American Journal of Transplantation 2006; 6: 1731–1736
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2006.01358.x

Brief Communication

How Useful is PET/CT Imaging in the Management of Post-Transplant Lymphoproliferative Disease After Liver Transplantation?

L. McCormack[a], T. I. Hany[b], M. Hübner[a], H. Petrowsky[a], B. Mullhaupt[c], A. Knuth[d], F. Stenner[d] and P.-A. Clavien[a,*]

[a] *Swiss Hepato-Pancreato Biliary Center, Department of Visceral and Transplant Surgery,* [b] *Department of Nuclear Medicine,* [c] *Division of Gastroenterology and Hepatology and* [d] *Department of Oncology, University Hospital of Zürich, Switzerland*
* *Corresponding author: Pierre Clavien, MD, Phd, clavien@chir.unizh.ch*

Post-transplant lymphoproliferative disease (PTLD) is a serious and potentially life-threatening complication after solid organ transplantation. Here, we report our first experience with the use of PET/CT (positron emission tomography combined with computed tomogram) for the management of patients with PTLD after liver transplantation. Four patients with histologically proven PTLD were analyzed. Conventional work-up included physical examination and head-to-pelvis CT. PET/CT was used in one patient for initial staging and in all patients for follow-up. PET/CT positive findings underwent biopsy. Information provided by PET/CT resulted in a change of medical management in three of the four patients. Conventional work-up missed residual disease after surgery in one and failed to detect a tumor relapse in another patient. However, one patient disclosed a false positive PET/CT finding in the lungs. In conclusion, PET/CT may be a useful tool for staging and therapy monitoring of PTLD after liver transplantation.

Key words: Liver transplant, liver transplantation, lymphoma, lymphoproliferative, positron emission tomography

Received 8 November 2005, revised and accepted for publication 23 March 2006

Introduction

Post-transplant lymphoproliferative disease (PTLD) is a rare but serious complication of immunosuppression after solid organ transplantation (1). The term PTLD encompasses a heterogeneous group of lymphoproliferative disorders ranging from benign polyclonal and polymorphic B-cell proliferation to malignant monoclonal and monomorphic lymphomatous lesions (1). The disease may be nodal or extranodal, limited to the allograft, to another organ or widely disseminated. Although no standard treatment for PTLD has been established yet, the reduction of immunosuppression in conjunction with the use of anti-CD20 monoclonal antibody therapy (Rituximab) has become first-line treatment in most transplant centers (2,3). However, the accuracy in staging of PTLD and assessment of tumor response after treatment is of paramount importance to evaluate and compare new treatment modalities.

Conventionally positron emission tomography (PET) with fluoro-2-deoxy-D-glucose (FDG) and computed tomogram (CT) scans has been used to detect several types of cancer including lymphomas (4). Both methods have severe limitations in this setting. CT scan cannot distinguish between vital and nonvital tumor lesions. PET scan has a poor resolution and poor anatomic localization of an FDG positive lesion. To overcome this, a new approach combining PET data with a multi-detector row helical CT has been developed (PET/CT) (5).

The efficacy of PET to stage PTLD has been recently reported in small series of lung and kidney transplant recipients (6–8). To our knowledge, no data are available on the use of PET/CT for the staging and follow-up of PTLD in recipients of solid organ transplants. Here, we present our initial experience with the use of PET/CT for staging and therapy monitoring of PTLD in liver transplant patients.

Patients and Methods

PET/CT was introduced in our center in April 2001, and we have used this technology as reported here for staging and follow-up in four patients with PTLD after liver transplantation. Diagnosis of PTLD was confirmed by immunohistochemistry and molecular clonal analysis. Histological grading of the disease was performed according to the modified WHO classification proposed by Nalesnik et al. (9) (Table 1). Once diagnosis was established, initial staging of the disease was performed by conventional work-up including head-to-pelvis contrast enhanced CT scan (ceCT), bone marrow biopsy and when indicated by ascites cytology. All patients were confirmed as Epstein-Barr virus seropositive at diagnosis. Only the last patient had a PET/CT for initial staging of the PTLD in addition to the conventional work-up.

Table 1: Demographic, clinical and pathological characteristics of patients with PTLD after liver transplantation

	Case 1	Case 2	Case 3	Case 4
Age at LT/gender	51 years/male	52 years/female	16 years/male	64 years/male
EBV serology pre-LT	Positive	Positive	Negative	Positive
Primary disease	HBV-cirrhosis	HCV-cirrhosis	Hyperoxaluria	Acute liver failure*
LT–PTLD[1]	5 months	6 months	73 months	20 months
Involved sites	Multiple	Single	Multiple	Multiple
Clinical presentation	Small bowel perforation	Biliary obstruction	Laryngeal obstruction	Poor general conditions
Tumor grading[2]	Polymorphic	Polymorphic	Polymorphic	Lymphomatous (B-cell lymphoma)
Clonality analysis	Monoclonal	Monoclonal	Monoclonal	Monoclonal
Tumor EBV status[3]	Positive	Positive	Positive	Positive
Nodal location	No	No	Yes	No
Extranodal location	Gastrointestinal tract	Liver	Laryngeal	Liver, peritoneum, bone marrow
PET/CT at diagnosis	Tumor at the right colon flexure	Not performed	Not performed	Not performed
Surgical treatment	Intestinal resection	None	Tumor resection	None
Additional therapy	Rituximab	Rituximab	Rituximab, radiotherapy & CHOP	Rituximab & CHOP
PET/CT 1-year follow-up	CR	FP[4]	CR	CR
Follow-up after PET/CT	8 months	15 months	42 months	10 months
Clinical outcome	CR	CR	TR [5]	CR

LT = liver transplantation; EBV = Epstein-Barr virus; CR = complete remission; TR = tumor relapse; FP = false positive finding in PET/CT.
*Unknown origin.
[1]Interval between liver transplantation and diagnosis of PTLD.
[2]Tumor grading according to the modified WHO classification proposed by Nalesnik et al. (9).
[3]Assessed with *in situ* hybridization.
[4]FP lesion confirmed by biopsy.
[5]Detected by PET/CT.

Contrast enhanced CT

CT imaging was performed with a multi-detector row scanner (Somatom Volume Zoom Siemens, Erlangen, Germany). For contrast enhancement, 120–150 mL of contrast media (Imagopaque, Amersham, AS, Oslo, Norway) was injected i.v. Scans covered the head, neck, thorax and abdomen to the level of the groins.

PET/CT imaging

All imaging and data acquisition was performed on a combined PET/CT system (Discovery LS, GE Medical Systems, Waukesha, WI) able to acquire CT images and PET data on the same patient in one session. A GE Advance NXi PET scanner and a multi-detector row helical CT (Light Speed Plus) are integrated in this dedicated system. An adequate coverage from head-to-pelvic floor in all patients examined was obtained. The patients were fasted for at least 4 h before the i.v. administration of an average dose of 10 mCi (370 MBq) of FDG. Additional technical information has been described in detail elsewhere (5). The attenuation-corrected PET images, the CT images and the coregistered PET/CT images were viewed by a board-certified radiologist and nuclear medicine physician using eNTEGRA software (GE Medical systems, Waukesha, WI). Image interpretation was based on the identification of regions with increased FDG uptake on the PET images and the anatomic delineation of all FDG-avid lesions on the coregistered PET/CT images. The maximal standard uptake value (SUV_{max}) of FDG-positive lesions was measured. A lesion was considered positive when SUV_{max} of a suspected lesion was more than 2.0.

Treatment of PTLD

Reduction of immunosuppression was immediately initiated after diagnosis in each patient with PTLD, as widely accepted (10). This strategy consisted in reduction of Cyclosporine of more than 50% to target C_2 plasmatic levels of 200–300 ng/mL and stopping other immunosuppressive drugs such as Mycophenolate Mofetil or Azathioprine (two cases). No patient was receiving prednisone at the time of diagnosis. Since all the patients developed CD20-positive PTLD lesions, monoclonal antibody therapy with rituximab was considered. In two patients with multiple sites PTLD, rituximab was initiated 2–3 weeks after diagnosis. Additional poor prognosis factors in these two patients were intra-peritoneal tumor rupture in one and rapid tumor progression in the other, i.e. weight loss, severe ascites, abdominal pain and pancytopenia (10). The other two patients were treated with rituximab after failure to control disease with reduction of immunosuppression: 8 weeks and 30 months after diagnosis due to increasing obstructive cholestasis and relapsing PTLD, respectively.

Rituximab was administered i.v. at a dose of 375 mg/m^2 once a week for 6–8 weeks. Surgical resection was indicated in two patients due to acute perforation of a small bowel tumor and airway obstruction. Additional chemotherapy (CHOP regimen: cyclophosphamine, doxorubicin, vincristine, prednisone) was used in one patient with B-cell lymphoma with poor performance status (ECOG 3 (11)) and in another patient with a relapsing CD20-negative upper airway tumor.

Tumor response and follow-up

Tumor response after treatment was assessed with conventional work-up 3–4 months after diagnosis. Complete remission was defined as complete clinical and radiological disappearance of tumor at all sites and the absence of new involved sites. Partial remission was defined as more than 50% of tumor size reduction. Further clinical follow-up included conventional work-up every 4–6 months. Additionally, each patient underwent a 1-year follow-up PET/CT (10–12 months from initial diagnosis). Relapse was defined as any tumor recurrence after complete response. Tumor biopsy was performed in each PET/CT positive finding. Information regarding how

PET/CT changed therapeutic strategies compared with conventional work-up was documented.

Results

The four cases are presented in Table 1. In each patient, complete tumor response was observed by conventional work-up 3–4 months after initial therapy.

Case 1

PET/CT was used to assess disease-free status after resection of a perforated PTLD tumor in the small bowel occurring 5 months after liver transplant. Surgical exploration and postoperative staging with conventional work-up failed to detect other tumors. However, a positive lesion (SUV_{max} 8.3) located in the right colon flexure was detected by PET/CT on 16th postoperative day (Figure 1). Based on this finding suggesting incomplete tumor clearance after surgery, a colonoscopic biopsy of the suspected lesion was performed. The existence of residual disease was confirmed histologically and considering the aggressive behavior of this tumor in the gastrointestinal tract (i.e. previous perforated tumor, multiple sites), systemic treatment with rituximab was initiated. The 1-year follow-up after treatment demonstrated a complete tumor response assessed by conventional work-up including PET/CT.

Case 2

Although a complete response was obtained with reduction of immunosuppression and rituximab, this patient developed multiple bilateral pulmonary nodules detected during a conventional follow-up 8 months after diagnosis of PTLD. In this case, we opted to follow the patient rather than changing management. PET/CT scan performed 2 months later demonstrated positive pulmonary lesions with low FDG uptake (SUV_{max} 2.2) (Figure 2). The lesions had increased in number and size as compared to the previous ceCT. Considering the clinical suspicion of PTLD recurrence based on morphological and functional criteria in this patient with already 10 months of reduction of immunosuppression, we opted for an aggressive diagnostic approach would be justified before modifying therapeutic strategy. Consequently, a video-assisted thoracoscopic pulmonary wedge resection was performed, but the pathological examination of the specimen showed only unspecific chronic granulomatous disease and no growth of microbiological cultures was observed (false positive PET/CT finding).

Case 3

This patient developed a late onset of PTLD as laryngeal tumor 73 months after liver transplantation. Because of incomplete surgical tumor resection, the patient received reduction of immunosuppression with radiotherapy. At 1 year of follow-up, no lesion was detected by PET/CT. However, conventional follow-up 30 months after initial diagnosis of PTLD showed enlarged cervical lymph nodes. A surgical biopsy revealed recurrent PTLD, and systemic treatment with rituximab in combination with local radiotherapy was applied. A partial response was achieved in the conventional work-up 4 months later and additional radiotherapy was given. One year later, it was difficult to differentiate vital tumor from scar tissue after surgery and radiotherapy in conventional ceCT, thus a PET/CT scan was performed. Although no tumor mass or pathological lymph nodes were detected, a new positive lesion (SUV_{max} 4.3) in the right submaxillar sinus was found (Figure 3). Tumor biopsy was performed confirming the lesion as PTLD. Due to the lack of CD-20 expression on the tumor cells at this point, CHOP chemotherapy was indicated for disease control.

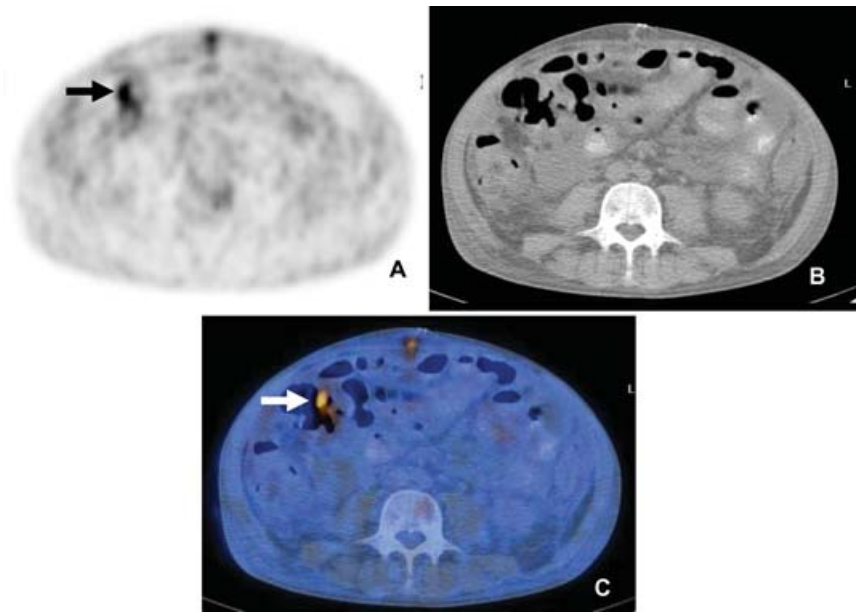

Figure 1: Axial abdominal images (A: PET; B: CT; C: fused PET/CT) demonstrating increased FDG uptake in the right colonic flexure (arrows) as well as in the surgical scar of the median laparotomy.

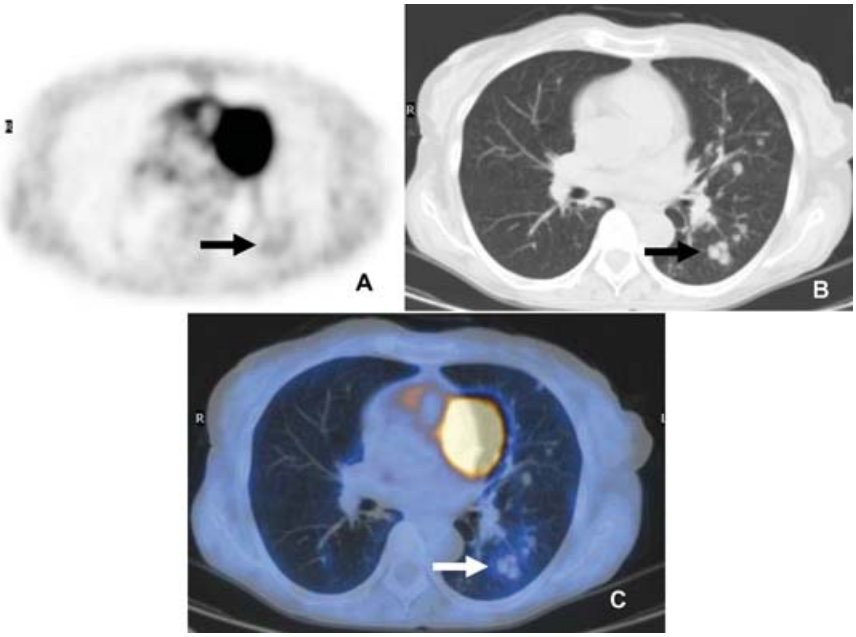

Figure 2: Axial pulmonary images (A: PET scan; B: CT scan; C: fused PET/CT) demonstrating a low FDG uptake in the left lower lobe as round-shaped nodular structures (arrows).

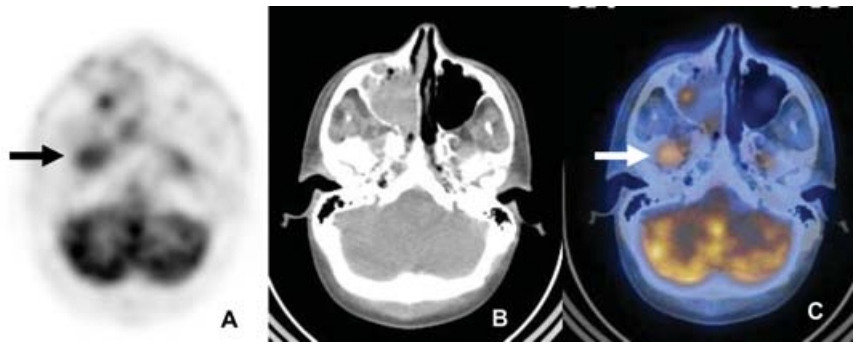

Figure 3: Axial cranial images (A: PET scan; B: CT scan; C: fused PET/CT) at the level of the maxillary sinuses. A soft-tissue obliteration with focal FDG uptake is observed in the region of right maxillary sinus (arrows).

Case 4

This patient presented with extra-nodal manifestation of PTLD 20 months after liver transplantation and reduced general status (ECOG 3 (11)). PTLD was proven histologically by liver biopsy, bone marrow puncture and ascites cytology. The patient completely responded to an aggressive combined treatment with reduction of immunosuppression, CHOP regimen and rituximab. PET/CT showed no FDG-positive lesions 1 year after treatment.

Discussion

This is the first study evaluating the novel imaging fusion technique combining PET and CT scan (PET/CT) for staging and therapy monitoring of PTLD in liver transplant recipients. Although only a small case series of four patients is presented, some insights in PET/CT as a tool for therapy monitoring of PTLD has been gained. Standard work-up missed the residual disease after surgery in one case and failed to detect tumor relapse in another patient. Compared to standard staging, the additional information provided by PET/CT resulted in change of medical management in three of four patients in our study.

In the absence of a clear consensus, the management of patients with PTLD after solid organ transplantation is one of the most controversial issues of this disease (12). While pathological examination is considered to be gold standard for diagnosis and classification of PTLD (9), no standardized imaging approach is available to assess tumor location, morphology and follow-up. Recently, the largest experience in treatment of PTLD with the anti-CD20 monoclonal antibody has been reported in patients after solid organ and bone marrow transplantation (13). Although a complete remission of PTLD was achieved in 20 of 32 patients (62%), no data were provided in terms of the imaging modality used for staging and tumor response assessment (13).

PET scan is a metabolic indicator of tumor viability in several types of tumors (5). Although, ceCT is currently the first-line imaging modality in Hodgkin disease (HD) and non-Hodgkin lymphoma (NHL), recent studies showed PET scan is more accurate for staging and follow-up (14). The

major advantage of PET over conventional imaging resided in its ability to detect disease in absence of morphological abnormalities (e.g. normal-size lymph nodes with tumor involvement) or to distinguish benign from malignant enlargement in lymph nodes and other tissues (4). Furthermore, ceCT may also fail to assess tumor response after treatment as fibrotic tissue cannot be distinguished from viable tumor (15). This limitation of ceCT scan was also observed in one patient of our series after surgery and radiotherapy (Case 3).

In most centers, ceCT scan is currently the imaging modality of choice for staging and follow-up patients with PTLD. In contrast to available data for different types of lymphomas (4,14–16), only sparse information has been reported regarding staging optimization of patients with PTLD after organ transplantation. One report suggested PET scan is a useful tool for staging PTLD in lung transplant recipients, but this study lacked pathological correlation of all positive findings (7). Poor resolution of PET scan images makes exact location of positive lesions difficult and histological confirmation of positive findings is sometimes ambiguous due to inexact mapping (5). The novel PET/CT technology provides simultaneous functional and anatomical information where PET positive lesions are projected directly in the CT scan. This advantage provides an exact anatomic identification of the lesions, which allows to accurately biopsy these lesions. The advantages of this imaging modality has been documented for staging of only a few tumor types including NHL or HD (5,17). While there are data suggesting that PET/CT is more accurate than ceCT for staging of patients with high-grade NHL or HD, the value of PET/CT in low-grade NHL and PTLD remains unclear (17).

Although we believe that PET/CT has interesting potential, it is crucial to take into account any shortcomings of PET scan to avoid misinterpretation of the PET findings. Small lesions can be missed, PET/CT cannot exclude minimal disease load. Although uncommon, it has been reported that some lymphomas with very low or negative FDG uptake can lead to underestimation of the extent of the disease (15,17). The accuracy for staging low-grade NHL or mucosa-associated lymphoid tissue (MALT)-type lymphoma has been disappointing (18,19). Therefore, given the histopatological variability of PTLD, there is reason to believe that the overall ability of FDG-PET to stage such patients, particularly those with polyclonal disease, could be limited (7). To overcome the problem of false negative results, our patients were followed after 1 year PET/CT with conventional work-up for a considerable period of time ranging from 8 to 42 months to detect occult FDG negative lesions. Since only one patient developed tumor recurrence 18 months after a negative PET/CT study (patient 3), we assumed that there was no false negative finding in our cases series. Therefore, a meticulous evaluation of the new PET/CT images along with routine follow-up is essential to overcome insecurities regarding extension of the disease in patients with PTLD.

Another potential limitation of PET/CT is the inability to differentiate between vital tumor tissue and chronic inflammation or infection. It remains a clinical challenge to distinguish a positive PTLD lesion from a false positive one which is likely to occur in immunosuppressed patients; e.g. sarcoidosis, mycosis, tuberculosis or any other infectious entity (15). In this case series, one patient with a false positive PET/CT finding during follow-up (Case 2) underwent an aggressive approach with pulmonary biopsy revealing a diseases-free status. Noteworthy, the false positive finding had a relatively low signal intensity (SUV_{max} 2.2) compared to the two true positive lesions (SUV_{max} 4.4 and 8.3). As over-staging of PTLD by PET/CT cannot be excluded, we recommend to biopsy all positive lesions to avoid excessive treatment. Larger series will define a safe SUV_{max} cut-off level of a PET positive signal intensity, and consequently, the dilemma of "what and when" to biopsy will be clarified thus avoiding unnecessary invasive procedures.

Equally important is the problem of under-staging of disease by standard work-up without PET/CT that could lead to delay of curative treatment in patients with PTLD. This issue is illustrated in one of our patients with a residual PTLD-positive colonic lesion after incomplete surgical resection (Case 1). This patient would have been treated, based on standard staging, with reduction of immunosuppression alone; however, PET/CT detected the remnant colonic tumor and treatment with rituximab could be immediately initiated.

We are aware that our study is somehow limited by the small size, its retrospective design, and that it could be influenced by a bias in favor of the new imaging technique. Having only monomorphic and no polymorphic PTLD cases, we cannot comment on the usefulness of PET for different subtypes that may significantly differ as in lymphomas (20). However, there are no data on the use of PET/CT in patients with PTLD after organ transplantation, and this report raises some potential pros and cons of the use of this novel imaging technique. Additionally, although most of previous studies have determined PET accuracy by comparison with results of CT or clinical follow-up but without inclusion of pathological data (6–8). Our study provides histological verification of all FDG-avid lesions in the PET/CT. Larger prospective multi-centric studies are needed to fully assess the usefulness of PET/CT for PTLD staging. Although, the current definition of PTLD is solely based on the histological classification, nonhistological modalities such as the novel PET/CT imaging could be of additional value for PTLD in terms of assessment of prognosis and treatment monitoring. The current case series illustrates that PET/CT information resulted in a substantial change of PTLD staging before and after therapy compared to standard work-up. In three out of four patients, PET/CT results led to a change of the medical management. It has to be stated that pathology remains the gold standard for diagnosis, and in some cases an aggressive approach to obtain histologically proven PTLD in patients with

PET/CT-positive findings is needed for best definition of the origin and extent of the disease and to find the optimal therapeutic strategy in these patients.

In conclusion, PET/CT is a very sensitive tool for follow-up of PTLD after liver transplantation. We find that PET/CT provides important additional information that may result in a modification of therapeutic strategy. Consequently, PET/CT is currently being prospectively evaluated for initial staging and follow-up of patients with PTLD in our program. However, accurate diagnosis with histology of all positive findings in the PET/CT remains mandatory, because a false positive result may result in unnecessary over-treatment. For this, the topographical information of PET/CT scan fusion imaging technique is superior to conventional PET or ceCT alone. PET/CT images improve guidance of biopsies resulting in less invasive procedures for patients and better material for pathologist. Further prospective studies are needed before implementing PET/CT in the routine clinical use in all solid organ transplant programs.

Acknowledgment

HP is the recipient of the Novartis fellowship in HPB surgery and liver transplantation.

References

1. Taylor AL, Marcus R, Bradley JA. Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation. Crit Rev Oncol Hematol 2005; 56: 155–167.
2. Bakker NA, van Imhoff GW, Verschuuren EA et al. Early onset post-transplant lymphoproliferative disease is associated with allograft localization. Clin Transplant 2005; 19: 327–334.
3. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.6.1. Cancer risk after renal transplantation. Post-transplant lymphoproliferative disease (PTLD): Prevention and treatment. Nephrol Dial Transplant 2002; 17 (Suppl. 4): 31–33, 35–36.
4. Kostakoglu L, Leonard JP, Kuji I, Coleman M, Vallabhajosula S, Goldsmith SJ. Comparison of fluorine-18 fluorodeoxyglucose positron emission tomography and Ga-67 scintigraphy in evaluation of lymphoma. Cancer 2002; 94: 879–888.
5. Selzner M, Hany TF, Wildbrett P, McCormack L, Kadry Z, Clavien PA. Does the novel PET/CT imaging modality impact on the treatment of patients with metastatic colorectal cancer of the liver? Ann Surg 2004; 240: 1027–1034; discussion 1035–1036.
6. Tamai K, Koyama T, Saga T et al. Posttransplant lymphoproliferative disorder in a lung transplant recipient. J Thorac Imaging 2005; 20: 280–283.
7. Marom EM, McAdams HP, Butnor KJ, Coleman RE. Positron emission tomography with fluoro-2-deoxy-D-glucose (FDG-PET) in the staging of post transplant lymphoproliferative disorder in lung transplant recipients. J Thorac Imaging 2004; 19: 74–78.
8. O'Conner AR, Franc BL. FDG PET imaging in the evaluation of post-transplant lymphoproliferative disorder following renal transplantation. Nucl Med Commun 2005; 26: 1107–1111.
9. Nalesnik MA. The diverse pathology of post-transplant lymphoproliferative disorders: The importance of a standardized approach. Transpl Infect Dis 2001; 3: 88–96.
10. Green M. ARaPJ. Epstein-Barr virus and lymphoproliferative disorders after transplantation. Am J Transplant 2004; 4 (Suppl. 10): 59–65.
11. Oken MM, Creech RH, Tormey DC et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649–655.
12. Dufour JF, Fey MF. What is the current treatment of PTLD after liver transplantation? J Hepatol 2006; 44: 23–26.
13. Milpied N, Vasseur B, Parquet N et al. Humanized anti-CD20 monoclonal antibody (Rituximab) in post transplant B-lymphoproliferative disorder: A retrospective analysis on 32 patients. Ann Oncol 2000; 11 (Suppl. 1):113–116.
14. Hicks RJ, Mac Manus MP, Seymour JF. Initial staging of lymphoma with positron emission tomography and computed tomography. Semin Nucl Med 2005; 35: 165–175.
15. Jerusalem G, Hustinx R, Beguin Y, Fillet G. Evaluation of therapy for lymphoma. Semin Nucl Med 2005; 35: 186–196.
16. Cremerius U, Fabry U, Wildberger JE et al. Pre-transplant positron emission tomography (PET) using fluorine-18-fluorodeoxyglucose (FDG) predicts outcome in patients treated with high-dose chemotherapy and autologous stem cell transplantation for non-Hodgkin's lymphoma. Bone Marrow Transplant 2002; 30: 103–111.
17. Schaefer NG, Hany TF, Taverna C et al. Non-Hodgkin lymphoma and Hodgkin disease: Coregistered FDG PET and CT at staging and restaging—do we need contrast-enhanced CT? Radiology 2004; 232: 823–829.
18. Najjar F, Hustinx R, Jerusalem G, Fillet G, Rigo P. Positron emission tomography (PET) for staging low-grade non-Hodgkin's lymphomas (NHL). Cancer Biother Radiopharm 2001; 16: 297–304.
19. Hoffmann M, Kletter K, Diemling M et al. Positron emission tomography with fluorine-18-2-fluoro-2-deoxy-D-glucose (F18-FDG) does not visualize extranodal B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT)-type. Ann Oncol 1999; 10: 1185–1189.
20. Elstrom R, Guan L, Baker G et al. Utility of FDG-PET scanning in lymphoma by WHO classification. Blood 2003; 101: 3875–3876.