INTRODUCTION

The prognosis of patients with diffuse large B-cell lymphoma (DLBCL) has been significantly improved after the introduction of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), and even more with...
the introduction of rituximab into the treatment regimens [1-4]. However, the improvement in treatment results with rituximab in the first-line treatment has been reported to adversely affect treatment outcomes when these patients recur [5]. Therefore, for patients with complete remission (CR) after treatment with rituximab, the importance of early diagnosis and treatment of disease recurrence has increased.

[18F]-fluorodeoxyglucose positron emission tomography-computed tomography (PET/CT) is a useful tool for the diagnosis and prognostication of DLBCL, as well as for evaluation of treatment response [6]. The usefulness of PET/CT follow-up to detect relapses after CR has been demonstrated [5,7]. However, whether this early detection of recurrence found by PET/CT surveillance leads to any survival benefit has not been proven yet. Moreover, considering the characteristics of DLBCL with its high cure rate, there is concern that tracking all patients with PET/CT will lead to an increase in medical costs [8].

In this study, we aimed to evaluate the role of PET/CT in patients with DLBCL in first remission along with an analysis of its effects on clinical outcomes and medical costs.

METHODS

Study design and patient population
A retrospective study of patients diagnosed with DLBCL at Seoul National University Hospital (SNUH) and Seoul National University Boramae Medical Center (SNU-BMC) was conducted. Costs incurred specifically for DLBCL from the date of CR after completion of standard chemotherapy through the subsequent 3 years were calculated. Patients newly diagnosed with DLBCL between January 2005 and January 2015 were eligible for inclusion. The Institutional Review Board at SNUH and SNU-BMC approved this study (IRB No.26-2014-98), and it was conducted in accordance with the Declaration of Helsinki. Written informed consent was not acquired because it was a retrospective study. All patients’ records/information were anonymized and deidentified prior to analysis.

Cost definitions and data sources
Costs consisted of the following two components: in-patient and outpatient costs. These data were retrieved from the institutional accounting system. Costs related to emergency room visits were regarded as inpatient costs. Costs of prescription drugs sold in the hospital pharmacy were included in the cost analysis. However, costs of drugs bought outside the hospital could not be included due to insufficient data. The proportion of medical expenses not covered by the National Health Insurance Service was determined to evaluate the economic burden on patients and the government separately. All cost estimates are represented according to the annual exchange rate in 2016 (1,189.50 Korean won = 1 US dollar).

The duration of follow-up was defined from the date of diagnosis to the end of follow-up at our institution. Relapse-free survival (RFS) was measured from the date of diagnosis to either the date of disease recurrence or death. The overall survival (OS) was defined as the interval from the date of diagnosis to death.

Statistical analysis
The t test was performed to evaluate the association between clinicopathological variables and undergoing surveillance PET/CT. Both hospitals in this study used the same PET/CT scan (Briograph mCT 40, Siemens Medical Solutions, Knoxville, TN, USA) for examination. RFS and OS were calculated using the Kaplan-Meier method, and the values were compared using the log-rank test. Costs were compared between variables by using the t test and analysis of variance, as appropriate. We used multivariate analysis with backward stepwise multiple linear regression to analyze clinicopathological factors as well as PET/CT surveillance that may have been associated with costs. p values of < 0.05 were considered significant. All analyses of data collected through February 2017 were performed by using SPSS software version 21 (IBM Co., Armonk, NY, USA) and GraphPad Prism 5 (GraphPad Software Inc., La Jolla, CA, USA).

RESULTS

Patient characteristics
Characteristics of 118 patients diagnosed with DLBCL are summarized in Table 1. A total of 76 patients (64.4%) received PET/CT surveillance after achieving CR (here-
after, PET/CT [+ group), whereas 42 patients (35.6%) did not (hereafter, PET/CT [–] group). The median age was 57 years in the PET/CT (–) group and 59 years in the PET/CT (+). The PET-CT (+) group was more likely to have poor performance status; however, stage and International Prognostic Index (IPI) risk were similar between the groups. Most of the patients received the R-CHOP regimen for their initial treatment. The median follow-up was 31.8 months for the PET/CT (–) group and 49.6 months for the PET/CT (+) group, respectively (p = 0.021).

**Univariate and multivariate analysis of medical costs**

Data on the outpatient number of clinic visits and admission, and costs by follow-up PET/CT are described in detail in Table 2. When the follow-up duration was

| Characteristic            | PET-CT (–) | PET-CT (+) | p value |
|---------------------------|------------|------------|---------|
| No. of patients           | 42 (35.6)  | 76 (64.4)  |         |
| Age, yr                   | 57 (29–85) | 59 (23–82) | 0.524   |
| Sex                       |            |            | 0.738   |
| Male                      | 24 (57.1)  | 41 (53.9)  |         |
| Female                    | 18 (42.9)  | 35 (46.1)  |         |
| ECOG PS                   |            |            | 0.022   |
| 0                         | 17 (40.5)  | 12 (15.8)  |         |
| 1                         | 21 (50.0)  | 52 (68.4)  |         |
| 2                         | 4 (9.5)    | 10 (13.2)  |         |
| 3                         | 0          | 12 (2.6)   |         |
| LDH, IU/mL                | 210.5 (99–5,110) | 216.0 (125–3,742) | 0.481 |
| Extranodal involvement    |            |            | 0.240   |
| No                        | 33 (78.6)  | 52 (68.4)  |         |
| Yes                       | 9 (21.4)   | 24 (31.6)  |         |
| Stage                     |            |            | 0.456   |
| 1                         | 13 (31.0)  | 14 (18.4)  |         |
| 2                         | 14 (33.3)  | 27 (35.5)  |         |
| 3                         | 6 (14.3)   | 13 (17.1)  |         |
| 4                         | 9 (21.4)   | 22 (28.9)  |         |
| IPI risk                  |            |            | 0.671   |
| Low                       | 24 (57.1)  | 36 (47.4)  |         |
| Low-intermediate          | 9 (21.4)   | 16 (21.1)  |         |
| High-intermediate         | 3 (7.1)    | 9 (11.8)   |         |
| High                      | 6 (14.3)   | 15 (19.7)  |         |
| Treatment                 |            |            | 0.125   |
| R-CHOP                    | 40 (95.2)  | 76 (100.0) |         |
| R-EPOCH                   | 2 (4.8)    | 0          |         |
| Duration of follow-up, mon| 32 (7–135) | 54 (11–133) | <0.001 |

Values are presented as number (%) or median (range).

PET-CT, positron emission tomography-computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; IPI, International Prognostic Index; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.
Table 2. Univariate analysis for medical costs during the first 3 years after achieving complete response

| Subject                          | PET-CT (–) (n = 42) | PET-CT (+) (n = 76) | p value |
|---------------------------------|---------------------|---------------------|---------|
| Duration of follow-up, mon     | 28 (3–36)           | 36 (6–36)           | < 0.001 |
| Relapse                         | 3 (7.1)             | 16 (21.1)           | 0.049   |
| No. of visits                   | 14 (4–103)          | 25 (6–57)           | < 0.001 |
| Costs                           | 2,256,327 (214,178–38,923,231) | 4,959,357 (1,621,569–10,941,483) | 0.021   |
| Hospitalization                 | 0 (0–15)            | 0 (0–14)            | 0.691   |
| No. of hospitalization          | 0 (0–91,291,439)    | 0 (0–6,440,852)     | 0.862   |
| Total costs                     | 2,499,689 (340,694–130,214,670) | 5,229,901 (1,596,393–71,140,025) | 0.755   |
| Total costs paid by patients a  | 326,819 (64,540–108,837,381) | 636,100 (176,051–33,422,478) | 0.460   |

Values are presented as median (range) or number (%). Statistical significance test was done by independent t test.

PET-CT, positron emission tomography-computed tomography.

aCosts that were not reimbursed by the National Health Insurance Service; thus, paid by the patients. Costs are stated in Korean won.

Table 3. Results of multivariate linear regression models analyzing total medical costs

| Variables a | B     | SE    | p value |
|-------------|-------|-------|---------|
| Age         | –185,986 | 101,263 | 0.069   |
| Relapse     | 11,618,666 | 4,320,967 | 0.008   |

Adjusted $R^2 = 0.403, F = 14.140$.

SE, standard error.

aOther variables in the model included International Prognostic Index risk score, and positron emission tomography-computed tomography follow-up.

limited to the first 3 years after achieving a CR for the medical cost comparison, the median duration of follow-up was longer in the PET-CT (+) group compared with the PET-CT (–) group (36 months [range, 6 to 36] vs. 28 months [range, 3 to 36], p < 0.001). Accordingly, the number of outpatient visits and associated costs were also higher in the PET/CT (+) group. There was no statistically significant difference in the number of hospitalizations and any associated costs between the two groups. Within 3 years, the total medical costs were 2,499,689 won for the PET/CT (–) group and 5,229,901 won for the PET/CT (+) group, respectively (p = 0.755). There was no significant difference in costs paid by patients (326,819 for the PET/CT (–) group vs. 636,100 for the PET/CT (+) group, p = 0.460).

In univariate analyses, factors associated with higher medical costs were relapse (p < 0.001) and IPI risk (p = 0.003; low risk vs. high-intermediate risk, p = 0.003; low-intermediate risk vs. high-intermediate risk, p = 0.012). Older age was associated with lower medical costs, but statistical significance was not reached (NR, p = 0.071). PET/CT surveillance and duration of follow-up were not associated with medical costs (p = 0.755 and p = 0.639, respectively). In the multivariate analysis, relapse was the only factor associated with medical costs (p = 0.008) (Table 3). Older age was associated with lower costs, but statistical significance was NR (p = 0.069).

Characteristics and medical costs of patients who received regular follow-up PET/CT and who did not receive any follow-up PET/CT

To more accurately analyze the medical costs of a group that routinely performed, PET/CT, we limited our analysis to patients who regularly performed PET/CT and patients who never performed PET/CT (n = 77). Baseline characteristics of these patients are described in Sup-
Supplementary Table 1. There was no significant difference in age, sex, stage, IPI risk, and treatment between the groups. Follow-up duration was longer in regular PET/CT surveillance group, and accordingly, number of outpatient visits was higher in regular PET/CT surveillance group. However, there was no significant difference in the medical costs associated with outpatient visits. There was no statistically significant difference in the number of hospitalizations and any associated costs between the two groups (Supplementary Table 2).

Propensity score matching
We used propensity score matching to analyze the effects of follow-up PET/CT on the costs. In order to minimize the bias caused by nonrandom allocation to follow-up PET/CT, we developed a matching scheme that included variables that were shown to be associated with costs. We included the following domains: age, IPI risk, and relapse. We then used propensity score matching to match 41 patients (96.7% of the relevant group) in the PET/CT (–) group and 41 patients (53.9% of the relevant group) in the PET/CT (+) group. With the exception of follow-up duration, there were no significant differences in age, ECOG PS, IPI risk, or relapse (Table 4). In this propensity-matched cohort, the number of outpatient clinic visits were significantly higher in the PET/CT (+) group compared with the PET/CT (–) group (median number of visits, 27 vs. 14, p = 0.003). Costs associated with outpatient clinic visits and hospitalization were numerically higher in the PET/CT (+) group, although statistical significance was NR (p = 0.077 and p = 0.535, respectively) (Table 4).

Clinical outcomes
Median RFS and OS were similar between the PET/CT (+) group and PET/CT (–) group (median RFS and OS NR for both groups, p = 0.133 and p = 0.542, respectively) (Fig. 1). A factor associated with both RFS and OS was IPI risk (median RFS NR for all subgroups, mean RFS 122.1 months for IPI low risk patients, 91.4 months for low-intermediate risk patients, 90.2 months for high-intermediate risk patients, and 57.4 months for high risk patients, p = 0.008; median OS NR for all subgroups, median OS 129.1 months for IPI low risk patients, 106.3 months for IPI low-intermediate risk patients, 122.8 months for high-intermediate risk patients, and 74.7 months for high risk patients, p = 0.022). Poor performance status was associated with shorter OS (median NR, mean OS 127.9 months for ECOG PS 0 to 1 patients vs. 73.6 months for ECOG PS 2 to 3 patients, p = 0.007).

Results of PET/CT and subsequent evaluations
Among 76 patients with follow-up PET/CT, 31 patients (40.8%) had findings suggestive of recurrence. Sixteen of these patients (51.6%) were confirmed to have recurrent disease at the time of PET/CT without further evaluation (n = 2; maximal standardized uptake value [SUVmax], 17.3 and 4.2, respectively), after follow-up CT evaluation (n = 3; SUVmax 2.5, 23.7, and 32.4), after follow-up PET/CT evaluation (n = 1; SUVmax, 5.3), and after biopsy with or without follow-up CT evaluation (n = 10; median SUVmax, 8.2; range, 3.1 to 15.9).

Fifteen patients (48.4%) had positive PET/CT findings yet were confirmed to have no recurrence without further evaluation (n = 1; SUVmax, 0.0), after follow-up...
CT evaluation \( (n = 9; \text{median SUVmax, 4.07; range, 1.5 to 4.9}); \) after follow-up PET/CT evaluation \( (n = 1; \text{SUVmax, 6.4}); \) and after biopsy with or without follow-up CT evaluation \( (n = 4; \text{SUVmax, 4.3, 5.2, 5.8, and 9.9}); \) None of the patients with negative PET/CT findings \( (n = 45); \) had disease recurrence. Sensitivity and specificity of PET/CT for detection of recurrences were 1 and 0.75, respectively, and positive and negative predictive values for PET/CT in detection of recurrences were 0.52 and 1, respectively.

**DISCUSSION**

In this study, we demonstrated that surveillance PET/CT resulted in similar clinical outcomes and medical costs compared to no surveillance PET/CT. Moreover, due to its low specificity and positive predictive value, approximately half of patients with PET/CT findings of recurrence were found to have no evidence of disease after followup imaging and occasionally biopsy, which would not have been carried out if PET/CT had not been performed in the first place.

Routine surveillance imaging in first remission is a common practice; however, the clinical utility of serial imaging in asymptomatic patients remains questionable [9,10]. The role of PET/CT in surveillance of patients with DLBCL in first remission remains even more unclear. PET/CT is useful for detecting recurrence and re-staging since it can discriminate residual cancer against fibrosis or necrosis following treatment. However, PET/CT has a risk of false negative results due to partial volume effects or suppression of metabolism after chemotherapy, as well as false positive results due to inflammatory changes [11]. Patient anxiety associated with imaging and false-positive results is also a problem to consider.

Despite this uncertainty, nearly 50% of patients receive at least one PET/CT during surveillance [9]. Simi-

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### Table 4. Patient characteristics and medical costs during the first 3 years after achieving complete response of propensity-score matched cohort \( (n = 82) \)

| Subject                        | PET-CT (–) \( (n = 41) \) | PET-CT (+) \( (n = 41) \) | \( p \) value |
|--------------------------------|---------------------------|---------------------------|--------------|
| Age \( (29–85) \)              | 56                        | 58                        | 1.000        |
| ECOG \( 0(0–1) \)             | 0                         | 0                         |              |
| IPI risk                       |                           |                           |              |
| Low \( 50 \)                   | 24                        | 24                        | 1.000        |
| Low-intermediate \( 50 \)     | 9                         | 5                         |              |
| High-intermediate \( 50 \)    | 2                         | 2                         |              |
| High \( 50 \)                  | 6                         | 6                         |              |
| FU duration \( 3–36 \)         | 28                        | 36                        | 0.002        |
| Relapse \( 7.3 \)              | 3                         | 3                         | 1.000        |
| Outpatient clinic              |                           |                           |              |
| No. of visits \( 4–103 \)      | 14                        | 27                        | 0.003        |
| Costs \( 2,270,235 (214,178–38,923,231) \) | 4,818,810 \( (2,005,402–7,646,772) \) | 0.077        |
| Hospitalization                |                           |                           |              |
| No. of hospitalization \( 0–15 \) | 0                         | 0                         | 0.539        |
| Costs \( 0–91,291,439 \)       | 0                         | 0                         | 0.535        |
| Total costs \( 2,461,140 (340,094–130,214,670) \) | 5,591,534 \( (2,005,402–71,140,025) \) | 0.930        |
| Total costs paid by patients*  | 306,155 \( (64,540–108,878) \) | 636,100 \( (176,823–33,422,478) \) | 0.509        |

Values are presented as median (range) or number (%). Statistical significance test was done by independent \( t \) test. PET-CT, positron emission tomography-computed tomography; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; FU, follow-up.

*Costs that were not reimbursed by the National Health Insurance Service; thus, paid by the patients. Costs are stated in Korean won.

https://doi.org/10.3904/kjim.2017.174
larly, in our study of 118 patients, 64.4% of patients had at least one PET/CT during their follow-up, in opposition to consensus guidelines that question the role of routine PET/CT during follow-up of asymptomatic patients [12-14].

Considering the prevalence of tests in the absence of validation of the usefulness of PET/CT, many investigators continue their efforts to find a subset of patients who could benefit from PET/CT follow-up with minimization of radiation burden and cost. Petrausch et al. [8] recommended surveillance PET/CT only in patients < 60 years with clinical signs of relapse and in all patients > 60 years.

Cost as well as clinical utility are also important issues, since cost is not only a burden to the patient but also a burden to the state. Huntington et al. [15] undertook a cost-effective analysis comparing three strategies: routine clinical follow-up without serial imaging, routine follow-up with CT scans every 6 months for 2 years, or routine follow-up with PET/CT every 6 months for 2 years. In this analysis, 2 years of routine PET/CT were associated with little survival benefit compared with clinical follow-up (life-years gained, 0.04 years) and with substantial costs (incremental cost-effectiveness ratios of $168,750 per quality-adjusted life year). In our small-scale study, PET/CT surveillance did not show an increase in overall medical costs. However, since there is a significant association between outpatient visits and related costs, it is anticipated that surveillance PET/CT in all patients will result in ineffective increases in medical costs. If a cost-effectiveness analysis had been performed in our study, the results for our patients would have been similar.

Our study has limitations. It was a retrospective analysis, and performing PET/CT scan was a matter of a physician discretion, which might have led to selection bias. In addition, cost-effectiveness was not analyzed and only a simple cost-analysis was performed. We calculated costs related to hospital admission and outpatient visits from the accounting system of SNUH and SNU-BMC, but patients may have visited other hospitals and incurred additional costs related to the disease, which were not captured. Moreover, cost comparisons with other countries are difficult because of different healthcare systems and reimbursement policies of the governments.

Despite these limitations, our study is the first attempt in Korea to better understand the role and cost of PET/CT surveillance in patients with DLBCL in first remission. More than 60% of DLBCL patients in first remission in two tertiary hospitals in Korea had PET/CT at least one time during their follow-up. Although PET/CT surveillance was not associated with significantly increased costs in our group of patients, there was no evidence of any survival benefit from PET/CT surveillance either. Moreover, a significant proportion of patients had to undergo additional imaging and biopsy due to false positive results of PET/CT. The role of routine surveillance PET/CT in DLBCL patients with first remission has not been elucidated yet. To confirm our results and establish the role of PET/CT in DLBCL in first remission, larger studies with a cost-effective analysis and quality-of-life measures addressing imaging-associated patient anxiety should also be considered.

**KEY MESSAGE**

1. Surveillance positron emission tomography-computed tomography (PET/CT) in diffuse large B-cell lymphoma (DLBCL) patients in first complete remission resulted in similar clinical outcomes and medical costs compared to no surveillance PET/CT.
2. Due to its low positive predictive value of 0.52, significant proportion of patients had to undergo additional imaging and biopsy due to false positive results of PET/CT.
3. The role of routine surveillance PET/CT in DLBCL remains unclear.

**Conflict of interest**

No potential conflict of interest relevant to this article was reported.

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### Supplementary Table 1. Baseline characteristics of patients who received regular follow-up PET-CT and who did not (n = 77)

| Characteristic                  | PET-CT (–) | PET-CT (+) | p value |
|---------------------------------|------------|------------|---------|
| No. of patients                 | 42 (54.5)  | 35 (45.5)  |         |
| Age, yr                         | 57 (29–85) | 55 (30–82) | 0.633   |
| Sex                             |            |            | 0.616   |
| Male                            | 24 (57.1)  | 18 (51.4)  |         |
| Female                          | 18 (42.9)  | 17 (48.6)  |         |
| ECOG PS                         |            |            | 0.001   |
| 0                               | 17 (40.5)  | 1 (2.9)    |         |
| 1                               | 21 (50.0)  | 29 (82.9)  |         |
| 2                               | 4 (9.5)    | 5 (14.3)   |         |
| LDH, IU/mL                      | 210.5 (99–5,110) | 235.0 (131–3,742) | 0.989   |
| Extranodal involvement          |            |            | 0.129   |
| No                              | 33 (78.6)  | 22 (62.9)  |         |
| Yes                             | 9 (21.4)   | 13 (37.1)  |         |
| Stage                           |            |            | 0.625   |
| 1                               | 13 (31.0)  | 8 (22.9)   |         |
| 2                               | 14 (33.3)  | 10 (28.6)  |         |
| 3                               | 6 (14.3)   | 5 (14.3)   |         |
| 4                               | 9 (21.4)   | 12 (34.3)  |         |
| IPI risk                        |            |            | 0.614   |
| Low                             | 24 (57.1)  | 16 (45.7)  |         |
| Low-intermediate                | 9 (21.4)   | 7 (20.0)   |         |
| High-intermediate               | 3 (7.1)    | 5 (14.3)   |         |
| High                            | 6 (14.3)   | 7 (20.0)   |         |
| Treatment                       |            |            | 0.191   |
| R-CHOP                          | 40 (95.2)  | 35 (100)   |         |
| R-EPOCH                         | 2 (4.8)    | 0          |         |
| Duration of follow-up, mon      | 32 (7–135) | 58 (11–131)| 0.002   |

Values are presented as number (%) or median (range).

PET-CT, positron emission tomography-computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; IPI, International Prognostic Index; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.
# Supplementary Table 2. Univariate analysis for medical costs during the first 3 years after achieving complete response in patients who received regular follow-up PET-CT and who did not (n = 77)

| Subjects | PET-CT (–) (n = 42) | PET-CT (+) (n = 35) | p value |
|----------|---------------------|---------------------|---------|
| Duration of follow-up, mon | 28 (3–36) | 36 (6–36) | < 0.001 |
| Relapse | 3 (7.1) | 6 (17.1) | 0.286 |
| Outpatient visits | | | |
| No. of visits | 14 (4–103) | 26 (6–56) | 0.003 |
| Costs | 2,256,327 (214,178–38,923,231) | 5,443,348 (1,021,569–7,646,772) | 0.061 |
| Hospitalization | | | |
| No. of hospitalization | 0 (0–15) | 0 (0–7) | 0.624 |
| Costs | 0 (0–91,291,439) | 0 (0–32,311,317) | 0.260 |
| Total costs | 2,499,689 (340,694–130,214,676) | 5,624,649 (2,005,402–39,468,247) | 0.690 |
| Total costs paid by patients a | 326,819 (64,540–108,837,381) | 709,808 (176,823–4,938,925) | 0.405 |

Values are presented as median (range) or number (%). Statistical significance test was done by independent t test.

PET-CT, positron emission tomography-computed tomography.

a Costs that were not reimbursed by the National Health Insurance Service; thus, paid by the patients. Costs are stated in Korean won.