의학박사 학위논문

새롭게 진단된 중추신경계 림프종 환자에서 전신 컴퓨터 단층촬영과 양전자 방출 단층촬영의 두개 외 림프종 발견율

Body CT and PET/CT Detection Rates of Extracranial Lymphoma in Patients with Newly Diagnosed Central Nervous System Lymphoma

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서 종 현

새롭게 진단된 중추신경계 림프종 환자에서 전신 컴퓨터 단층촬영과 양전자 방출 단층촬영의 두개 외 림프종 발견율

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이 논문을 의학박사 학위 논문으로 제출함

2020년 8월

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서종현의 의학박사학위 논문을 인준함

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Abstract

Purpose: 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.

Patients and Methods: An international multicenter cohort study of consecutive immunocompetent patients with a new diagnosis of CNS DLBCL confirmed by brain biopsy who underwent contrast-enhanced chest/abdomen/pelvis CT and/or whole-body PET/CT to evaluate for sites of extracranial disease between 1998 and 2019. The primary outcome was the detection rate of extracranial lymphoma by chest/abdomen/pelvis CT or whole-body PET/CT and the secondary outcome was the false-referral rate. Subgroup analyses according to age and Epstein Barr virus (EBV) status were also performed. Logistic regression analyses were performed to determine factors related to sites of extracranial disease. Detection rates of chest/abdomen/pelvis CT and whole-body PET/CT were compared.

Results: 1043 patients with a mean age of 61 years (SD 13) were included. The overall detection rate of CT or PET/CT was 2.6% (27 of 1043; 95% CI, 1.7–3.7%). The treatment approach was adjusted in 65% of these patients. The false-referral rate was 5.8% (60 of 1043; 95% CI, 4.4–7.3%). The detection rate was 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 (odds ratio [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 associated with greater odds of extracranial lymphoma. There was no statistically significant difference in detection rate between chest/abdomen/pelvis CT and whole-body 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 thus support current guidelines to exclude extracranial lymphoma by body CT or body PET/CT. Body 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 and younger age was associated with a substantially higher false-referral rate.

차 례

그림목차

Introduction

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, 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.

Materials and 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.A. 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) or immunocompromised Epstein-Barr virus (EBV), 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 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 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, 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 0.2 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%]).

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%). 13 of 20 patients (65%) 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]).

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%). In patients ≤ 61 years old, the detection rate was 1.2% (6 of 519; 95% CI,

0.4–2.5%). In patients ≤ 61 years old, the false-referral rate was 6.4% (33 of 519; 95% CI, 4.4–8.8%). 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 2.2% (9 of 417; 95% CI, 1.0–4.1%). Types of malignancy were lung cancer (n = 4), thyroid cancer (n = 4), breast cancer (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 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 50% 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 50% of these patients. In addition, other malignancies were detected by whole-body PET/CT in 9 of 417 patients (2.2%; 95% CI, 1.0–4.1%). Smaller previous studies reported similar but slightly higher rates of 2.8% (5 of 180)[8] and 4.8% (2 of 42)[10] of patients having other malignancies detected by whole-body PET/CT. 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; $P = .016$) 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; $P = .045$) 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 due to the higher probability of extracranial sites of disease in this patient group.

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). A potential problem of the whole-body work-up for patients ≤ 61 years old with a new diagnosis of CNS DLBCL is that incidental lesions are frequently detected and false-positive findings may delay

and confuse the final diagnosis. In addition, the high false-referral rate may result in unnecessary surgery, endoscopy, radiation exposure, and increased medical costs. Furthermore, 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.[17-19] 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. It could be attributed to the fact that evaluation of testicular ultrasound was not a part of this study, particularly because most patients with testicular involvement may be picked up on whole-body PET/CT. 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.

Conclusion

Our results support the current guidelines for the use contrast-enhanced chest/abdomen/pelvis CT, whole body PET/CT, or their combination for extent of disease evaluation in patients with newly diagnosed CNS DLBCL. This study identified similar detection rates for sites of extracranial lymphoma with both contrast-enhanced chest/abdomen/pelvis CT, whole body PET/CT, and their combination. The false-referral rate was also similar. Older age (> 61 years) was associated with increased odds of the presence of extracranial lymphoma. Younger age was associated with a substantially higher false-referral rate.

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Captions for Illustrations

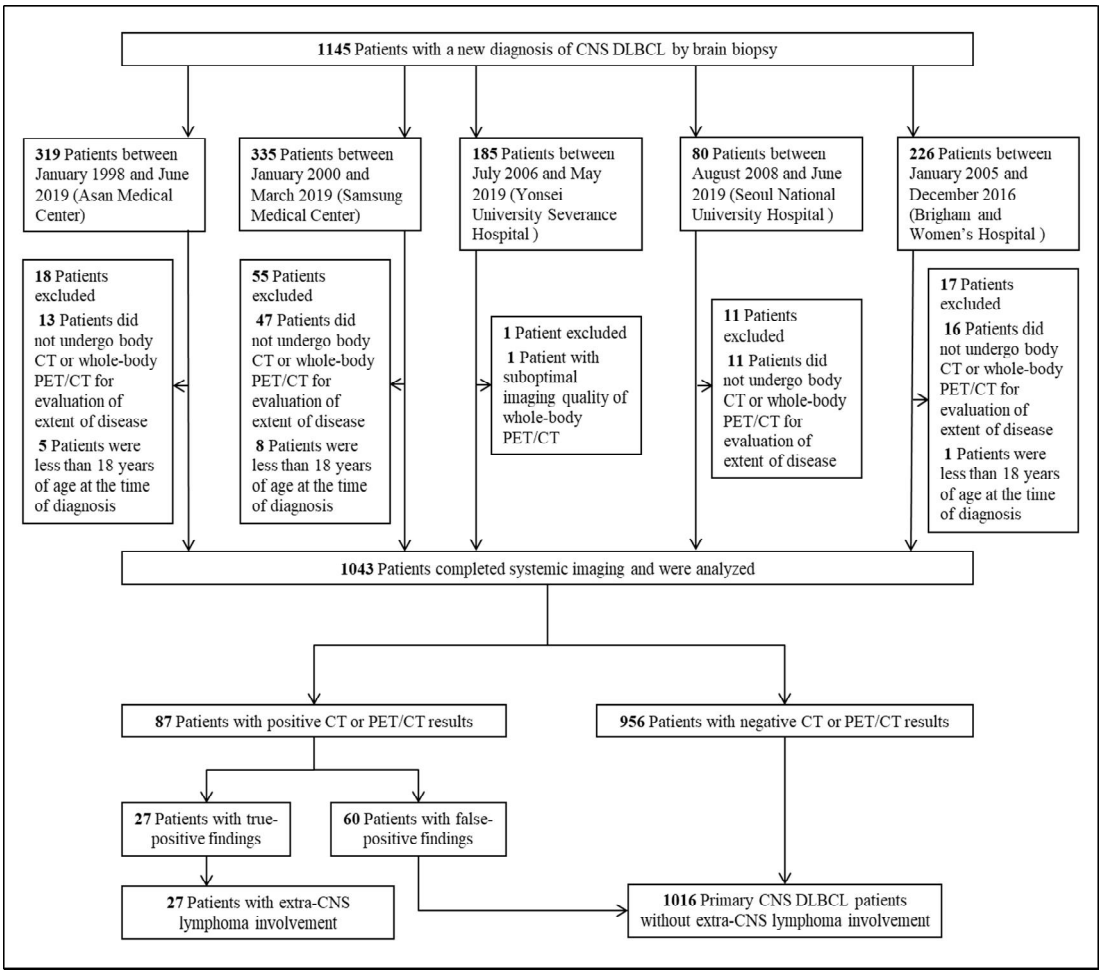

Figure 1. Flow Diagram of the International Multicenter Cohort Patient Inclusion Process.

CNS, central nervous system; DLBCL, diffuse large B cell lymphoma; CT, computed tomography; PET, positron emission tomography

국문요약

새롭게 진단된 중추신경계 림프종 환자에서
전신 컴퓨터 단층촬영과 양전자 방출 단층촬영의 두개 외 림프종 발견율

목적

본 연구에서는 새롭게 진단된 중추신경계 림프종 환자에서 전신 컴퓨터 단층촬영과 양전자 방출 단층촬영의 두개 외 림프종 발견율을 조사하고 두개 외 림프종과 연관된 요인을 분석하고자 한다.

연구재료와 연구방법

본 연구는 국제 다기관 연구이고 1998 년부터 2019 년까지 병리학적으로 확인된, 새롭게 진단된 중추신경계 림프종 환자 중에서 두개 외 림프종 발견을 위해 전신 컴퓨터 단층촬영과 양전자 방출 단층촬영을 시행한 환자를 대상으로 하였다. 일차적인 결과 변수는 전신 컴퓨터 단층촬영과 양전자 방출 단층촬영의 두개 외 림프종 발견율이었고 이차적인 결과 변수는 거짓 의뢰율이었다. 나이와 Epstein Barr virus(EBV) 상태에 따라 하위 그룹 분석도 수행하였다. 두개 외 림프종과 연관된 요소 결정을 위해 로지스틱 회귀 분석이 수행되었다. 전신 컴퓨터 단층촬영과 양전자 방출 단층촬영의 발견율을 비교하였다.

결과

총 1043 명이 포함되었고 평균 나이는 61 세였다. 전신 컴퓨터 단층촬영 혹은 양전자 방출 단층촬영의 전반적인 발견율은 2.6% (27/1043; 95% CI, 1.7–3.7%) 이었다. 이 환자들 중 65%의 환자에서 치료 방침이 변경되었다. 거짓 의뢰율은 5.8% (60/1043; 95% CI, 4.4–7.3%) 이었다. 61 세 이상에서는 발견율이 4.0% (21/524) 이었고 EBV 양성 환자에서는 8.3% (3 of 36) 이었다. 다변량분석에서 61 세 초과(오즈비, 3.10; 95% CI: 1.23–7.79; P = .016)와 EBV 양성(오즈비, 3.78; 95% CI: 1.03–13.87; P = .045)이 두개외 림프종과 연관되었다. 전신 컴퓨터 단층촬영과 양전자 방출 단층촬영의 발견율에는 통계적인 차이가 없었다 (P = .802). 61 세 이하에서는 거짓 의뢰율이 발견율보다 유의하게 높았다.

결론

본 연구는 두개 외 림프종 발견을 위한 전신 컴퓨터 단층촬영과 양전자 방출 단층

촬영에 대한 현재의 가이드라인을 지지하는 결과를 보였다. 새롭게 진단된 중추신경계 림프종 환자에서 전신 컴퓨터 단층촬영과 양전자 방출 단층촬영은 비슷한 발견율을 보였다. 61 세 초과의 고령과 EBV 양성은 두개 외 림프종과 연관성이 높았고 61 세 이하에서는 거짓 의뢰율이 높았다.

Tables

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%)	37 (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%)
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%)	NA	NA	NA	2 of 166 (1.2%, 0.2–4.3%)	9 of 417 (2.2%, 1.0–4.1%)

SD, standard deviation; CT, computed tomography; PET, positron emission tomography.

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, 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	
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	
Patient 9	66	Female	Chest/abdomen/pelvis CT and whole-body PET/CT	Abdominal/pelvic CT and whole-body PET/CT	Lymph node	
Patient 10	46	Female	Chest/abdomen/pelvis CT and whole-body PET/CT	Neck CT and whole-body PET/CT	Nasal cavity	
Patient 11	79	Female	Chest/abdomen/pelvis CT and whole-body PET/CT	Whole-body PET/CT	Cheek, lymph node	
Patient 12	49	Male	Chest/abdomen/pelvis CT and whole-body PET/CT	Whole-body PET/CT	Nasal cavity, lymph node	
Patient 13	64	Female	Chest/abdomen/pelvis CT and whole-body PET/CT	Abdominal/pelvic CT and whole-body PET/CT	Adrenal gland	

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
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

CNS, central nervous system; CT, computed tomography; PET, positron emission tomography; R-CHOP, rituximab cyclophosphamide

doxorubicin vincristine prednisone

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

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

CNS, central nervous system; DLBCL, diffuse large B cell lymphoma; SD, standard deviation; CT, computed tomography; PET, positron emission tomography.

[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