Value of FDG-PET/CT using unfractionated heparin for managing primary cardiac lymphoma and several key findings

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Case Report. A 66-year-old woman, who had history of surgical resection of tongue cancer and implantation of a pacemaker for sick sinus syndrome, complained of a recurring fever and dry cough for 2 months. Because the origin of the fever was not clear and because of a high inflammatory reaction with a white blood cell count of 12650/μL and a C-reactive protein (CRP) of 20.3 mg/dL, she was referred to our hospital for further examination.

Contrast enhanced computed tomography (CECT) was first performed to investigate the focus of the fever. CECT showed irregular thickness with heterogeneous contrast enhancement of the left atrium and the ventricle wall. Lymph node swelling at the mediastinal and paraaortic region was also seen continuous to the lesion in the left ventricle wall (Figure 1). Since the CECT was performed without ECG gating or dynamic contrast enhancement, evaluation of the coronary arteries was not adequate, even though the proximal left coronary artery (LCA) appeared to pass through the thickened wall.

Coronary angiography showed no evidence of vascular infiltration in a coronary artery, but abnormal vascularization presenting as a feeding artery to the cardiac mass was confirmed in the LCA (Figure 2). A trans-catheter biopsy of the cardiac tumor was performed at the same time, but the biopsy specimen did not indicate pathological malignancy.

Both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) revealed a 2.5 × 5.5 cm low echoic lesion along the cardiac wall from the left atrium to ventricle. Left ventricular function was good with an ejection fraction of 60.4%.

Ga-67 scintigraphy showed abnormal uptake at the mediastinum and weak uptake in the left ventricle wall (Figure 3). Dual imaging with Tl-201 and iodine-123 beta-methyl-iodophenyl-pentadecanoic acid (^{123}I-BMIPP) revealed no evidence of myocardial ischemia. In addition, abnormal uptake as an indication of cardiac tumor was not confirmed in this case (Figure 4).

[^{18}F]-2-fluoro-2-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) was performed using intravenous contrast agent to define the structure of the cardiac wall (Figure 5). FDG-PET/CT showed high FDG accumulation in the heart and mediastinum. FDG was diffusely accumulated in the cardiac wall, and appeared to spread over the thickened left atrium to the ventricle wall, as defined in CECT. The FDG-avid area extended to the mediastinal and paraaoric region, and was suspected to be the invasive lesion from the cardiac tumor. In addition, the FDG-avid area was much more extensive than the area of abnormal uptake on Ga-67 scintigraphy, especially for a cardiac lesion.

Finally, according to the World Health Organization classification, PCL with DLBCL was pathologically diagnosed by a specimen obtained from the open chest biopsy. A second FDG-PET/CT examination was then performed for restaging the malignant lymphoma (ML). In this examination, 4000 units of unfractionated heparin was intravenously administered 15 minutes before FDG administration. High physiological FDG uptake in the myocardium often interferes with evaluation of cardiac lesions. Pre-loaded unfractionated heparin suppressed FDG accumulation in the cardiac wall, so FDG accumulation at the cardiac lesion could be clearly defined.

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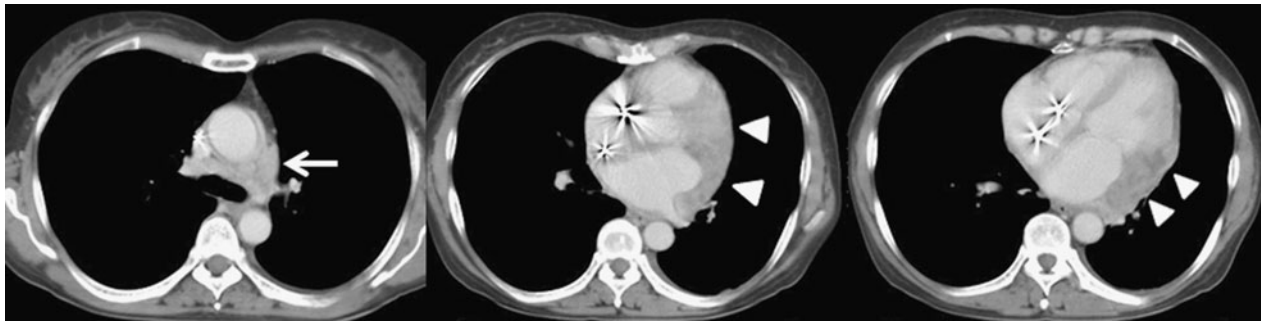

Figure 1. Transaxial images of contrast enhanced computed tomography (CECT). CECT revealed irregular thickness with heterogeneous contrast enhancement in the left atrium to the ventricle wall (*arrow head*). The lesion invaded the mediastinum (*arrow*).

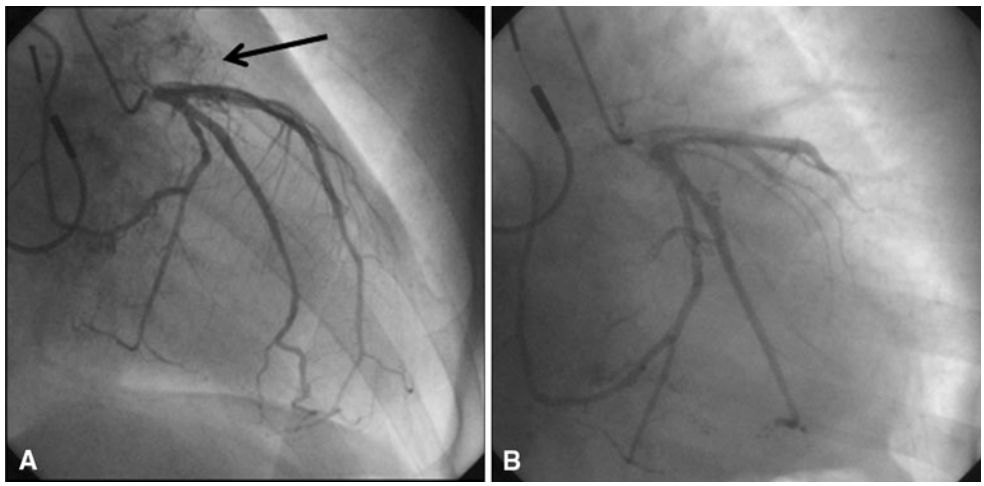

Figure 2. Image of left coronary artery by coronary angiography. **A** Right anterior oblique (RAO) views, **B** left cranial view. The left coronary artery had no evidence of infiltration by cardiac lesion, but abnormal vascularization presenting as a feeding artery to the cardiac mass was confirmed in the LCA (*arrow*).

The extra FDG uptake was seen in the thickened lateral wall of the left ventricle and in the mediastinal and paraaortic region. Moreover, an FDG-avid area was clearly confirmed in the base of the septal wall, indicating an invasive lesion. In contrast, FDG accumulation in the cardiac wall, excepting the thickened lateral wall, was clearly suppressed (Figure 6).

In the second FDG-PET/CT scan, ML was confirmed to be localized in a part of the cardiac wall and the mediastinal and paraaortic region. After this scan, R-CHOP therapy was started. After 4 cycles of R-CHOP therapy, FDG-PET/CT was repeated to evaluate the therapeutic effect. In this examination, 4000 units of unfractionated heparin was intravenously administered 15 minutes before FDG administration. FDG-PET/CT showed disappearance of abnormal FDG uptake in the left cardiac ventricle wall, and the mediastinum and paraaortic region (Figure 7). Radiation therapy with 30 Gy was added after the 6 cycles of R-CHOP therapy. Complete remission was present 52 months later.

Discussion. We presented the utility of FDG-PET/CT using unfractionated heparin for managing PCL, and some characteristic findings from several imaging modalities. Malignant cardiac tumors mostly consist of metastatic lesions, with primary cardiac tumors accounting for only 5% of all tumors in the heart.[1] The majority of malignant primary cardiac tumors are sarcomas including angiosarcomas, osteosarcomas, leiomyosarcomas, and rabdomyosarcomas. In contrast, PCL is a rare tumor which accounts for only 5% of primary cardiac tumors.[2]

Typical symptoms of PCL are dyspnea, arrhythmia, chest pain, and heart failure. However, PCL presents with various symptoms which depend on the disease

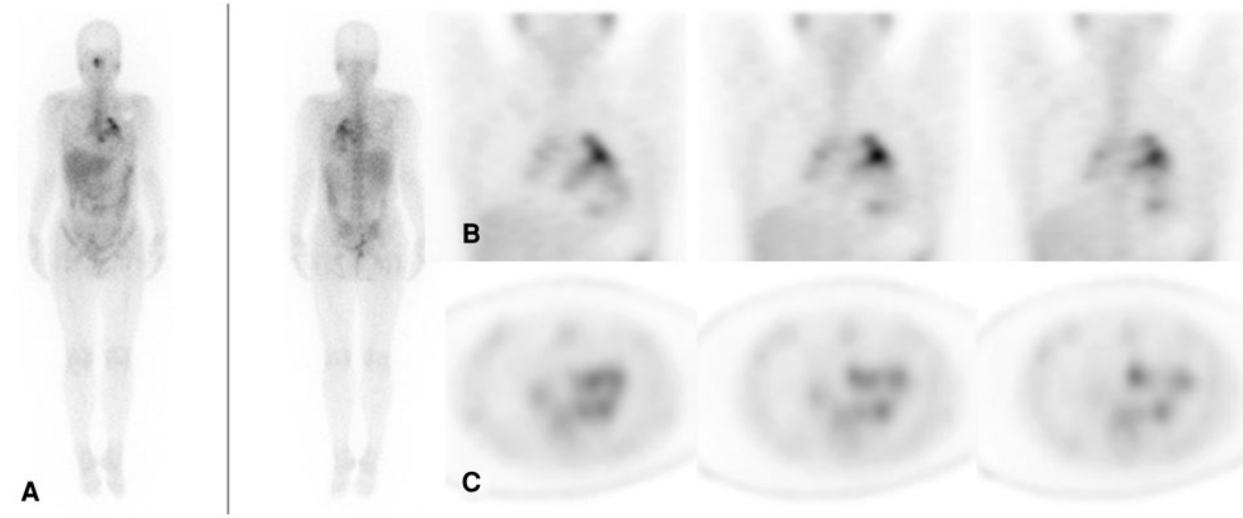

Figure 3. ^{67}Ga scintigraphy images **A** planar image, **B** coronal single photon emission computed tomography (SPECT) image, **C** transaxial SPECT image. ^{67}Ga-image showed abnormal focal uptake in the mediastinum. This is not specific for a lesion in the cardiac wall, as confirmed in the contrast enhanced computed tomography image.

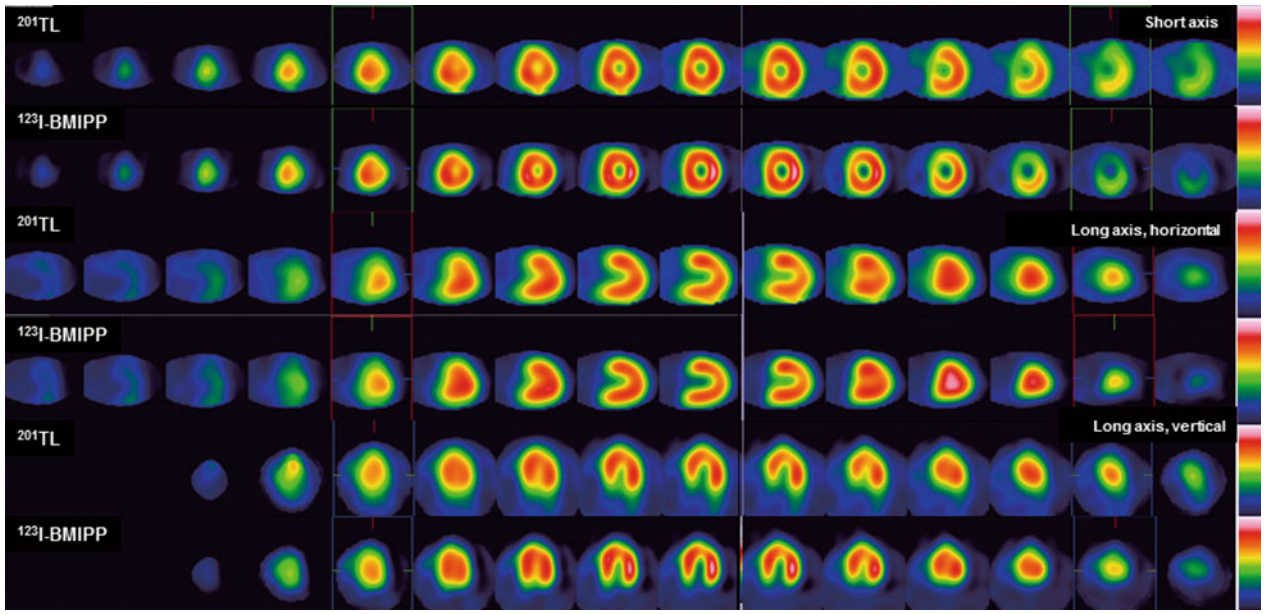

Figure 4. Dual imaging with Tl-201 and iodine-123 beta-methyl-iodophenyl-pentadecanoic acid (^{123}I-BMIPP) showed no evidence of myocardial ischemia. In addition, no abnormal uptake indicating a cardiac tumor was seen.

site.[3,4] Pathological PCL is mainly DLBCL, and thus, CHOP, R-CHOP and radiation therapy have a great potential to lead to a good prognosis.[3] PCL has established treatment, but several types of cardiac sarcomas have no definitive treatment regimens excepting complete resection.[5] Therefore, the diagnostic accuracy for assessing PCL is crucial.

Echocardiography has been the most common modality used to identify cardiac tumors, including PCL. Since TTE provides only a moderate sensitivity for cardiac tumor detection,[6] TEE has been recommended for evaluation of cardiac masses due to high sensitivity and distinctive images.[7] In the present case, TEE clearly visualized the cardiac tumor as a hypoechoic area.

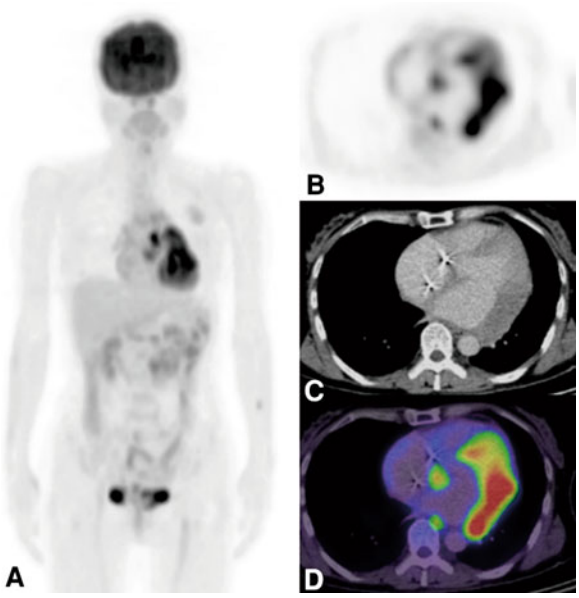

Figure 5. FDG-PET/CT image (without heparin administration). **A** Maximum intensity projection image of PET, **B** PET portion of the PET/CT, **C** CT portion of PET/CT, **D** PET-CT fused image. FDG-PET/CT showed FDG avidity in the heart and mediastinum. The FDG-avid area was wider than extent of uptake on Ga-67 scintigraphy, especially for the cardiac lesion.

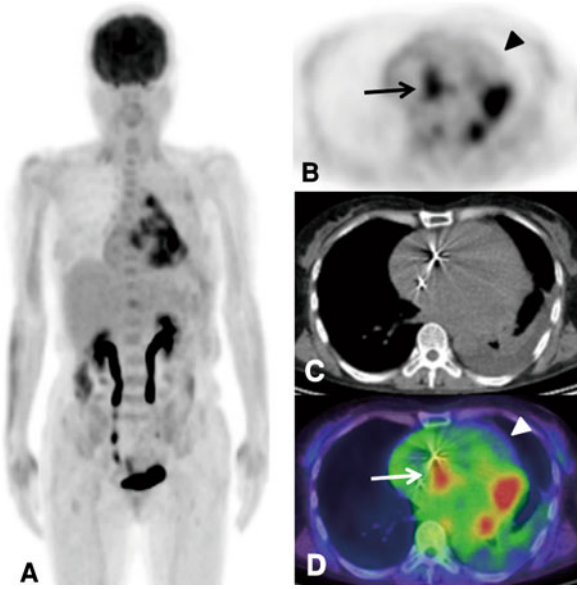

Figure 6. FDG-PET/CT image for restaging (combined heparin administration). **A** Maximum intensity projection image of PET, **B** PET portion of the PET/CT, **C** CT portion of PET/CT, **D** PET-CT fused image. FDG uptake was confirmed in the thickened lateral wall of the left ventricle and in the mediastinal and paraaortic regions. In addition, a lesion with FDG uptake was seen in base of septal wall (*arrow*). In contrast, FDG accumulation for normal cardiac wall was clearly suppressed (*arrow head*).

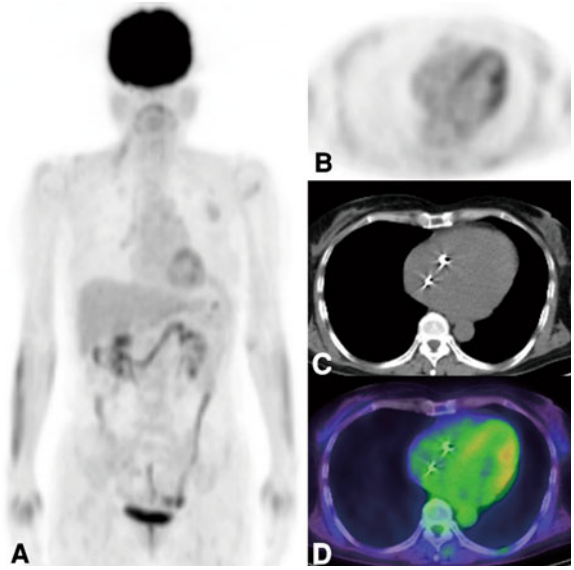

Figure 7. FDG-PET/CT image for the evaluation of therapeutic response (combined heparin administration). **A** Maximum intensity projection image of PET, **B** PET portion of the PET/CT, **C** CT portion of PET/CT, **D** PET-CT fused image. The abnormal FDG uptake in the left cardiac ventricle wall disappeared. Physiological FDG accumulation in cardiac wall was suppressed in this examination as same as previous FDG-PET/CT scan (*arrow head*).

However, TEE is invasive, and drawbacks include a narrow field of view.

Recently, several reports have showed the utility of CT and magnetic resonance imaging (MRI) for identifying PCL.[8] MRI contributes to tissue characterization of cardiac tumors.[9] Unfortunately, MRI was contraindicated due to implantation of a pacemaker in the present case.

Cardiac angiography showed no evidence of ML infiltration to a coronary artery, even though it was encased by a cardiac tumor. However, because the CT coronary angiogram showed no vascular infiltration in cardiac liposarcoma, this finding might be characteristic but not distinctive for PCL.[10] Typical symptoms in PCL are chest pain from possible coronary spasm. Assessment of myocardial perfusion and metabolic damage by ^{201}Tl/^{123}I-BMIPP dual single photon emission computed tomography (SPECT) myocardial imaging might help to confirm the myocardial status in PCL patients.

^{201}Tl, ^{99m}Tc sestamibi and Ga-SPECT have been reported to show positive uptake in PCL.[11] Recently, several reports have shown FDG-PET/CT imaging of PCL.[12,13]

The critical role of FDG-PET and PET/CT for ML has been widely reported.[14] Given the frequency of infiltration in ML, whole body inspection is needed for PCL patients to evaluate the extent of the lesion. FDG-

PET/CT has the greatest potential for assessing PCL patients due to a higher diagnostic accuracy than CT and Ga-67 scintigraphy.[15,16]

Physiologic accumulation of FDG in the cardiac wall usually interferes with evaluation of cardiac lesions. Ishimaru et al. reported the significant role of heparin administration before FDG injection for the detection of cardiac sarcoidosis.[17] Heparin causes the release of free fatty acids into the circulation, and it works to reduce physiological FDG uptake of myocardium.[18,19] In this case, heparin administration assisted FDG-PET/CT imaging for confirming the precise area of PCL, including the lesion in the septal wall. Heparin administration prior to FDG improved the assessment of the location and extent of the cardiac tumor. However, focal FDG uptake in cardiac wall is not particular to PCL even if it is clearly identified by heparin administration. The different diagnosis such as sarcoidosis and angiosarcoma were considered as principal different diagnoses.

PCL is generally diagnosed by biopsy. Since FDG-PET/CT contributes to detection of extra-cardiac lesions, it can potentially be an indicator of suitable biopsy sites for diagnosis.[20] Moreover, an extra-cardiac lesion suggested by FDG-PET/CT may enable diagnostic biopsy more safely and easily than a direct biopsy of a cardiac tumor. Even in the case of cardiac metastasis, which is a probable cause of a cardiac mass, FDG-PET/CT may be helpful for detection of the primary site.

FDG-PET/CT is useful for monitoring the therapeutic response of ML.[21] In the present case, heparin preloading prior to FDG-PET/CT was helpful for cardiac imaging and assessment of the therapeutic response for PCL.

In conclusion, PCL is a rare tumor, but it has an effective treatment so an immediate diagnosis for subsequent appropriate treatment is optimal. FDG-PET/CT using unfractionated heparin contributes to the early diagnosis of this tumor, documentation of the extent of the lesion, and evaluation of the therapeutic response to treatment.

Conflicts of Interest

The authors have indicated they have no functional conflicts of interest.

References

1. Konety SH, Wooldridge JE, Kerber RE. Primary cardiac non-Hodgkin's lymphoma diagnosed by transthoracic echocardiography. Echocardiography 2006;23:147-8.
2. Butany J, Nair V, Naseemuddin A, Nair GM, Catton C, Yau T. Cardiac tumours: Diagnosis and management. Lancet Oncol 2005;6:219-28.
3. Petrich A, Cho SI, Billett H. Primary cardiac lymphoma: An analysis of presentation, treatment, and outcome patterns. Cancer 2011;117:581-9.
4. Miguel CE, Bestetti RB. Primary cardiac lymphoma. Int J Cardiol 2010 (online first).
5. Devbhandari MP, Meraj S, Jones MT, Kadir I, Bridgewater B. Primary cardiac sarcoma: Reports of two cases and a review of current literature. J Cardiothorac Surg 2007;2:34.
6. Moore JA, DeRan BP, Minor R, Arthur J, Fraker TD Jr. Transesophageal echocardiographic evaluation of intracardiac lymphoma. Am Heart J 1992;124:514-6.
7. Mügge A, Daniel WG, Haverich A, Lichtlen PR. Diagnosis of noninfective cardiac mass lesions by two-dimensional echocardiography. Comparison of the transthoracic and transesophageal approaches. Circulation 1991;83:70-8.
8. Araoz PA, Eklund HE, Welch TJ, Breen JF. CT and MR imaging of primary cardiac malignancies. Radiographics 1999;19:1421-34.
9. Ryu SJ, Choi BW, Choe KO. CT and MR findings of primary cardiac lymphoma: Report upon 2 cases and review. Yonsei Med J 2001;42:451-6.
10. Zhang M, Li B, Jiang X. PET/CT imaging in a case of cardiac liposarcoma. J Nucl Cardiol 2008;15:473-5.
11. Kosuda S, Kusano S, Ohsuzu F. Primary myocardial lymphoma demonstrated by Tl-201, Tc-99m sestamibi, and Ga-67 SPECT. Clin Nucl Med 1998;23:482-3.
12. Su HY, Huang HL, Sun CM, Hou SM, Chen ML. Primary cardiac lymphoma evaluated with integration of PET/CT and contrast-enhanced CT. Clin Nucl Med 2009;34:298-301.
13. Cho JM, Sohn IS, Yang YJ. Heart in the heart: Dual faced primary cardiac lymphoma on PET-CT. Int J Cardiol 2010;142:e40-1.
14. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-86.
15. Tsukamoto N, Kojima M, Hasegawa M, Oriuchi N, Matsushima T, Yokohama A, et al. The usefulness of (18)F-fluorodeoxyglucose positron emission tomography ((18)F-FDG-PET) and a comparison of (18)F-FDG-pet with (67)gallium scintigraphy in the evaluation of lymphoma: Relation to histologic subtypes based on the World Health Organization classification. Cancer 2007;110:652-9.
16. Hicks RJ, Mac Manus MP, Seymour JF. Initial staging of lymphoma with positron emission tomography and computed tomography. Semin Nucl Med 2005;35:165-75.
17. Ishimaru S, Tsujino I, Takei T, Tsukamoto E, Sakaue S, Kamigaki M, et al. Focal uptake on 18F-fluoro-2-deoxyglucose positron emission tomography images indicates cardiac involvement of sarcoidosis. Eur Heart J 2005;26:1538-43.
18. Nuutila P, Koivisto VA, Knuuti J, Ruotsalainen U, Teräs M, Haaparanta M, et al. Glucose-free fatty acid cycle operates in human heart and skeletal muscle in vivo. J Clin Invest 1992;89:1767-74.
19. Wisneski JA, Gertz EW, Neese RA, Gruenke LD, Morris DL, Craig JC. Metabolic fate of extracted glucose in normal human myocardium. J Clin Invest 1985;76:1819-27.
20. Watanabe R, Tomita N, Takeuchi K, Sakata S, Tateishi U, Tanaka M, et al. SUVmax in FDG-PET at the biopsy site correlates with the proliferation potential of tumor cells in non-Hodgkin lymphoma. Leuk Lymphoma 2010;51:279-83.
21. Mikhaeel NG. Use of FDG-PET to monitor response to chemotherapy and radiotherapy in patients with lymphomas. Eur J Nucl Med Mol Imaging 2006;33:22-6.