lactate dehydrogenase; NA: not applicable; PS: performance status; R-CHOP: rituximab plus cyclophosphamide, doxorubicine, vincristine, and prednisone; R-CMOPP: rituximab plus cyclophosphamide, vincristine, procarbazine, and prednisone; R-CVP: rituximab plus cyclophosphamide, vincristine, and prednisone; RT: radiation therapy; ULN: upper limit normal.
[a]BM biopsy was performed at the time of relapse for 56 patients.
[b]Biopsy was performed immediately at the time of relapse for 36 patients (16 in surveillance CT group and 20 in non-surveillance CT group).
[c]Clinical transformation was suspected in 15 patients. Eight of those patients were pathologically diagnosed with DLBCL. The biopsy results of three of those patients indicated no transformation.
[d]Sixty-seven patients received R-CHOP, 6 R-CMOPP, 4 R-CHOP + R-maintenance, 2 R-CVP, 2 R-CHOP + RT, 3 R-monotherapy, and 1 BR.

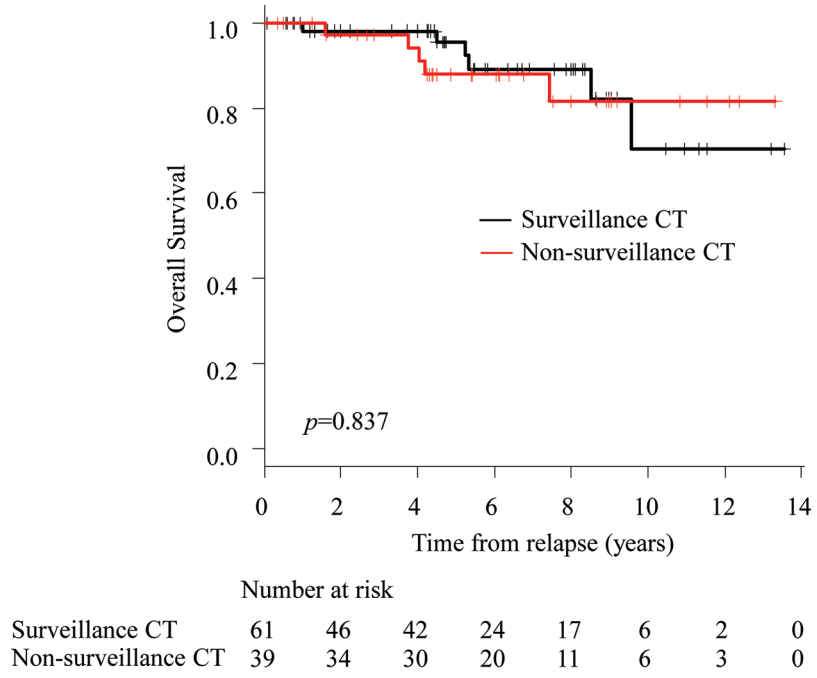

Figure 2. Overall survival after relapse in patients with follicular lymphoma detected by surveillance computed tomography (CT) and means other than surveillance CT.

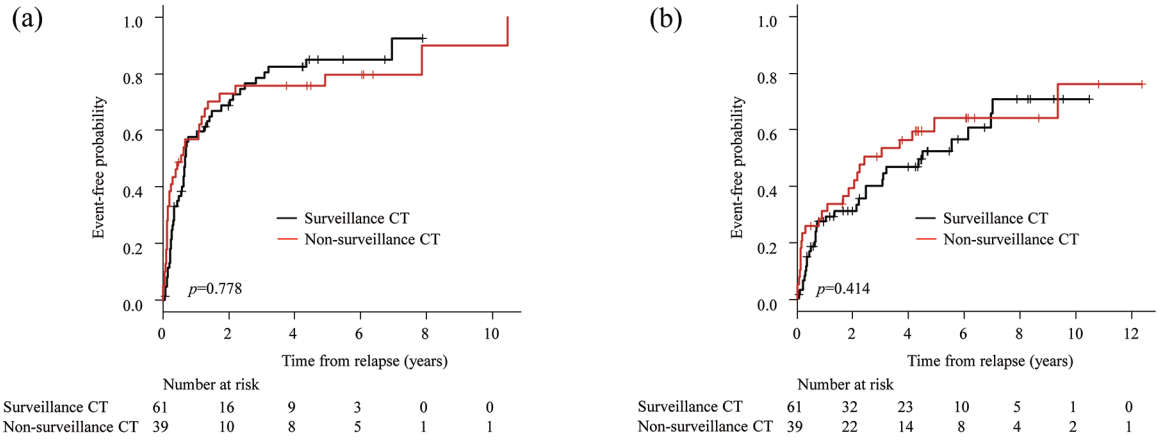

Figure 3. Time to next treatment from relapse detected by surveillance computed tomography (CT) and means other than surveillance CT: (a) any anti-lymphoma treatment and (b) cytotoxic chemotherapy.

had only deep lesions (intra-abdominal mass, $n=33$; intrathoracic mass, $n=2$; both, $n=2$; intracranial mass, $n=1$; Table 3). Surveillance CT (86.8% (33/38) was used to detect relapse in a larger proportion of patients with only deep lesions than non-surveillance CT (13.2% (5/38)). In surveillance CT and non-surveillance CT group, 54.1% (33/61) and 12.8% (5/39) of patients had only deep lesions, respectively.

POD24

POD24 was more prevalent in non-surveillance CT group (13/39, 33.3%) than in surveillance CT group (9/61, 14.8%), although the difference was not significant ($p=0.054$). There was no significant difference in the OS after relapse between POD24 and non-POD24 patients (OS at 10 years: 83.9%; 95% CI, 56.8–94.7% *vs* 65.0%; 95% CI, 27.4–86.7%; $p=0.759$). The proportion

Table 3. Relationship between relapse lesions and relapse detection method.

	Surveillance CT group ($n=61$)	Non-surveillance CT group ($n=39$)
Superficial[a] ± deep[b] lesions ($n=62$)	28	34
Only deep lesions ($n=38$)	33	5

CT, computed tomography.
[a]Superficial lesions include Waldeyer's ring, cervical lymph node, axillary lymph node, inguinal lymph node, and extranodal mass, which are palpable.
[b]Deep lesions include all lesions that were not superficial.

of patients who received the next anti-lymphoma treatment within 1 year of relapse was 68.8% (15/22) among the POD24 patients and 52.6% (41/78) among the non-POD24 patients; the difference was not significant ($p=0.289$). However, POD24 patients were more likely to receive cytotoxic chemotherapy within 1 year of relapse than the non-POD24 patients, although the difference was not significant (45.4% (10/22) *vs* 23.1% (18/78); $p=0.073$).

Discussion

As described in the National Comprehensive Cancer Network (NCCN) guidelines, existing data on the clinical benefit of surveillance CT in patients with incurable lymphoma subtypes, such as FL, are limited.[26] This study was a retrospective evaluation of the role of surveillance CT in patients with FL after they achieved the first CR/CRu. Of the 100 enrolled patients, relapse was detected in 61 patients using surveillance CT and in 39 patients using means other than surveillance CT. Follow-up CT was performed strictly, in accordance with our departmental guidelines. There was no significant difference in the OS after relapse between the two groups. Moreover, there was no significant difference in the time from relapse to initiation of the next treatment between the two groups. However, relapse was detected in 33/38 patients with only deep lesions using surveillance CT, and in five using means other than surveillance CT. These results suggest that surveillance CT was not beneficial for patients with FL in CR/CRu; however, it seemed to lead to early relapse detection in patients with deep lesions.

In a similar retrospective study, 78/257 patients who achieved CR after induction therapy relapsed, with a median follow-up duration of 101 months.[18] Of the 78 patients with relapse, it was detected using surveillance CT in only 11 (14%) of them. However, unlike our study, the routine surveillance CT used in this study was only abdominal and/or pelvic CT. Moreover, the interval at which the surveillance CT was performed was not regular. In another study by Goldman *et al.*,[20] 18/55 (33%) patients in a retrospective cohort and 50/117 (43%) in a prospective validation cohort had asymptomatic imaging-detected relapses, and there was no significant difference in the OS between patients with surveillance imaging-detected relapse and clinically detected relapse. However, in their study, surveillance imaging methods were not defined, and they used CT or PET. In our study, 61% of relapses were detected using surveillance CT. The proportion of surveillance CT-detected relapses in our study was higher than that in the cited previous studies. The shorter interval and longer duration of surveillance CT after achieving CR in our study may explain this discrepancy. However, in our study and the studies mentioned above, more relapses were detected using surveillance imaging than in previous studies on DLBCL, in which surveillance CT detected 10–20% of the relapses;[1,3,6] the differences in the indolent nature and aggressiveness of the tumors might be an explanation. Despite routine blood tests, only one relapse was detected by blood abnormalities in this study. This result was in line with that of a previous study of aggressive lymphoma in which routine blood tests did not reliably detect relapse in asymptomatic patients (only 5% of relapse cases were detected) and had no impact on survival.[27] These results suggest that routine blood tests, similar to routine surveillance CT, may have limited value in the detection of lymphoma relapse.

Several studies showed that PET-CT more accurately detected lesions at staging or response

evaluation in patients with FL than CT.[28–30] Especially, the sensitivity of PET-CT to detect extranodal disease or bone marrow involvement is higher than that of CT. In this study, patients whose relapse was detected by means other than surveillance CT had a higher incidence of extranodal involvement than patients whose relapse was detected by surveillance CT. If surveillance with PET-CT had been performed, then extranodal relapse may have been detected before clinical symptoms appeared. However, PET-CT is not recommended as a standard follow-up modality because of its unclear survival benefit, high false-positive rate, and low cost-effectiveness according to the latest NCCN guideline.[26] PET was not routinely used as an imaging modality for surveillance at our institution; only four patients were followed-up using PET-CT. These patients were excluded from the analysis because they did not undergo surveillance CT.

Goldman *et al.*[20] reported that surveillance imaging did not contribute to survival improvement in patients with FL; this was consistent with our study for both groups. OS is the most relevant endpoint; however, it has become more challenging to use OS for FL patients as an endpoint because of its long-term clinical course and treatment improvement. In fact, the median survival time after relapse was not reached in both groups. Since patients with FL usually have a long life expectancy, and the clinical course is characterized by recurrent relapse, the type of drug administered and the time of treatment initiation are also important when considering the benefit to the patient. Therefore, we assessed the time to the next treatment after relapse and the drugs used; however, these were soft endpoints. In our study, the proportion of patients who had received the next anti-lymphoma treatment and the time to the next anti-lymphoma treatment did not differ between both groups. Moreover, there was no significant difference in the proportion of patients who received the next cytotoxic chemotherapy and the time to initiation of the next cytotoxic chemotherapy.

Surveillance CT is considered to contribute to the early detection of deep relapse lesions that could be missed with non-imaging modalities. In our study, of the 38 patients who had only deep relapse lesions, 33 were detected using surveillance CT, and only five were detected by means other than surveillance CT, indicating that the lesions in approximately one-third of the patients with relapse were detected early using surveillance CT. Based on our results, surveillance CT is not associated with clinical outcomes of patients with FL in CR/CRu, but it seems to lead to early relapse detection in patients with deep lesions.

POD24 is a predictor of shorter patient survival in patients with FL, and similar endpoints of early progression after diagnosis or initiation of first-line treatment have also been reported.[31–34] However, previous studies did not differentiate the method of progression detection: clinical, radiography, or other means. Bitansky *et al.*[19] reported that incidental POD24 detection did not necessarily indicate a worse outcome, in a comparison of POD24 between patients diagnosed clinically and those diagnosed using incidental imaging findings. However, their study had several limitations: the retrospective nature, unknown surveillance intervals, and non-unified surveillance modalities. Unlike previous studies, POD24 did not influence poor outcomes in our study because we enrolled only CR patients, and only few patients died during the follow-up period. According to the attending physician's discretion, patients with POD24 tended to receive cytotoxic chemotherapy within 1 year of relapse, compared to non-POD24 patients. This might have led to the improved prognosis of POD24 patients. Given these results, it is important to detect early progression when considering the next treatment. Moreover, the latest NCCN guidelines also recommend that surveillance CT for patients with FL can be performed at most every 6 months for the first 2 years.[26]

This study had several limitations. First, it was a retrospective study. Second, the sample sizes of relapse lesion or POD24 analysis were too small to account for the differences in each subgroup. Third, it was difficult to evaluate whether surveillance CT actually had no clinical benefit for patients with CR/CRu because there was no control group (patients followed-up without surveillance CT after achieving the first CR/CRu). Fourth, only patients who achieved the first CR/CRu after the first treatment were enrolled; however, surveillance CT is also performed for patients with FL in partial response or stable disease in clinical practice. Moreover, only one patient was treated with BR (bendamustine plus

rituximab); only four patients were treated with rituximab maintenance therapy as initial therapy, and no patient was treated with obinutuzumab, which is the available treatment option for untreated FL; these treatment modalities were recently approved for patients with previously untreated FL in our country. These novel therapies showed a superior progression-free survival (PFS), compared to R-CHOP (rituximab plus cyclophosphamide, doxorubicine, vincristine, and prednisone) in a randomized phase-III trial.[35–38] These new treatment strategies prolong PFS even further, which means that more regular surveillance CT is needed to detect one relapse. However, despite these limitations, the strengths of our study lie in the uniform follow-up of the patients with surveillance CT, performed in accordance with our departmental guidelines. Moreover, given the increase in the number of imaging sessions required to detect one relapse following PFS prolongation, surveillance imaging should be performed for selected patients who benefit from it to reduce radiation exposure and health care costs. However, patients undergoing rituximab maintenance therapy may receive additional benefits with the monitoring of active treatment using surveillance imaging. If surveillance imaging detects asymptomatic progression, then toxicity can be reduced by early discontinuation of maintenance therapy. As mentioned, only four patients with rituximab maintenance therapy were included in our study; therefore, further specific studies of the value of surveillance CT for patients undergoing maintenance therapy are required.

In conclusion, our results suggest that surveillance CT is not beneficial to patients with FL in CR/CRu, but it may lead to early relapse detection in patients with deep lesions. Further studies are needed to identify patients with FL for whom surveillance CT is beneficial and to develop an optimal follow-up strategy.

Author contribution(s)

Shunsuke Hatta: Conceptualization; Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

Suguru Fukuhara: Conceptualization; Data curation; Project administration; Supervision; Writing – review & editing.

Takahiro Fujino: Conceptualization; Methodology; Writing – review & editing.

Yo Saito: Conceptualization; Methodology; Writing – review & editing.

Yuta Ito: Conceptualization; Methodology; Writing – review & editing.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplemental material

Supplemental material for this article is available online.

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