Neuro-Oncology

Body CT and PET/CT detection of extracranial lymphoma in patients with newly diagnosed central nervous system lymphoma

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Abstract

Background. We aimed to investigate the detection rate of body CT or PET/CT for sites of extracranial disease in patients with a new pathological diagnosis of CNS DLBCL and to identify factors associated with sites of extracranial disease.

Methods. An international multicenter cohort study of consecutive immunocompetent patients with a new diagnosis of CNS DLBCL confirmed by brain biopsy who underwent CT and/or PET/CT to evaluate for sites of extracranial disease between 1998 and 2019. The primary outcome was the detection rate of extracranial lymphoma by CT or PET/CT. Subgroup analyses according to age and EBV status were also performed. Logistic regression analyses were performed to determine factors related to sites of extracranial disease. Detection rates of CT and PET/CT were compared.

Results. One thousand and forty-three patients were included. The overall detection rate of CT or PET/CT was 2.6% (27/1043). The treatment approach was adjusted in 74% of these patients. Multivariable analysis demonstrated that age >61 years (OR, 3.10; *P* = .016) and EBV positivity (OR, 3.78; *P* = .045) were associated with greater odds of extracranial lymphoma. There was no statistically significant difference in detection rate between CT and PET/CT (*P* = .802). In patients ≤61 years old, the false-referral rates were significantly higher than the detection rates (*P* < .001).

Conclusion. Our results showed increased odds of extracranial lymphoma in patients with older age or EBV-positive lymphoma. Treatment was adjusted in a majority of patients diagnosed with extracranial lymphoma, thereby supporting the current guidelines for the use of contrast-enhanced body CT or PET/CT in patients with newly diagnosed CNS DLBCL.

Key Points

1. The overall detection rate of CT or PET/CT for sites of extracranial disease in patients with a new pathological diagnosis of CNS DLBCL was 2.6%.

2. Age >61 years and EBV positivity were associated with greater odds of extracranial lymphoma.

Importance of the Study

Consensus guidelines recommend body imaging with either a body CT or a whole-body PET/CT in patients with a confirmed pathological diagnosis of CNS DLBCL to evaluate for disease outside the CNS. However, the evidence of such imaging is limited in that the guidelines are based on a few studies with small sample sizes that were published >20 years ago. In this international multicenter cohort study of 1043 patients, the overall detection rate of CT or PET/CT was 2.6% (27/1043). The treatment approach was adjusted in 74% of these patients. Multivariable analysis demonstrated that age >61 years (OR, 3.10; P = .016) and EBV positivity (OR, 3.78; P = .045) were associated with greater odds of extracranial lymphoma. There was no statistically significant difference in detection rate between CT and PET/CT (P = .802). Our results thus support current guidelines to exclude extracranial lymphoma by CT or PET/CT. CT and PET/CT showed similar detection rates for sites of extracranial disease in patients with newly diagnosed CNS DLBCL. Older age (>61 years) and EBV positivity were associated with higher odds of extracranial disease.

Primary central nervous system (CNS) diffuse large B-cell lymphoma (DLBCL) is a rare, aggressive, extranodal non-Hodgkin lymphoma with an overall incidence rate of 0.34 per 100 000 people.[1,2] Consensus guidelines recommend body imaging with either a contrast-enhanced chest/abdomen/pelvis computed tomography (CT) examination or a whole-body positron emission tomography (PET)/CT examination in patients with a confirmed pathological diagnosis of CNS DLBCL to evaluate for disease outside the CNS.[1,3–5] Discovering extracranial lymphoma influences initial treatment and disease prognosis. However, the evidence for the value of such imaging is limited in that the guidelines are based primarily on a few studies with small sample sizes that were published > 20 years ago and that showed rates of extracranial lymphoma involvement of 3.9% (5 of 128)[6] and 12.5% (2 of 16).[7]

Recent studies have reported variable rates of extracranial lymphoma detection by whole-body PET/CT of 3.9% (7 of 180),[8] 4.3% (2 of 46),[9] 7.1% (3 of 42),[10] 10% (5 of 50),[11] and 16% (4 of 25)[12] of patients. One study demonstrated a detection rate of 2% (6 of 304) for contrast-enhanced chest/abdomen/pelvis CT or whole-body PET/CT with an associated false-positive rate of 4% (13 of 304).[13] Given the high false-positive rate relative to the true-positive rate, it would be helpful to develop patient selection criteria for whole-body imaging according to factors associated with extracranial involvement in newly diagnosed CNS DLBCL. Moreover, a comparison of the diagnostic performance of contrast-enhanced chest/abdomen/pelvis CT versus whole-body PET/CT is needed.

In this international multicenter cohort study, we investigated: 1) the body CT and body PET/CT detection rate of extracranial lymphoma in patients with a new pathological diagnosis of CNS DLBCL; and 2) potential factors associated with extracranial lymphoma involvement.

Methods

Patients

This study was a multicenter retrospective study of patients who presented with a new diagnosis of CNS DLBCL, confirmed by brain biopsy, and who underwent contrast-enhanced chest/abdomen/pelvis CT or whole-body PET/CT to evaluate for extracranial involvement between 1998 and 2019. The data were obtained from the four largest hospitals in the Republic of Korea and one hospital in the U.S. The institutional review boards of Asan Medical Center, Samsung Medical Center, Yonsei University Severance Hospital, Seoul National University Hospital, and Partners Healthcare (Brigham and Women's Hospital and Dana-Farber Cancer Institute) approved this study and granted a waiver for the requirement of written informed consent from study participants because of the retrospective nature of the study.

The eligibility criteria were as follows: 1) consecutive patients who presented with a new diagnosis of CNS DLBCL by brain biopsy, 2) patients who underwent contrast-enhanced chest/abdomen/pelvis CT or whole-body PET/CT screening for extracranial disease, 3) patients who did not have human immunodeficiency virus (HIV), and 4) patients with post-transplant lymphoproliferative disease. Following the National Comprehensive Cancer Network (NCCN) guidelines,[1] the diagnostic protocols of all five hospitals for CNS DLBCL included these imaging

examinations. Detailed patient enrollment data is outlined in Figure 1.

Contrast-Enhanced Chest/Abdomen/Pelvis CT and Whole-Body PET/CT

Contrast-enhanced chest/abdomen/pelvis CT was acquired in a single session using 16, 32, or 64 channel multidetector CT scanners from various vendors. The CT scan parameters generally included 120 kVp, automated tube current modulation with a quality reference set at 200 mAs, a beam pitch of 1, gantry rotation time of 0.5 s, and field of view to fit. The acquired images were generally reconstructed in axial and coronal planes with a 5 mm slice thickness without an interslice gap. In the sites in the Republic of Korea, from 130–150 mL of a 300 mg I/mL contrast agent were typically used at an injection rate of 3 mL/s. In the U.S. site, weight-based dosing up to 100 mL of a 350 mg I/mL contrast agent was typically used at an injection rate of 3 mL/s. Imaging initially performed at other institutions was also included and was sometimes variable from that of these primary institutions.

Nonenhanced whole-body ^{18}F-FDG PET/CT imaging was obtained using scanners from various vendors. The fluorine 18 (^{18}F)-labeled glucose analog ^{18}F-FDG was injected into the patients as the PET radiotracer. The acquisition range was from the upper thighs to the skull base. All PET images were reconstructed using an iterative algorithm with attenuation correction on the scanner. All contrast-enhanced chest/abdomen/pelvis CT and whole-body PET/CT were conducted within a week of the time of the initial pathological diagnosis of CNS lymphoma.

Image Interpretation

All contrast-enhanced chest/abdomen/pelvis CT and whole-body PET/CT acquisitions were interpreted as a part of daily clinical practice according to institutional protocols. Chest CT images were interpreted by board-certified thoracic radiologists and abdominopelvic
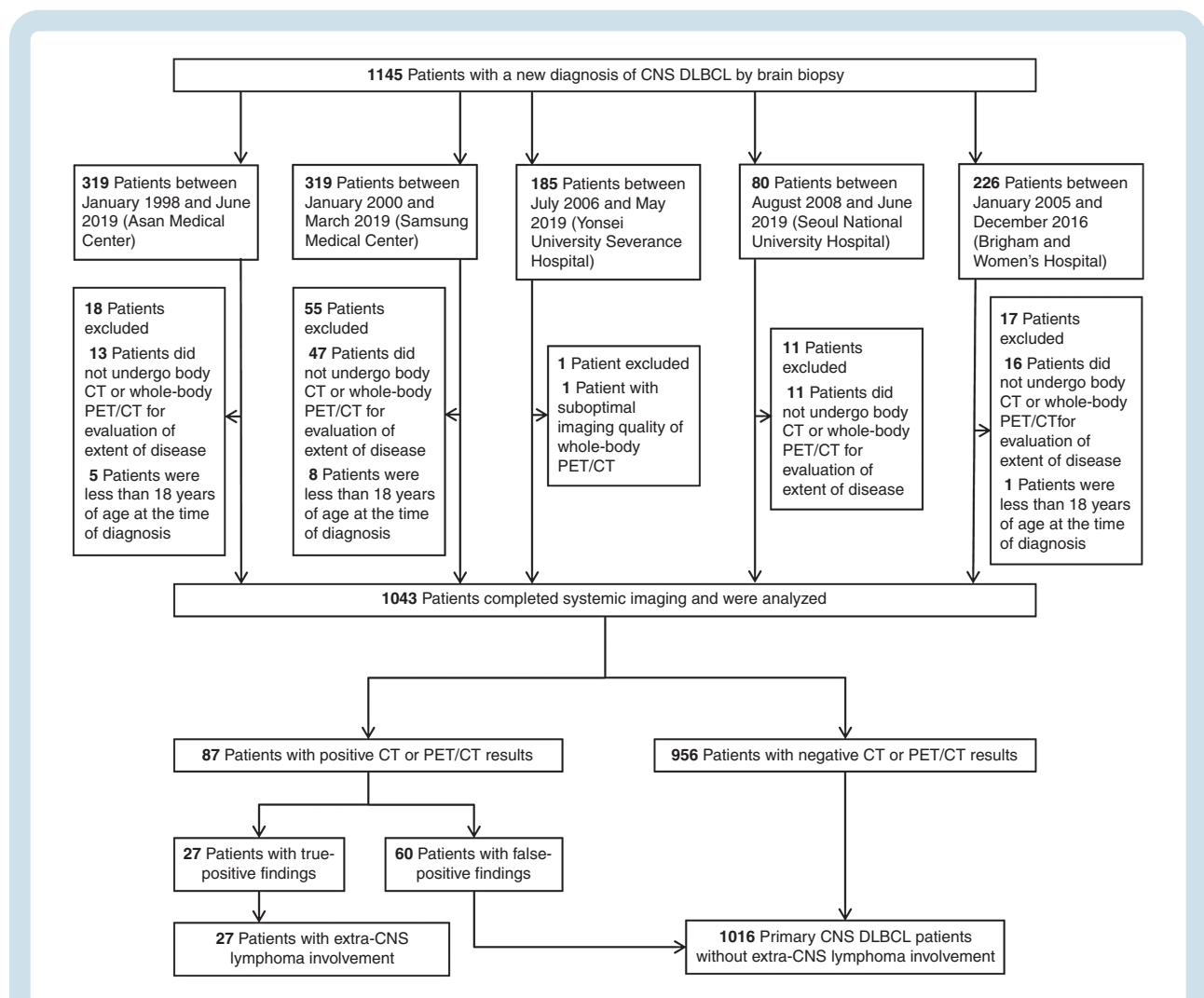

Fig. 1 Flow diagram of the international multicenter cohort patient inclusion process. Abbreviations: CNS, central nervous system; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; PET, positron emission tomography.

CT images were interpreted by board-certified abdominal radiologists. Whole-body PET-CT images were visually interpreted by nuclear medicine board-certified physicians.

Contrast-enhanced chest/abdomen/pelvis CT and whole-body PET/CT results were reported as positive when any lesions suggestive of potential extracranial lymphoma involvement were detected. The reference standard (true lesion identity) was based on histopathologic reports or follow-up imaging reports. All true-positive lesions were pathologically confirmed by biopsy. False-positive lesions were confirmed 1) by biopsy, 2) no lesion was found by additional endoscopy or additional imaging, or 3) if a lesion is discordantly stable after completion of chemotherapy on follow-up imaging. Lesion validation was performed with the consensus of two neuroradiologists (C.H.S. and H.S.K.) who were blinded to all clinical information. The following baseline patient characteristics were collected: age, sex, nation, Epstein-Barr virus (EBV) status, and modality of systemic imaging.

Study Outcomes and Statistical Analysis

The primary outcome was the detection rate of contrast-enhanced chest/abdomen/pelvis CT or whole-body PET/CT for evaluation of the extent of disease. The detection rate was defined as the proportion of patients with biopsy-proven true-positive imaging findings of extracranial DLBCL involvement among all eligible patients on a per-patient basis (true-positive/total number of patients).[14] The secondary outcome was the false-referral rate of contrast-enhanced chest/abdomen/pelvis CT or whole-body PET/CT for evaluation of the extent of disease. The false-referral rate was defined as the proportion of patients with false-positive imaging findings of extracranial DLBCL involvement among all eligible patients on a per-patient basis (false-positive/total number of patients).[14] The detection rate and false-referral rate were reported with exact 95% confidence intervals.

Predefined multiple subgroup analyses were performed as follows: 1) patients ≤61 years old (the median age of overall cohort), 2) patients >61 years old, 3) EBV-positive DLBCL, and 4) EBV-negative DLBCL. In addition, we evaluated cases of malignancy other than extracranial lymphoma detected by initial screening whole-body PET/CT.

To determine independent factors related to the presence of extracranial lymphoma, univariable and multivariable logistic regression analyses were performed using multiple covariates including age, sex, nation, and EBV status. A *P* value of less than .2 was considered to indicate significant covariates in the univariable analysis and these covariates were subsequently entered in the multivariable analysis.

Comparison of contrast-enhanced chest/abdomen/pelvis CT and whole-body PET/CT for detection of extracranial DLBCL was performed. All statistical analyses were conducted using SPSS software (SPSS, version 21; IBM, Armonk, NY) and the level of statistical significance was defined as *P* < .05.

Results

Baseline Characteristics of the Multicenter Cohort

There were 1145 patients with a new diagnosis of CNS DLBCL by brain biopsy. Patients did not undergo body CT or whole-body PET/CT (*n* = 87), less than 18 years of age at the time of diagnosis (*n* = 14), and suboptimal imaging quality of whole-body PET/CT (*n* = 1) were excluded. A total of 1043 patients were included in the analysis (*n* = 301 [28.9%] at Asan Medical Center; *n* = 280 [26.8%] at Samsung Medical Center; *n* = 184 [17.6%] at Yonsei University Severance Hospital; *n* = 69 [6.6%] at Seoul National University Hospital; *n* = 209 [20.0%] at Brigham and Women's Hospital and Dana-Farber Cancer Institute; Table 1). The mean age of the multicenter cohort of 1043 patients was 61 years (SD 13), and 561 patients (53.7%) were male. Patients underwent contrast-enhanced chest/abdomen/pelvis CT (*n* = 920 [88.2%], whole-body PET/CT (*n* = 854 [81.9%]), and both two separate studies (*n* = 733 [71.0%]). Among 561 male patients, 12.8% (72 of 561) of the patients underwent testicular US and none of the patients had lymphoma involvement in the testis.

Detection Rate and Treatment Adjustment

In the 1043 patients with a pathological diagnosis of primary CNS DLBCL, contrast-enhanced chest/abdomen/pelvis CT or whole-body PET/CT yielded findings suspicious for extracranial lymphoma involvement in 87 patients (8.3%, 87 of 1043; Table 1). Of these 87 patients, 27 were pathologically confirmed as having extracranial DLBCL by biopsy (Table 2). Therefore, the per-patient detection rate of DLBCL by contrast-enhanced chest/abdomen/pelvis CT or whole-body PET/CT was 2.6% (27 of 1043; 95% CI, 1.7–3.7%). 20 of 27 patients (74%) who were confirmed as having extracranial DLBCL had their treatment adjusted and received methotrexate and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

False-Referral Rate

The suspicious imaging findings by contrast-enhanced chest/abdomen/pelvis CT or whole-body PET/CT in the other 60 patients were proven to be benign by surgery, biopsy, endoscopy, follow-up imaging, or additional imaging. Therefore, the contrast-enhanced chest/abdomen/pelvis CT or whole-body PET/CT resulted in a false-referral rate of 5.8% (60 of 1043; 95% CI, 4.4–7.3%). The detection of these false-positive findings resulted in biopsy (*n* = 19), follow-up imaging (*n* = 14), additional imaging (*n* = 10), additional imaging/endoscopy and biopsy (*n* = 8), endoscopy (*n* = 5 [esophagogastroduodenoscopy, colonoscopy, and cystoscopy]), and surgery (*n* = 4 [polypectomy, tonsillectomy or lymph node excision]).

Table 1 Baseline Characteristics, Systemic Imaging, and Outcomes of the Multicenter Cohort of Patients with a Positive Diagnosis of Primary CNS Diffuse Large B-Cell Lymphoma

Parameters	Asan Medical Center (n = 301)	Samsung Medical Center (n = 280)	Yonsei University Severance Hospital (n = 184)	Seoul National University Hospital (n = 69)	Brigham and Women's Hospital (n = 209)	Total (n = 1043)
Baseline						
Age, mean (SD), year	59(13)	59 (13)	61 (13)	61 (12)	65 (12)	61 (13)
Sex, no. (%)						
Women	123 (40.9%)	131 (46.8%)	91 (49.5%)	34 (49.3%)	103 (49.3%)	483 (46.3%)
Men	178 (59.1%)	149 (53.2%)	93 (50.5%)	35 (50.7%)	106 (50.7%)	561 (53.7%)
EBV-positive	14 (4.7%)	8 (2.9%)	2 (1.1%)	NA	12 (5.7%)	36 (3.8%)
EBV-negative	200 (66.4%)	200 (71.4%)	84 (45.7%)	NA	110 (52.6%)	594 (60.9%)
EBV not evaluated	87 (28.9%)	72 (25.7%)	98 (53.3%)	NA	87 (41.6%)	344 (35.3%)
Systemic imaging						
Contrast-enhanced chest/abdomen/pelvis CT	299 (99.3%)	278 (99.3%)	158 (85.9%)	21 (30.4%)	164 (78.5%)	920 (88.2%)
Whole-body PET/CT	251 (83.4%)	249 (88.9%)	129 (70.1%)	63 (91.3%)	162 (77.5%)	854 (80.6%)
Testicular US	7 of 178 (4.0%)	7 of 149 (4.7%)	3 of 93 (3.2%)	0 of 35 (0%)	55 of 106 (51.9%)	72 of 561 (12.8%)
Outcomes						
True-positive	6 of 301 (2.0%, 0.7–4.3%)	7 of 280 (2.5%, 1.0–5.1%)	6 of 184 (3.3%, 1.2–7.0%)	0 of 69 (0.0%, 0.0–5.2%)	8 of 209 (3.8%, 1.7–7.4%)	27 of 1043 (2.6%, 1.7–3.7%)
False-positive	12 of 301 (4.0%, 2.1–6.9%)	17 of 280 (6.1%, 3.6–9.5%)	8 of 184 (4.3%, 1.9–8.4%)	5 of 69 (7.2%, 2.4–16.1%)	18 of 209 (8.6%, 5.2–13.3%)	60 of 1043 (5.8%, 4.4–7.3%)
Subgroup analysis (true-positive)						
Patients > 61 years old	4 of 132 (3.0%, 0.8–7.6%)	5 of 127 (3.9%, 1.3–9.0%)	6 of 96 (5.6%, 2.3–13.1%)	0 of 34 (0.0%, 0.0–10.3%)	6 of 135 (4.4%, 1.7–9.4%)	21 of 524 (4.0%, 2.5–6.1%)
Patients ≤ 61 years old	2 of 169 (1.2%, 0.1–4.2%)	2 of 153 (1.3%, 0.2–4.6%)	0 of 88 (0.0%, 0.0–4.1%)	0 of 35 (0.0%, 0.0–10.0%)	2 of 74 (2.7%, 0.3–9.4%)	6 of 519 (1.2%, 0.4–2.5%)
EBV-positive DLBCL	1 of 14 (7.1%, 0.2–33.9%)	0 of 8 (0%, 0.0–36.9%)	0 of 2 (0.0%, 0.0–84.2%)	NA	2 of 12 (16.7%, 2.1–48.4%)	3 of 36 (8.3%, 1.8–22.5%)
EBV-negative DLBCL	4 of 200 (1.6%, 0.6–5.0%)	5 of 200 (2.5%, 0.8–5.7%)	1 of 84 (1.2%, 0.3–8.3%)	NA	6 of 110 (5.5%, 2.0–11.5%)	16 of 594 (2.7%, 1.6–4.3%)
DLBCL without EBV status	1 of 87 (1.2%, 0.3–6.2%)	2 of 72 (2.8%, 0.3–9.7%)	5 of 98 (5.1%, 1.7–11.5%)	NA	0 of 87 (0.0%, 0.0–4.2%)	8 of 344 (2.3%, 1.0–4.5%)
Other outcome						
Other malignancy detected by whole-body PET/CT	7 of 251 (2.8%, 1.1–5.7%)	2 of 249 (0.8%, 0.1–2.9%)	1 of 129 (0.8%, 0.0–4.2%)	1 of 63 (1.6%, 0.0–8.5%)	2 of 162 (1.2%, 0.2–4.4%)	13 of 854 (1.5%, 0.8–2.6%)

Abbreviations: CT, computed tomography; PET, positron emission tomography; SD, standard deviation; US, ultrasound
Data are numbers with percentages in parentheses.

Table 2 Patients With Extracranial Diffuse Large B-Cell Lymphoma Involvement

Patient	Age	Sex	Imaging for evaluation of the extent of disease	Positive imaging	Extracranial lymphoma involvement site	Treatment adjustment
Patient 1	38	Male	Chest/abdomen/pelvis CT and whole-body PET/CT	Whole-body PET/CT	Sacrum	Rituximab, high dose methotrexate, vincristine, and procabarzine
Patient 2	83	Female	Chest/abdomen/pelvis CT and whole-body PET/CT	Whole-body PET/CT	Upper arm	High dose methotrexate and R-CHOP
Patient 3	78	Female	Chest/abdomen/pelvis CT and whole-body PET/CT	Abdominal/pelvic CT	Lymph node	Surgical resection
Patient 4	66	Male	Chest/abdomen/pelvis CT and whole-body PET/CT	Abdominal/pelvic CT and whole-body PET/CT	Colon	High dose methotrexate and R-CHOP
Patient 5	59	Male	Chest/abdomen/pelvis CT and whole-body PET/CT	Whole-body PET/CT	Lumbar spine pedicle	High dose methotrexate and cytarabine
Patient 6	70	Female	Chest/abdomen/pelvis CT and whole-body PET/CT	Whole-body PET/CT	Gluteus maximus muscle	High dose methotrexate and cytarabine
Patient 7	75	Male	Chest/abdomen/pelvis CT and whole-body PET/CT	Abdominal/pelvic CT and whole-body PET/CT	Adrenal gland	High dose methotrexate and R-CHOP
Patient 8	68	Male	Chest/abdomen/pelvis CT and whole-body PET/CT	Abdominal/pelvic CT and whole-body PET/CT	Adrenal gland, spine, rib, iliac bone	High dose methotrexate and R-CHOP
Patient 9	66	Female	Chest/abdomen/pelvis CT and whole-body PET/CT	Abdominal/pelvic CT and whole-body PET/CT	Lymph node	High dose methotrexate, vincristine, and procabarzine
Patient 10	46	Female	Chest/abdomen/pelvis CT and whole-body PET/CT	Neck CT and whole-body PET/CT	Nasal cavity	High dose methotrexate, vincristine, and procabarzine
Patient 11	79	Female	Chest/abdomen/pelvis CT and whole-body PET/CT	Whole-body PET/CT	Cheek, lymph node	Whole brain radiation therapy
Patient 12	49	Male	Chest/abdomen/pelvis CT and whole-body PET/CT	Whole-body PET/CT	Nasal cavity, lymph node	High dose methotrexate and R-CHOP
Patient 13	64	Female	Chest/abdomen/pelvis CT and whole-body PET/CT	Abdominal/pelvic CT and whole-body PET/CT	Adrenal gland	High dose methotrexate and R-CHOP
Patient 14	82	Female	Whole-body PET/CT	Whole-body PET/CT	Nasopharynx	R-CHOP
Patient 15	79	Female	Chest/abdomen/pelvis CT and whole-body PET/CT	Chest CT and whole-body PET/CT	Heart, lymph node	R-CHOP
Patient 16	71	Male	Chest/abdomen/pelvis CT and whole-body PET/CT	Chest/abdomen/pelvis CT or whole-body PET/CT	Adrenal gland, lymph node	R-CHOP
Patient 17	74	Male	Chest/abdomen/pelvis CT and whole-body PET/CT	Neck CT and whole-body PET/CT	Lymph node	High dose methotrexate, vincristine, and dexamethasone
Patient 18	77	Male	Chest/abdomen/pelvis CT and whole-body PET/CT	Abdominal/pelvic CT and whole-body PET/CT	Adrenal gland	High dose methotrexate, vincristine, and dexamethasone
Patient 19	65	Male	Chest/abdomen/pelvis CT and whole-body PET/CT	Abdominal/pelvic CT and whole-body PET/CT	Acetabulum	High dose methotrexate, ifosfamide, etoposide, and cytarabine
Patient 20	20	Male	Chest/abdomen/pelvis CT	Chest/abdomen/pelvis CT		Whole brain radiation therapy and rituximab

Table 2 Continued

Patient	Age	Sex	Imaging for evaluation of the extent of disease	Positive imaging	Extracranial lymphoma involvement site	Treatment adjustment
Patient 21	57	Female	Chest/abdomen/pelvis CT and whole-body PET/CT	Abdominal/pelvic CT and whole-body PET/CT	Adrenal gland	High dose methotrexate and R-CHOP
Patient 22	70	Female	Chest/abdomen/pelvis CT and whole-body PET/CT	Abdominal/pelvic CT and whole-body PET/CT	Lymph node	High dose methotrexate and rituximab
Patient 23	74	Female	Chest/abdomen/pelvis CT and whole-body PET/CT	Chest/abdomen/pelvis CT	Lymph node	High dose methotrexate
Patient 24	68	Male	Chest/abdomen/pelvis CT and whole-body PET/CT	Whole-body PET/CT	Adrenal gland	High dose methotrexate and R-CHOP
Patient 25	80	Female	Chest/abdomen/pelvis CT and whole-body PET/CT	Abdominal/pelvic CT and whole-body PET/CT	Retroperitoneum	High dose methotrexate and R-CHOP
Patient 26	68	Female	Chest/abdomen/pelvis CT and whole-body PET/CT	Chest CT and whole-body PET/CT	Lymph node	High dose methotrexate and R-CHOP
Patient 27	80	Male	Chest/abdomen/pelvis CT and whole-body PET/CT	Abdominal/pelvic CT and whole-body PET/CT	Liver	High dose methotrexate and R-CHOP

Abbreviations: CNS, central nervous system; CT, computed tomography; PET, positron emission tomography; R-CHOP, rituximab cyclophosphamide doxorubicin vincristine prednisone.

Detection Rates in the Multiple Subgroups and Other Outcomes

In patients >61 years of age, the detection rate was 4.0% (21 of 524; 95% CI, 2.5–6.1%) and the false-referral rate was 5.2% (27 of 524; 95% CI, 3.4–7.4%). In patients ≤61 years old, the detection rate was 1.2% (6 of 519; 95% CI, 0.4–2.5%) and the false-referral rate was 6.4% (33 of 519; 95% CI, 4.4–8.8%). There was no statistical difference in false-referral rate (P = .407). In patients with EBV-positive DLBCL, the detection rate was 8.3% (3 of 36; 95% CI 1.8–22.5%). In patients with EBV-negative DLBCL, the detection rate was 2.7% (16 of 594; 95% CI, 1.6–4.3%). The proportion of malignancy other than extracranial lymphoma detected by whole-body PET/CT was 1.5% (13 of 854; 95% CI, 0.8–2.6%). Types of malignancy were lung cancer (n = 5), thyroid cancer (n = 4), breast cancer (n = 1), rectal cancer (n = 1), neuroendocrine carcinoma (n = 1), and duodenal GIST (n = 1).

Factors Associated with Extracranial Lymphoma Involvement

In the univariable logistic regression analysis, patient age of 61 (OR, 2.99; 95% CI: 1.20–7.47; P = .019) and was significantly associated with extracranial lymphoma involvement (Table 3). Other covariates including sex (P = .552), nation (P = .212), EBV status (P = .069) were not associated with extracranial lymphoma involvement. Multivariable logistic regression analysis demonstrated that patient age > 61 years (OR, 3.10; 95% CI: 1.23–7.79; P = .016) and EBV positivity (OR, 3.78; 95% CI: 1.03–13.87; P = .045) were

Table 3 Univariable and Multivariable Logistic Regression Analyses to Determine the Factors Associated With Extracranial Diffuse Large B-Cell Lymphoma Involvement

	Univariable Analysis		Multivariable Analysis	
	Odd Ratio	P value	Odd Ratio	P value
Age				
Age ≤61 years	Reference		Reference	
Age >61 years	2.99 (1.20–7.47)	.019	3.10 (1.23–7.79)	.016
Sex				
Male	Reference			
Female	1.26 (0.59–2.71)	.552		
Nation				
Republic of Korea	Reference			
United States of America	1.71 (0.74–3.96)	.212		
EBV status				
EBV negative	Reference		Reference	
EBV not evaluated	0.71 (0.30–1.68)	.441	0.74 (0.31–1.75)	.489
EBV positive	3.28 (0.91–11.84)	.069	3.78 (1.03–13.87)	.045

associated with a greater risk of extracranial lymphoma involvement.

Comparisons of Detection Rates between CT and PET/CT

The detection rates and false-referral rates according to image modalities are shown in Table 4. The detection rate of contrast-enhanced chest/abdomen/pelvis CT was 2.8% (26 of 920; 95% CI, 1.9–4.1%), while that of whole-body PET/CT was 3.0% (26 of 854; 95% CI, 2.0–4.4%). There was no statistically significant difference in detection rate between contrast-enhanced chest/abdomen/pelvis CT and whole-body PET/CT (P = .802). The detection rate of combining both chest/abdomen/pelvis CT and whole-body PET/CT was 3.4% (25 of 733; 95% CI, 2.2–5.0%).

Contrast-enhanced chest/abdomen/pelvis CT demonstrated a false-referral rate of 5.3% (49 of 920; 95% CI, 4.0–7.0%), while whole-body PET/CT showed a false-referral rate of 6.7% (57 of 854; 95% CI, 5.1–8.6%), with the difference between these modalities not being statistically significant (P = .214). The false-referral rate of combining both chest/abdomen/pelvis CT and whole-body PET/CT was 6.3% (46 of 733; 95% CI, 4.6–8.3%). In patients ≤61 years old, the false-referral rates were significantly higher than the detection rates in body CT only, whole-body PET/CT only, and both body CT and whole-body PET/CT (P < .001).

Discussion

In our study, the detection rate of extracranial lymphoma by chest/abdomen/pelvis CT or whole-body PET/CT for extracranial disease was 2.6% (27 of 1043). The treatment was adjusted in 74% of these patients discovered to have extracranial lymphoma. The detection rate was notably higher in two subgroups, 4.0% (21 of 524) in patients >61 years of age and 8.3% (3 of 36) in patients with EBV-positive DLBCL. Multivariable analysis demonstrated that age >61 years (OR, 3.10; P = .016) and EBV positivity (OR, 3.78; P = .045) were associated with greater odds of extracranial lymphoma involvement. Chest/abdomen/pelvis CT, whole-body PET/CT, and their combination showed a statistically similar detection rate for extracranial lymphoma involvement.

As primary CNS DLBCL is a rare malignancy with an overall incidence rate of 0.43 cases per 100 000 people,[2] a prospective study examining the utility of chest/abdomen/pelvis CT or whole-body PET/CT would be challenging. This international multicenter cohort study with large sample sizes offers a number of strengths in comparison with prior single-institution studies with small sample sizes.

The current major guidelines[1,4,5] and review articles[15,16] recommend contrast-enhanced chest/abdomen/pelvis CT or whole-body PET/CT for evaluation of the extent of disease in patients with a new pathological diagnosis of "primary" CNS DLBCL. However, evidence of the value of these expensive and time-consuming imaging studies remains limited, based on older single-institution studies, and no large multicenter cohort study has been reported. This study included 1043 patients and identified 27 (2.6%) with extracranial sites of DLBCL, resulting in adjustments to treatment in 74% of these patients. In the previous meta-analysis, the pooled detection rate of body CT and whole-body PET/CT were 2.5% and 4.9%, respectively, which were similar results with our study.[17] In addition to the previous meta-analysis, we verify that age

Table 4 Comparison of Contrast-Enhanced Chest/Abdomen/Pelvis CT and Whole-Body PET/CT for Detection of Extracranial Lymphoma Involvement in Patients With a Positive Diagnosis of Primary CNS DLBCL

Outcome	Contrast-Enhanced Chest/Abdomen/Pelvis CT (n = 920)	Whole-Body PET/CT (n = 854)	Both Contrast-Enhanced Chest/Abdomen/Pelvis CT and whole-body PET/CT (n = 733)	P value[a]	P value[b]	P value[c]
True-positive	26 of 920 (2.8%; 95% CI, 1.9–4.1%)	26 of 854 (3.0%; 95% CI, 2.0–4.4%)	25 of 733 (3.4%; 95% CI, 2.2–5.0%)	.802	.482	.651
False-positive	49 of 920 (5.3%; 95% CI, 4.0–7.0%)	57 of 854 (6.7%; 95% CI, 5.1–8.6%)	46 of 733 (6.3%; 95% CI, 4.6–8.3%)	.214	.386	.748
Patients >61 years old						
True-positive	20 of 455 (4.4%; 95% CI, 2.7–6.7%)	21 of 435 (4.8%; 95% CI, 3.0–7.3%)	20 of 367 (5.5%; 95% CI, 3.4–8.3%)	.776	.468	.654
False-positive	25 of 455 (5.5%; 95% CI, 3.6–8.0%)	27 of 435 (6.2%; 95% CI, 4.1–8.9%)	25 of 367 (6.8%; 95% CI, 4.5–9.9%)	.656	.438	.731
Patients ≤61 years old						
True-positive	6 of 465 (1.3%; 95% CI, 0.5–2.8%)	5 of 419 (1.2%; 95% CI, 0.4–2.8%)	5 of 366 (1.4%; 95% CI, 0.5–3.2%)	.894	.901	.805
False-positive	24 of 465 (5.2%; 95% CI, 3.3–7.6%)	30 of 419 (7.2%; 95% CI, 4.9–10.1%)	21 of 366 (5.7%; 95% CI, 3.6–8.6%)	.217	.752	.395

Abbreviations: CNS, central nervous system; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; PET, positron emission tomography; SD, standard deviation.
[a]P values between CT and PET/CT.
[b]P values between CT and both CT and PET/CT.
[c]P values between PET/CT and both CT and PET/CT.

>61 years and EBV positivity were associated with extracranial lymphoma involvement. Our results thus support the current, consensus-based guidelines for initial extent of disease assessment in patients with newly diagnosed CNS lymphoma.

In our study, the detection rate was 4.8% (20 of 419) in patients >61 years of age and multivariable analysis revealed that age >61 (OR, 3.10) was associated with greater odds extracranial sites of lymphoma. In addition, the detection rate was 8.3% (3 of 36) in patients with EBV-positive DLBCL and EBV positivity (OR, 3.78) was also associated with greater odds extracranial sites of lymphoma. Therefore, extensive systemic work-up combining both chest/abdomen/pelvis CT and whole-body PET/CT may be justifiable in the population of patients >61 years of age or patients with EBV positivity.

On the other hand, in patients ≤61 years old, the detection rate was 1.2% (6 of 519) with a false-referral rate of 6.4% (33 of 519). The high false-referral rate may result in unnecessary surgery, endoscopy, radiation exposure, and increased medical costs. In addition, chest/abdomen/pelvis CT (1.3%), whole-body PET/CT (1.2%), and their combination (1.4%) showed a similar detection rate for extracranial lymphoma involvement in patients ≤61 years old without statistical significant difference in detection rate between three modalities. Thus, for patients ≤61 years old, we recommend considering the utilization of only one imaging exam, either contrast-enhanced chest/abdomen/pelvis CT or whole-body PET/CT, to evaluate for extracranial sites of disease in newly diagnosed CNS DLBCL.

The major limitation of the present study is that it is based on observational data, which may be vulnerable to bias and confounding. To overcome this inherent limitation, we conducted an international multicenter cohort study including consecutive patients scanned over a period of more than 20 years and there was no difference between the cohorts of the two countries. Second, the imaging studies were generated with CT and PET/CT scanners from multiple vendors over a 20 year period, and the technical qualities of contrast-enhanced chest/abdomen/pelvis CT and whole-body PET/CT have improved over this period.[18–20] However, it has been previously shown that there is no statistically significant difference in detection rate between patients diagnosed before 2009 and after 2009.[13] Third, we did not find any patients with uptake in the testes which is a common extranodal DLBCL with high incidence of CNS involvement. Only 12.8% (72 of 561) of the patients underwent testicular US and none of the patients had lymphoma involvement in the testis. In a previous meta-analysis (AJR 2021; 216:1172–1182), only 1 case among the 701 patients had paratesticular mass detected by PET/CT (0.1%, 1 of 701). Fourth, evaluation of molecular factors was not a part of this study and may possibly contribute to further understanding of factors associated with finding systemic/extracranial disease.

Conclusions

Our results showed increased odds of extracranial lymphoma in patients with older age or EBV-positive lymphoma. Treatment was adjusted in a majority of patients diagnosed with extracranial lymphoma, thereby supporting the current guidelines for the use contrast-enhanced body CT or PET/CT in patients with newly diagnosed CNS DLBCL.

Keywords

CT | Epstein-Barr virus | PET | primary central nervous system lymphoma

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