REVIEW ARTICLE

Usefulness of Nuclear Medicine:"PET/SPECT Imaging" for Management of Recipients after Heart Transplantation

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Abstract

Heart transplantation (HTx) in Japan started in 1992 after putting the Organ Transplant Law into force. Even after the amendment of this law in 2010, numbers of HTx performed in Japan has been much less than other countries, however, the outcome of HTx in Japan is much superior to that of international registry. For the management after HTx, surveillance of acute cellular rejection, cardiac allograft vasculopathy (CAV), infections, renal dysfunction, malignancies is essential.

Nuclear medicine, such as myocardial perfusion imaging, ^{67}Ga scintigraphy, ^{18}F-FDG PET, etc., has been utilized for detection of these rejections and complications, adding to other modalities.

Moreover, re-innervation from denervated heart is unique phenomenon which is observed in HTx recipients. For the evaluation of re-innervation in transplanted heart, ^{123}I-metaiodobenzylguanidine (MIBG), which is the analogue of norepinephrine, has been utilized. Then, several reports described that the degree of re-innervation was related to sympathetic functional recovery, such as responses of the heart rate and contractile function to exercise.

As described above, nuclear medicine has contributed to recipient's care and management after HTx. However, invasive techniques, such as endomyocardial biopsy, coronary angiography, etc., have played a major role in management of recipients, because of high reliability for detection of rejections and complications, compared with other non-invasive modalities. So, we professional of imaging diagnosis have to keep on challenging to offer securer and easier care to HTx recipients.

Keywords: Nuclear medicine, Heart transplantation, PET, SPECT

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Heart transplantation (HTx) has been performed as the ultimate therapy for patients with end-stage heart failure for long time in the world, and the number of HTx reported to the International Society of Heart and Lung Transplantation (ISHLT) registry worldwide has been 3,500-4,000 annually (1). On the other hand, in Japan, the first heart transplantation in accordance with the Organ Transplant Law was operated in 1999 (2), then second and third cases were operated in our National Cerebral and Cardiovascular Center (3). So, history of HTx in Japan is less than 20 years, which is shorter than other countries. After this first case, the number of annual transplantations has gradually increased until the revision of this law in Jan. 2010. This amendment was so beneficial that the number of transplantations has increased dramatically (Fig. 1). From "the Registry Report of Heart Transplantation in Japan", outcome of HTx recipients in Japan has been superior to that of ISHLT registry (4, 5). Fig. 2 shows the latest report about cumulative survival rate

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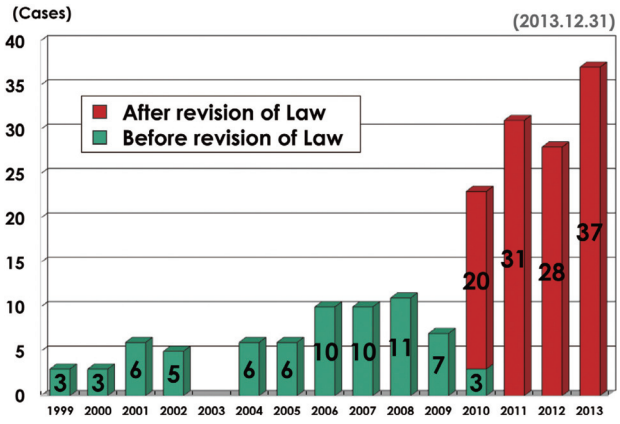

Fig. 1 Numbers of HTx performed in Japan by year
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After the revision of the law, numbers of HTx were dramatically increased.

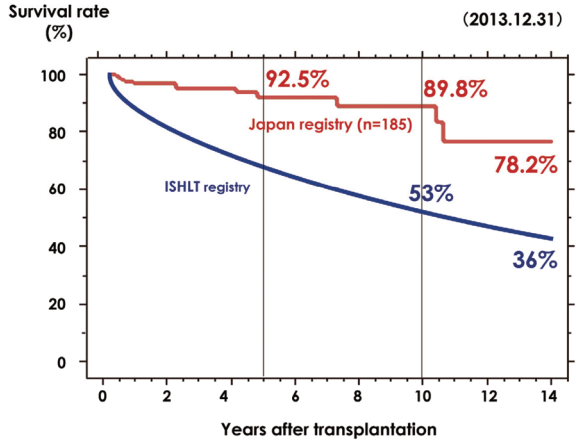

Fig. 2 Cumulative survival rates following HTx recipients in Japan: comparison with international registry
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ISHLT: International Society for Heart & Lung Transplantation

Table 1 Schedule of surveillance after HTx in NCVC

Methods	Schedule
EMB	Once a week（～3rd W） 5th, 11th, and 19th W Once every 3M（～1Y） Once every 6M（1Y～）
CAG & IVUS	Once a year（～10Y） Once every 2Y（10Y～）
CFR by UCG	Twice a year
Right heart cathe.	Twice a year（～5Y） Once a year（5～10Y） Once every 2Y（10Y～）

EMB: endomyocardial biopsy, CAG: coronary angiography, IVUS: intravascular ultrasound, CFR: coronary flow reserve, UCG: ultrasound cardiography, cathe.: catheter, W: week, Y: year

of Japanese HTx recipients with comparison to international registry. This excellent result has been brought by a great deal of efforts of transplant team in Japan.

So, in this article, I will review the management of recipients after HTx and the contribution of nuclear medicine associated with the post-HTx management.

Current Status of HTx in Japan（5）

Until 2013. Dec. 31st, numbers of HTx recipients in Japan are 185. Unfortunately, 12 patients have died with multiple organ failure, infections, cardiac allograft vasculopathy（CAV）, cancers, renal failures, and others. Remainder 173 recipients are in life at the present time.

Even after the amendment of Organ Transplant Law, numbers of recipients in Japan are still much less than those in other countries, where HTx is performed. However, as described above, outcome of HTx recipients in Japan has been superior to that of international registry. This excellent result has been achieved in very short period after first HTx case with great efforts of transplant team in Japanese hospitals.

Important points for the surveillance after HTx and its schedule

For better management of HTx recipients, medical stuffs have to pay a lot of attentions to several points as follows;

1. Acute cellular rejection
2. Cardiac allograft vasculopathy
3. Infection
5. Renal dysfunction
6. Malignancy
7. Re-innervation from dennervated heart

The schedule of surveillance for these matters after HTx is different from each hospital. In National Cerebral and Cardiovascular Center（NCVC）, the schedule of surveillance has been planned as listed in Table 1. Endomyocardial biopsy（EMB）is performed regularly and frequently for detection of rejection. And coronary angiography（CAG）, intravascular ultrasound（IVUS）, and coronary flow reserve（CFR）by UCG are also performed regularly for evaluation of CAV.

Acute Cellular Rejection（ACR）

Etiology of ACR is considered to be immune reaction mediated by T-cell. This rejection is frequently observed in first 6 months～1 year after transplant. About the incidence of this reaction, 20-40% of HTx

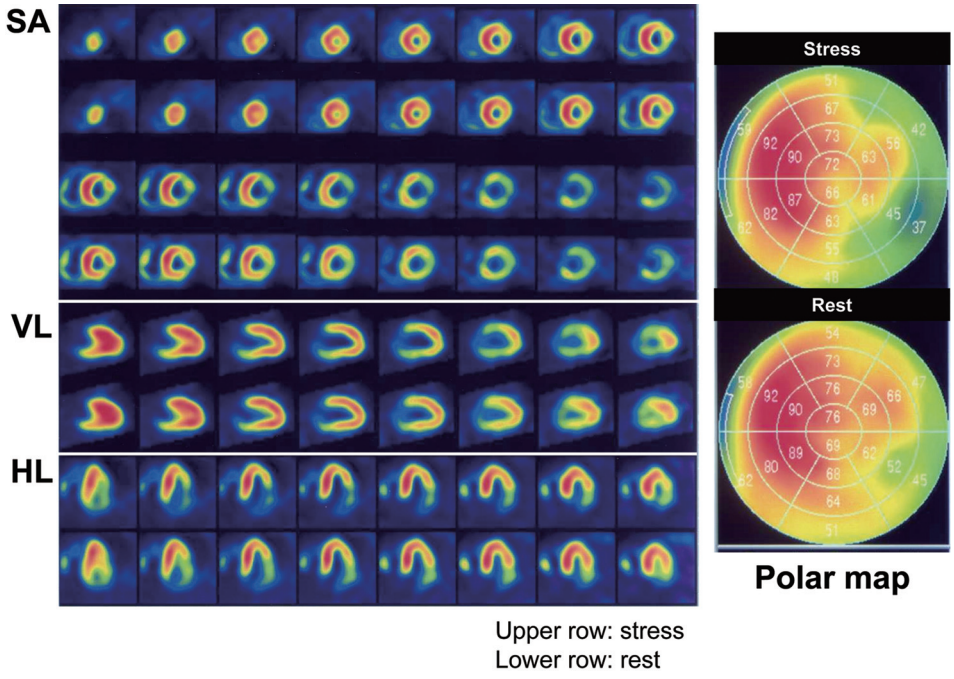

Fig. 3 Representative case in which stress myocardial perfusion SPECT（MPS）was useful for the detection of CAV
This recipients received HTx 13 years ago.
Moderate to severe ischemic finding is observed in lateral region.
After this stress MPS, significant coronary stenosis in LCX was confirmed by CAG, and PCI was adopted.
SA: short axis, VL: vertical long, HL: horizontal long

recipients will experience at least 1 episode in the first postoperative year（6）.

Since this reaction induced almost no symptom in early stage, its detection from physical findings is difficult.

Therefore, surveillance of ACR is mandatory for the HTx recipients and mainly performed by endomyocardial biopsy, which is only means of this purpose. Since biopsy is the invasive surveillance, detection with non-invasive imaging modalities such as UCG, MRI, and nuclear medicine, have been evaluated, however, the results were insufficient for detection of ACR in current clinical settings.

Cardiac Allograft Vasculopathy: CAV

CAV is atherosclerotic lesion in coronary artery, and this is also one of the most important complications after HTx.

Etiology of CAV is unknown precisely, however, the association with chronic rejection is thought to be one of the reasons. And advanced CAV leads severe myocardial ischemia, which causes heart failure. Therefore, CAV sometimes limits the long-term success of HTx. For the treatment of CAV, not only revascularization with PCI or CABG, but also Everolimus（Certican®）, which is one of the immune suppressive agents, is accepted.

From the report by ISHLT, incidence of CAV detected by coronary angiography within first year is 8%, 32%（within first 5-year）, and 43%（within first 8-year）（7）. Moreover, incidence of death or re-HTx（as a result of CAV）at 5-year follow up was 7%（8）. In NCVC, 2 recipients received PCI and 3 recipients received CABG among total 60 HTx recipients.

Early diagnosis of CAV is limited by lack of clinical symptoms for ischemia in the denervated allograft. So, surveillance for CAV is performed by coronary angiography（CAG）and intravascular ultrasound（IVUS）mainly. As a non-invasive surveillance, stress myocardial perfusion SPECT imaging（MPS）is classified to "Class Ⅱ" for cases who are not favorable for invasive surveillance by ISHLT guideline（9）. Stress MPS is applied for making decision of indication of revascularization after diagnosis of CAV by CAG. However, in some cases with CAV, due to diffuse and multiple lesions, stress MPS shows no significant perfusion abnormality. So, interpretation of MPS findings in case with CAV needs some attentions.

Representative case, in which stress MPS was useful for the evaluation of severity of CAV, is shown in Fig. 3. After stress MPS, significant coronary stenosis in left circumflex（LCX）artery was confirmed by CAG, and

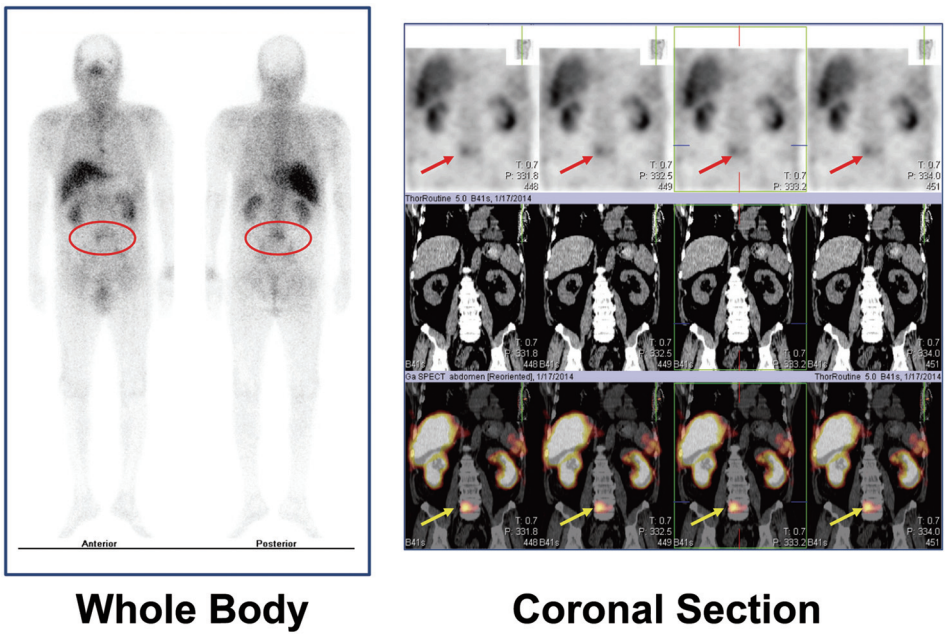

Fig. 4 Representative case of infection after HTX: vertebral osteomyelitis detected by ^{67}Ga scintigraphy
This patient received HTx 5-month before, and have felt back pain for 3-month. Vertebral osteomyelitis was suspected, then ^{67}Ga scintigraphy was performed. ^{67}Ga-SPECT/CT showed abnormal ^{67}Ga uptake in 5th lumber vertebra（red circle, red arrow, yellow arrow）.

PCI was performed in this LCX lesion.

Infections

Infections are most important complication after transplantation, and they are mostly caused by immunosuppressive therapy. Among infections, cytomegalovirus and EB virus（EBV）are paid to special attention for the recipients. For detection of respiratory infections, chest X-ray and CT are first choices.

In recipients who are assisted by left ventricular assist device（LVAD）before transplantation, subcutaneous abscess of access route is frequently observed.

For examination of unknown cause of infections, ^{67}Ga scintigraphy（Ga）and ^{18}F-FDG（FDG）PET are useful for detection of sources of infections. However, since ^{18}FDG PET for infectious/inflammatory diseases is not covered with health insurance in Japan, its indication has to be decided carefully.

Representative case of infection is shown in Fig. 4. In this patient, ^{67}Ga scintigraphy was checked for inspection of back pain. ^{67}Ga-SPECT/CT showed abnormal ^{67}Ga uptake in 5th lumber vertebra and diagnosed as vertebral osteomyelitis.

Drug-induced nephropathy: Interstitial nephritis

Since most immunosuppressive agents have nephrotoxicity, interstitial nephritis is sometimes induced by those agents. In particular, calcineurin inhibitor（tacrolimus, cyclosporin）is known as a responsible agent of this "interstitial nephritis".

For the diagnosis of interstitial nephritis, ^{67}Ga scintigraphy is known as a useful tool. Representative case is shown in Fig. 5, in which bilateral kidney was clearly visualized with the homogeneous accumulation of ^{67}Ga.

Malignancy

Malignancy is also known as major complication induced by immunosuppression. Incidence of malignancy is reported that 15.1% within first 5-year, 31.9% within 10-year（10）, and 14.4% more than 20-year follow up（11）.

Types of malignancy are cutaneous malignancy＝50%, lymphoma＝10%, solid tumor（prostate・lung・breast, etc.）＝40%（11）. In spite of long-term immunosuppression, frequency of many common solid tumors did not increase, compared to individuals without any transplantation.

Among malignancies after HTx, lymphoma which is known as post-transplant lympho-proliferative disorder（PTLD）is major concern. Most PTLDs are of B-cell origin non-Hodgkin's lymphoma, associated with EB virus（EBV）. This PTLD is unusual in immunologically intact individuals. Incidence of PTLD in NCVC is 2 recipients among total 60 recipients. Managements after the occurrence of PTLD are the reduction of immuno-

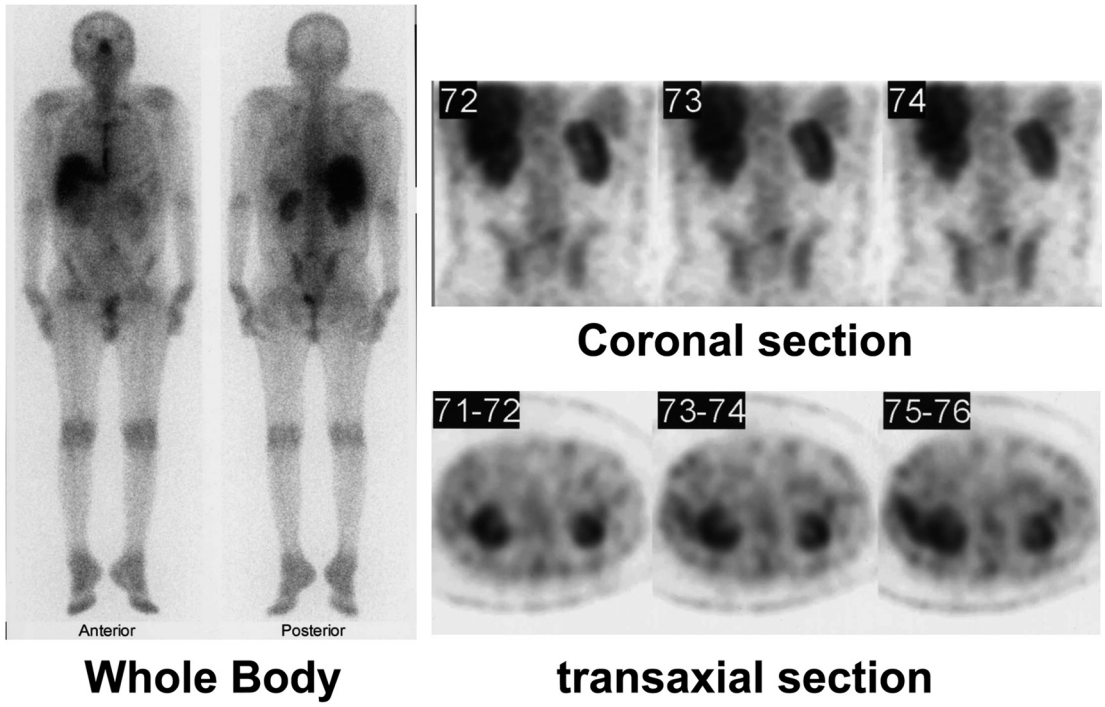

Fig. 5 Representative case of renal dysfunction after HTx
This patients received HTx 5-month before. And progressive renal dysfunction was observed after HTx, then ^{67}Ga was performed. Bilateral kidney was clearly visualized with the homogeneous ^{67}Ga accumulation.
After this diagnosis, immunosuppressive agent; calcineurin inhibitor was reduced, then renal dysfunction improved.

suppressive agents, and chemotherapy. Surveillance of PTLD is mainly performed with quantitative PCR of EBV. However, non-invasive imaging diagnosis, such as CT, ^{67}Ga, and ^{18}F-FDG PET etc., is also utilized as useful tools for inspection of PTLD.

Representative cases, who were diagnosed as PTLD by ^{67}Ga scintigraphy and ^{18}F-FDG PET imaging, are shown in Fig. 6 and 7.

Re-innervation after HTx: from denervation to innervation

Transplanted heart is isolated by operation. So, sympathetic neurons of transplanted heart are also completely separated by excision of heart.

^{123}I-metaiodobenzylguanidine（MIBG), which is norepinephrine analogue, is able to evaluate cardiac sympathetic nervous function. It is well known that no myocardial accumulation of MIBG is observed in recipients early after HTx.

However, re-innervation in transplanted heart is gradually occurred, and the process of this re-innervation is also evaluated by MIBG. De Marco, et al. reported that sympathetic re-innervation occur more than 1 year after HTx evaluated by MIBG（12). Serial changes of MIBG findings after HTx, which was followed in NCVC, are shown in Fig. 8. This recipients received HTx at the age of 30's. In MIBG images at 1 year after HTx, no myocardial uptake was observed, however, MIBG images at 3-year after HTx showed slight uptake in basal anterior region on anterior planar（arrow head) and short axis SPECT images（red arrow).

On the contrary, in pediatric recipients, earlier re-innervation can be observed even less than 1 year after HTx（13). MIBG images of pediatric recipients are shown in Fig. 9. This patient received HTx at the age of 3 years old. Different from previous adult case, even less than 1 year after HTx, myocardial uptake was observed in anteroseptal region clearly. Moreover, at 2-year after HTx, MIBG uptake extended to inferoseptal and lateral regions. In pediatric recipients, the speed of re-innervation is much faster than that in adult cases.

Momose, et al. reported that basal anterior region followed by basal septal and lateral regions are more likely to be re-innervated（14). However, the reason of frequent site of earlier re-innervation is not well-understood.

Relation to sympathetic functional improvement:

One of the major sympathetic functions is heart rate response to exercise（=heart rate variability). Bengel, et al. reported that sympathetic re-innervation evaluated by ^{11}C-HDE PET was associated with improved responses of the heart rate and contractile function to

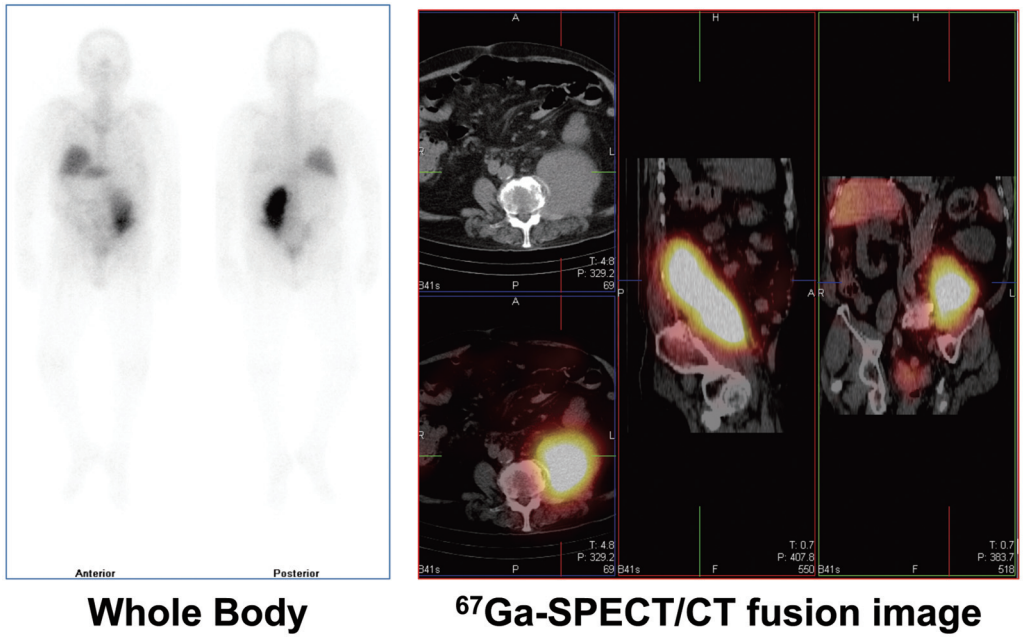

Fig. 6 Representative case of PTLD after HTx; detected by ^{67}Ga scintigrapy
This patient received HTx 8 years ago. CT was performed for inspection of hypoxemia, and accidentally detected mass lesion in iliopsoas region. Then, ^{67}Ga scintigraphy was performed for confirmation of malignancy. Significant uptake of ^{67}Ga was clearly observed in iliopsoas mass lesion.

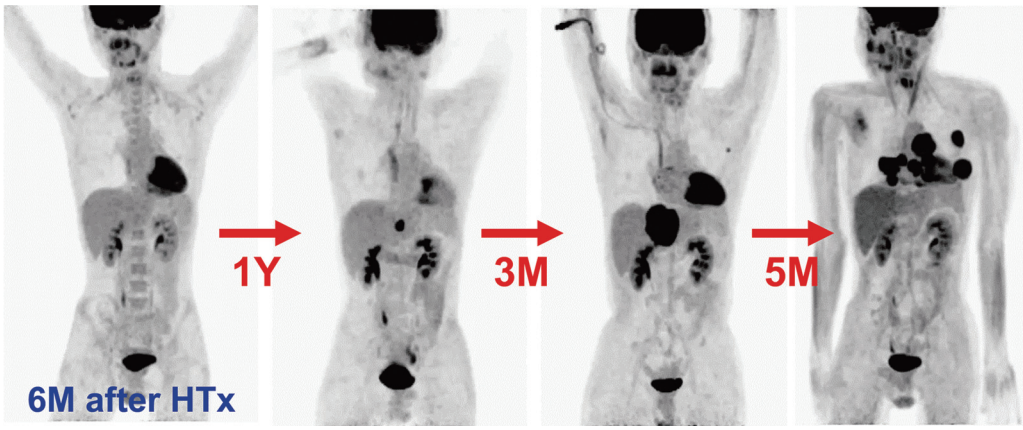

Fig. 7 Serial findings of ^{18}F-FDG PET imaging in patients with typical PTLD
This patient received HTx 6-month before. For the inspection of decrease of neutrophil and increase of quantitative PCR of EBV, ^{18}F-FDG PET was performed. Initial finding of ^{18}F-FDG PET did not show significant abnormality. However, after 1 year of this initial study, significant abnormal findings were observed. Although several therapies and intensive cares were adopted, PTLD could not be controlled, then this patient terminated in death.

exercise（15）.

On the contrary, several authors reported that heart rate variability and ventricular sympathetic re-innervation evaluated with ^{123}I-MIBG do not occur simultaneously（16, 17）. Toba, et al. reported that in the follow-up from 1 to 2-year after HTx, MIBG distribution was improved markedly, but the impaired autonomic control of heart rate persisted（17）.

Conclusion

As mentioned above, nuclear medicine has contributed to the management after HTx. However, invasive surveillance, such as EMB, CAG, etc., is major technique to detect rejections and complications. For the reduction of invasive procedure to patients, improvement and evolution of technology in non-invasive imaging modalities including nuclear medicine, molecular imaging, etc., are necessary.

We professional of imaging diagnosis have to keep on challenging to offer securer and easier care for HTx recipients.

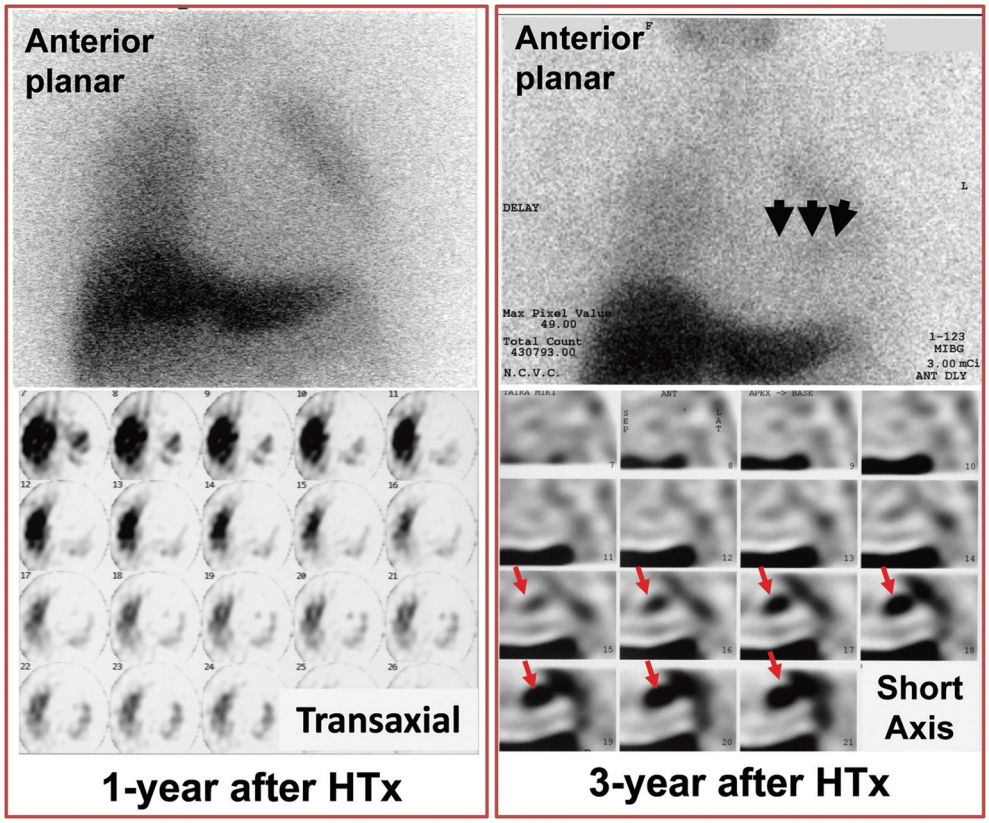

Fig. 8 Serial change of MIBG findings after HTx
This recipients received HTx at the age of 30's. In MIBG images at 1 year after HTx, no myocardial uptake was observed, however, MIBG images at 3-year after HTx showed slight uptake in basal anterior region on anterior planar（arrow head）and short axis SPECT images（red arrow）

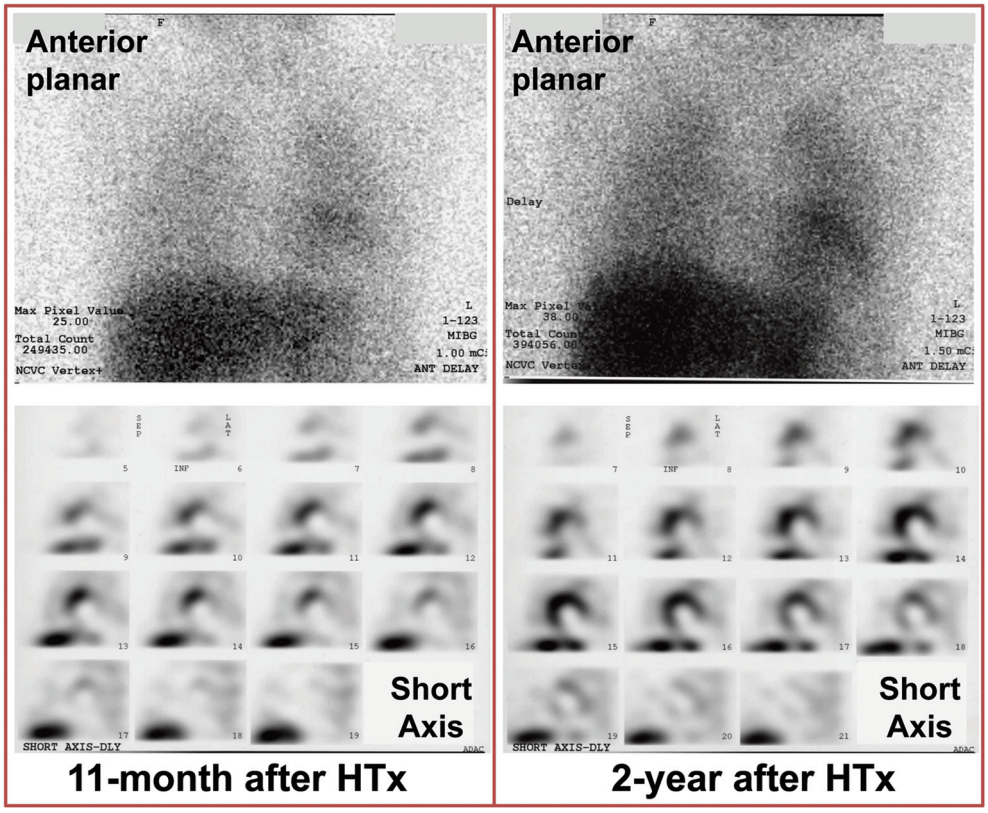

Fig. 9 MIBG images of pediatric HTx recipients
This patient received HTx at the age of 3 years old. Different from previous adult case, even less than 1 year after HTx, myocardial uptake was observed in anteroseptal region clearly. Moreover, at 2-year after HTx, MIBG uptake extended to inferoseptal and lateral regions.

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Conflicts of Interest

Author and co-authors of this manuscript: Keisuke Kiso, Naomi Morita, Yoshihiro Nishimura, Yusuke Terakawa, Msahiro Higashi, Masanobu Yanase, and Takeshi Nakatani, have no financial conflicts of interest to disclose concerning this manuscript.

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