Effect of Whole-Body ^{18}F-FDG PET Imaging on Clinical Staging and Management of Patients with Malignant Lymphoma

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Correct staging is important in selecting the appropriate treatment for lymphoma patients. PET imaging with ^{18}F-FDG is useful for staging of lymphoma as well as for monitoring of therapy. However, to our knowledge, the clinical impact of PET on staging and management of lymphoma patients has not been reported. **Methods:** Standardized questionnaires were mailed to referring physicians asking them whether and how the results of PET imaging had influenced clinical staging and management of the disease in their patients. Management changes, when present, were classified as intermodality (e.g., medical to surgical, surgical to radiation, medical to no treatment) or intramodality (e.g., altered medical, surgical, or radiotherapy approach). **Results:** The referring physicians returned 52 of 108 questionnaires (48.1%). Physicians indicated that PET led to a change in the clinical stage in 44% of patients: 21% were upstaged and 23% were downstaged. Findings of the PET examination resulted in intermodality changes in management in 42% of patients, in intramodality changes in 10%, and in a combination of the management changes in 10%. Other, not further specified, treatment changes were reported in 6% of patients. PET did not result in any management changes in only 32% of patients. **Conclusion:** This survey-based study of referring physicians indicates that FDG PET has a major impact on the management of lymphoma patients, contributing to changes in clinical stage in 44% and changes in treatment in >60% of cases.

Key Words: lymphoma; ^{18}F-FDG; PET; patient management

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Lymphoma—that is, Hodgkin's disease (HD)—and non-Hodgkin's lymphoma (NHL) are the fifth most common type of cancer diagnosed and the third most common form of cancer deaths in the United States (*1*). In the past 15 y, NHL has shown an approximately 50% increase in incidence (*2*).

HD tends to develop in an orderly fashion: It typically originates in lymphoid tissues and can spread to other organs (*3*). In contrast, NHL is a heterogeneous group of lymphoproliferative malignances with different patterns of behavior and varying responses to treatment. Its course is less predictable than that of HD and it has a greater predilection for extranodal sites (*4*). However, for both entities, HD and NHL, the prognosis depends on the histologic type, stage of disease, and treatment.

Correct staging is important in selecting the appropriate treatment for lymphoma patients. For instance, >70% of patients with newly diagnosed HD are curable with stage-adjusted radiation therapy or combination chemotherapy regimens (or both) (*5,6*). In addition to history, physical examination and laboratory data, clinical staging, restaging after treatment, and detection of recurrence depend to a large degree on imaging studies, including CT, MRI, and gallium scanning.

Because tumors rely on glucose as their substrate for energy production and replication, whole-body PET imaging with ^{18}F-FDG is useful for staging of lymphoma patients as well as for monitoring of therapeutic effects. Oxidative metabolism through the Krebs cycle is nearly absent in cancer cells (*7*). Therefore, tumors switch to glycolysis, requiring a 19-fold increase in glucose consumption per mole of adenosine triphosphate produced compared with use of the Krebs cycle. In addition, through the hexose-monophosphate shunt, further increases in glycolysis provide necessary substrate for DNA and RNA synthesis required for cell replication (*8*). Because of the accelerated rate of glycolysis in neoplasms, PET imaging of glucose utilization with FDG permits an excellent differentiation of malignant tumors from normal tissue and benign processes.

Although the usefulness of PET for staging and treatment evaluation of lymphoma patients has been established (*9–17*), the degree to which the information obtained from whole-body PET is incorporated into the clinical manage-

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ment of lymphoma patients by the referring physician remains to be determined. The present survey was undertaken to evaluate the effect of FDG PET on clinical staging and management of patients with HD and NHL from the referring physician's perspective.

MATERIALS AND METHODS

Questionnaires were sent to 65 referring physicians of 108 patients with lymphoma who underwent whole-body PET at a university-based clinical service in the Ahmanson Biological PET Imaging Clinic of the University of California, Los Angeles (UCLA) Medical Center ($n = 44$) and at a private clinical service in the Northern California PET Imaging Center (NCPIC) in Sacramento ($n = 64$) between October 1998 and January 2000. After the PET report had been issued, standardized questionnaires were mailed to the referring physicians asking them whether and how the results of PET imaging had influenced clinical staging and management of their patients. The characteristics of the pre-PET and post-PET questionnaires have been described (*18*). In brief, the pre-PET questionnaire asked the referring physicians to indicate the clinical indication for the PET scan as well as the chosen management plan before PET. The post-PET questionnaire inquired whether and how the results of the PET study had altered the stage of disease (using the Ann Arbor Classification (*19*)) and patient management. Management changes were classified into 2 categories as follows: intermodality changes were defined as changes between treatment modalities—for example, from surgery to radiation therapy. Intramodality changes were defined as changes within 1 treatment modality—for instance, from 1 to another chemotherapeutic treatment. All completed questionnaires were returned within a 4-wk period.

Patient Population

The study population consisted of 61 male and 47 female patients (mean age, 50 ± 18 y; age range, 15–79 y). Only questionnaires with completed pre-PET and post-PET evaluation were included in the analysis. Fifty-two of the returned questionnaires met the above criteria and were therefore included in the analysis. Thus, the resulting overall response rate was 48.1% (it was higher with 57% at UCLA [25/44 forms] vs. 42% at the NCPIC [27/64 forms]; $P = 0.033$).

This group of 52 respondents consisted of 27 male and 25 female patients (mean age, 51 ± 18 y; age range, 15–79 y). Eighteen patients had HD and 34 had NHL. Seventy-two percent of the patients were referred by oncologists, 6% by radiation oncologists, and 22% by general internists and general practitioners.

Six patients with HD (33%) and 13 with NHL (38%) were referred for more accurate staging, 5 patients with HD (28%) and 8 with NHL (24%) for monitoring of therapy, 2 patients with HD (11%) and 5 with NHL (15%) for monitoring of the course of disease and restaging, and 2 patients with HD (11%) and 3 with NHL (9%) for more accurate diagnosis. The category "more accurate diagnosis" referred to abnormalities identified on CT or MRI after treatment that could not be classified clearly as malignant or benign. For instance, abnormal soft tissue can be found after the treatment of lymphoma, but anatomic imaging frequently cannot distinguish whether this represents residual tumor tissue or scar. Finally, 3 patients with HD (17%) and 5 with NHL (15%) were referred for >1 or other than the above reasons.

PET Image Acquisition and Interpretation

An ECAT EXACT HR or HR+ whole-body PET scanner (CTI/Siemens, Knoxville, TN) was used. These tomographs cover an axial field of view of 15 cm and acquire 47 or 62 image planes simultaneously. The resolution of reconstructed images ranges from 8 to 10 mm (*20*,*21*).

A routine clinical PET imaging protocol was used: After a 6-h fasting period, approximately 555 MBq (15 mCi) FDG were injected intravenously. This was followed by a 45-min uptake period to allow for trapping of FDG-6-phosphate in tumor tissue. Images were acquired from 6 to 9 bed positions (each covering a 15-cm axial field of view) per patient, with an acquisition time of 6 min per bed position.

AT UCLA, the images were reconstructed using standard filtered backprojection. No attenuation correction was performed. At the NCPIC, attenuation correction was performed and iterative reconstruction algorithms were used. A previous study showed that these reconstruction algorithms yield a comparable diagnostic accuracy (*22*). The images were then reoriented into coronal, sagittal, and transaxial views.

Image interpretation and reporting of findings were part of daily routine clinical read-out sessions. A 3-dimensional volume display was used for lesion detection. Clinical data and CT images (or reports) were available at the time of readout in most cases. A semiquantitative analysis of FDG uptake, such as standardized uptake value, was not performed because this is not part of the routine clinical protocol at our institutions.

Statistical Analysis

Barnard's unconditional exact test (*23*) was used for intergroup comparison between patients with HD versus those with NHL. The following categoric variables were compared: indication for PET, pre-PET management strategies, PET-induced changes in clinical stage, and PET-induced changes in patient management. $P < 0.05$ was considered significant.

RESULTS

Impact of PET Findings on Clinical Stage

PET led to a change in the clinical stage in 44% of patients ($n = 23$): 21% were upstaged ($n = 11$) and 23% were downstaged ($n = 12$). No change in the clinical stage was reported in 52% of respondents ($n = 27$), and in 4% of questionnaires ($n = 2$) this question was not answered. In the group with HD, 5 patients were upstaged (28%) and 5 were downstaged (28%) as the result of PET findings. No change in the clinical stage was noted in another 7 patients (39%), and the question was not answered in 1 case (6%). PET findings did not alter the clinical stage in 59% of patients with NHL ($n = 20$), whereas upstaging occurred in 6 patients (18%) and downstaging occurred in 7 patients (20%). The question was not answered in 1 case (3%).

Notably, in 12 patients (3 with HD, 9 with NHL) the referring physicians indicated a pre-PET stage 0 (complete remission, no further treatment planned) on the basis of clinical findings and CT or MRI. In these cases, PET was ordered to confirm the remission of disease. However, only 6 of these patients had negative FDG PET scans, whereas residual or recurrent disease was found in the remaining 6 patients (2 with HD, 4 with NHL).

Overall, the effect of PET on clinical staging did not differ between patients with HD and those with NHL (P = not significant).

PET-Induced Changes in Patient Management

Before PET, the therapeutic strategy was medical treatment in 40% of patients (n = 21), radiation therapy in 11.5% (n = 6), surgical treatment in 4% (n = 2), and a combination of the above in 13.5% of patients (n = 7). Moreover, 14 patients (27%) were believed to be in remission on the basis of clinical and CT findings and were therefore not scheduled for any further therapy. In these cases, PET was ordered to confirm remission and rule out residual tumor foci that had not been detected by CT or MRI. The question of PET-induced changes in management was not answered for 2 patients (4%).

In the group with HD, 8 patients were scheduled to undergo medical treatment (44%). Radiation treatment was planned in 4 patients (22%), and no further treatment was planned in 4 patients who were thought to be in remission (22%). A combination of radiation and chemotherapy was planned in 2 patients (11%).

In patients with NHL, the chosen pre-PET therapeutic option was medical treatment in 13 patients (38%), radiation in 2 (6%), surgery in 2 (6%), and a combination of the above in 5 patients (15%). No further treatment was planned in 10 patients (30%) because they were thought to be in remission; the question was not answered in 2 cases (6%).

PET resulted in intermodality management changes in 42% of patients (n = 22; 7 with HD, 15 with NHL), in intramodality changes in 10% (n = 5; 2 with HD, 3 with NHL), and in a combination of the management changes in 10% (n = 5; 2 with HD, 3 with NHL). PET did not affect patient management in 32% of the patients (n = 17; 7 with HD, 10 with NHL). Other, not further specified, treatment changes were reported in 3 patients (6%).

The specific management changes for patients with HD and NHL are listed in Table 1. No significant differences were found between the 2 patient groups (P = not significant). Two examples of patients in whom the PET findings led to a change in clinical stage or change in treatment modality (or both) are shown in Figure 1.

TABLE 1
Management Changes for Individual Patients as Result of PET Findings

Change	HD		NHL	
	n	%	*n*	%
Intermodality	7	38.8	15	44.1
From surgery to medical treatment	1		0	
From surgery to radiation	0		0	
From surgery to no treatment	0		0	
From medical treatment to surgery	0		0	
From medical treatment to radiation	1		2	
From medical treatment to no treatment	1		4	
From radiation to surgery	0		0	
From radiation to medical treatment	1		2	
From radiation to no treatment	1		1	
From no treatment to surgery	0		1	
From no treatment to medical treatment	1		4	
From no treatment to radiation	1		1	
Intramodality	2	11.1	3	8.8
Change in surgical approach	0		1	
Change in medical approach	2		1	
Change in radiation approach	0		1	
Combination of management	2	11.1	2	5.9
None	7	38.8	10	29.4
Other management changes	0		4	11.8

No significant differences were found between 2 patient groups.

DISCUSSION

The current survey shows that PET has a major impact on staging and managing lymphoma patients. The clinical stage changed in 44% and the clinical management changed in 62% of the patients. Stage and management were affected to a similar degree in HD and NHL patients.

Thus, the effects of PET on managing lymphoma patients appear to be more dramatic than reported previously. In these studies, PET led to changes in the clinical stage and management in 10%–20% of the patients (*10,12,14,17,24*). This discrepancy is likely explained by several factors. First, to our knowledge, this study is the first to evaluate the effects of whole-body PET on staging and management from the referring physician's perspective. Thus, images were not reinterpreted retrospectively for the purpose of this study; rather, referring physicians used the information provided by the original written clinical PET reports for their clinical management decisions. Second, survey studies are subject to a responder bias, as evidenced by the current response rate of 48.1%. Although this is within the range of response rates reported for similar studies (*25–31*), only those physicians who believed that PET was useful for patient management might have completed the questionnaire. However, it is important to note that if (in the extreme case) all of the remaining 51.9% of questionnaires had concluded that PET did not affect stage and management (which is unlikely), PET still would have altered the stage in 21% and management in 30% of all patients. These results would then be comparable with the above studies (*10,12,14,24*). A third reason might be that referring physicians have now gained more experience with PET and have become more confident in the information it provides. This, among other factors, might also explain the higher response rate at UCLA (57% vs. 42% at the NCPIC), where PET imaging has been available for research and clinical purposes for more than a decade.

Several factors influence the participation of physicians in clinical trials and surveys. Among them are the physician's appreciation of the scientific purpose and clinical value of a trial, the simplicity of the study protocol and questionnaires, ethical aspects, and the quality of communication with the trial center (*32*). Other factors include the physicians' need to share their experience and to self-

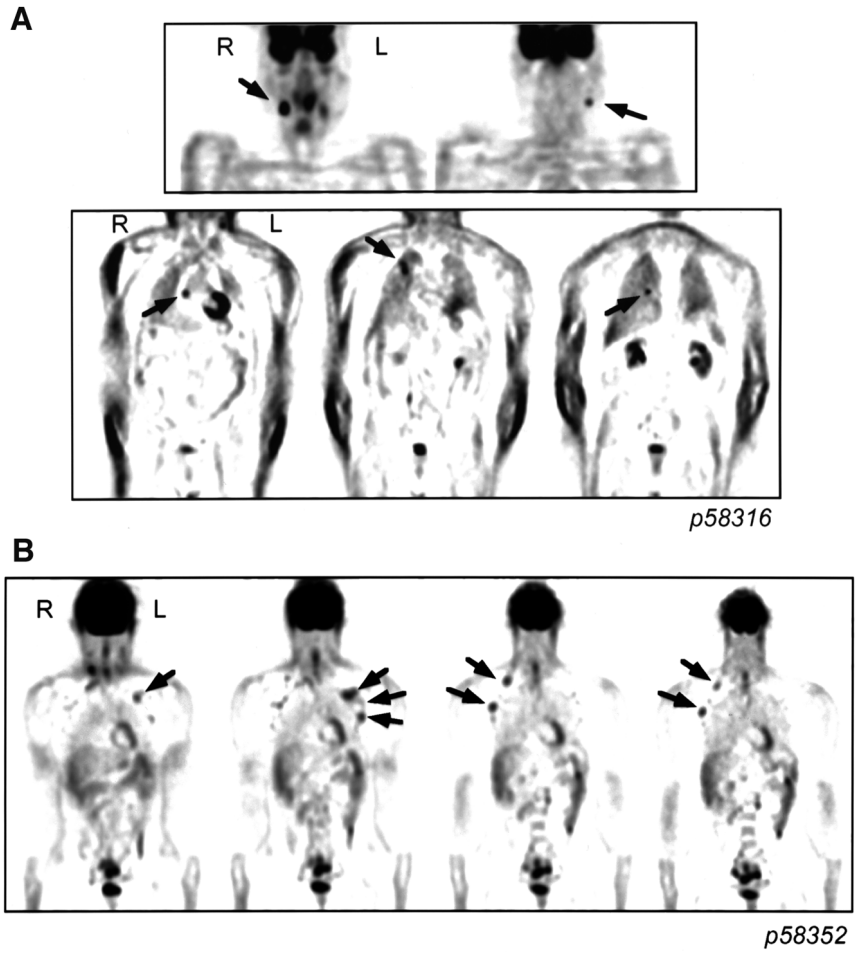

FIGURE 1. (A) A 70-y-old male patient who presented initially with NHL of right neck. PET was performed for staging and revealed additional involvement of left cervical and mediastinal lymph nodes as well as right lung (arrows). This finding resulted in upstaging from stage I to stage II and change in treatment from irradiation to medical treatment. (B) A 27-y-old female patient with HD. After treatment with chemotherapy, she had cervical recurrence 2 y later. Repeated chemotherapy resulted in remission. Five months later, CT scan revealed multiple equivocal 8- to 10-mm lymph nodes in right axilla. PET revealed right axillary lymphadenopathy, right supra- and infraclavicular and left infraclavicular nodes (arrows), and retroperitoneal and pelvic involvement. As result of PET, patient underwent salvage chemotherapy followed by allogenic bone marrow transplantation.

evaluate in comparison with colleagues in the same field (*33*). Finally, several studies have also indicated that seemingly minor issues such as financial incentives for the referring or participating physicians, use of prestamped envelopes, and personalized mail packages may increase the response rate by up to 18% (*27,29*). Others have emphasized the influence of the physician's specialty in trial participation (*26*). However, this was not confirmed in the current study. For instance, 72% of the referring physicians were oncologists and 22% were general practitioners or internists; the respective survey response rates were 46% and 50%. Another limitation of the study is that referring physicians may have responded to the questionnaires by recalling the intended management plan rather than obtaining the information from chart review. However, because all questionnaires were returned within 4 wk after PET, it appears likely that the referring physicians were familiar with each patient and their treatment plan.

The clinical usefulness of whole-body FDG PET for staging of lymphoma has been established (*9–17,24*). FDG PET has a higher sensitivity and specificity for the detection of nodal and extranodal disease than anatomic imaging (*9–12,17*). As a whole-body imaging device, PET also has a higher sensitivity for the detection of bone marrow involvement compared with marrow biopsy, which is usually limited to the bony pelvis (*14,15*).

Hoh et al. (*17*) were the first to evaluate the use of whole-body PET for staging of lymphoma patients. Compared with a conventional staging algorithm (including a combination of CT or MRI, gallium and bone scanning, lymphography, and staging laparotomy), whole-body PET showed additional sites of tumor involvement in 28% of patients. These authors also provided evidence for the cost-effectiveness of whole-body PET imaging in comparison with the conventional staging algorithm. Moog et al. (*10*) compared CT and PET in 81 patients with newly diagnosed lymphoma. Compared with CT, the PET study revealed an additional 24 sites of tumor involvement, leading to a change in the clinical stage in 16% of patients. Bangerter et al. (*12*) studied 44 patients with newly diagnosed HD with FDG PET and compared these findings with those from other modalities, including CT, sonography, bone marrow biopsy, liver biopsy, conventional bone scanning, and laparotomy. FDG PET detected additional lesions in 5 cases; it was negative in 1 patient with suspicious CT findings, which was proven by biopsy as a true-negative finding. As a consequence of PET findings, the treatment strategy had to be changed in all 6 cases—that is, 14% of patients.

The prognostic value of FDG PET in patients with malignant lymphoma also has been addressed in prior studies (*34–37*). The degree of decrease in FDG uptake in response to chemotherapy predicted the response to treatment as early as 42 d after initiation of treatment (*37*). Consistently, Jerusalem et al. (*16*) showed that residual FDG uptake in tumor tissue is a strong predictor of relapse or progression of disease as well as a predictor of survival. Zinzani et al. (*13*) reported similar findings in a study of 44 patients with HD and aggressive NHL.

These earlier studies provided the evidence for the Health Care Finance Administration to approve reimbursement for whole-body PET imaging for staging and restaging of lymphoma patients. Financial reimbursement and the reproducibly high accuracy of whole-body FDG PET have contributed to its growing acceptance as a clinical imaging tool for staging and restaging of lymphoma patients. Findings in the current survey contribute further to this growing body of data, showing that whole-body FDG PET imaging led to changes in the clinical stage in as many as 44% and changes in clinical management in 62% of lymphoma patients.

CONCLUSION

In this study, whole-body PET imaging led to changes in the clinical stage in 44% and changes in treatment strategy in 62% of patients with lymphoma. These data suggest that PET has become an accepted imaging modality for staging and restaging of lymphoma patients among university and community physicians. Future studies should evaluate whether and to what extent these PET-induced changes in the clinical stage and management translate into an improvement in patient outcome and survival.

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REFERENCES

1. Landis SH, Marray T, Bolden S, Wingo PA. Cancer statistics 1999. *Cancer J Clin.* 1999;49:8–31.
2. Devesa S, Fears T. Non-Hodgkin's lymphoma time trends: United States and international data. *Cancer Res*. 1992;52(19 suppl):5432S–5439S.
3. Urba WJ, Longo DL. Hodgkin's disease. *N Engl J Med*. 1992;326:678–687.
4. Shipp MA, Mauch PM, Harris NL. Non-Hodgkin's lymphoma. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. Philadelphia, PA: Lippincott-Raven; 1997:2165–2220.
5. Rosenberg SA, Kaplan HS. The evolution and summary results of the Stanford randomized clinical trials of the management of Hodgkin's disease: 1962–1984. *Int J Radiat Oncol Biol Phys*. 1985;11:5–12.
6. Anderson H, Crowther D, Deakin D, et al. A randomized study of adjuvant MVPP chemotherapy after mantle radiotherapy in pathologically staged IA-IIB Hodgkin's disease: 10-year follow-up. *Ann Oncol*. 1991;2:9–15.
7. Warburg O. *Metabolism of Tumors*. New York, NY: Richard R. Smith; 1931.
8. Weber G. Enzymology of cancer cells: part 2. *N Engl J Med*. 1977;296:541–551.
9. Moog F, Bangerter M, Diedrichs C, et al. Lymphoma: role of whole body 2-deoxy-2-[F-18]fluoro-D-glucose (FDG) PET in nodal staging. *Radiology*. 1997;203:795–800.
10. Moog F, Bangerter M, Diedrichs C, et al. Extranodal malignant lymphoma: detection with FDG PET versus CT. *Radiology*. 1998;206:475–481.
11. Stumpe KDM, Urbinelli M, Steinert HC, Glanzmann C, Buck A, von Schulthess GK. Whole body positron emission tomography using fluorodeoxyglucose for staging of lymphoma: effectiveness and comparison with computed tomography. *Eur J Nucl Med*. 1998;25:721–728.
12. Bangerter M, Moog F, Buchmann I, et al. Whole body 2-[^{18}F]-fluro-2-deoxy-D-glucose positron emission tomography (FDG-PET) for accurate staging of Hodgkin's disease. *Ann Oncol*. 1998;9:1117–1122.
13. Zinzani PL, Magagnoli M, Chierichetti F, et al. The role of positron emission tomography (PET) in the management of lymphoma patients. *Ann Oncol*. 1999;10:1181–1184.
14. Moog F, Bangerter M, Kotzerke J, Guhlmann A, Frickhofen A, Reske S. 18-F-fluorodeoxyglucose positron emission tomography as a new approach to detect lymphomatous bone marrow. *J Clin Oncol*. 1998;16:603–609.
15. Carr R, Barrington SF, Madan B, et al. Detection of lymphoma in bone marrow by whole body positron emission tomography. *Blood*. 1998;91:3340–3346.
16. Jerusalem G, Beguin Y, Fassotte MF, et al. Whole body positron emission tomography using ^{18}F-fluorodeoxyglucose for posttreatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. *Blood*. 1999;94:429–433.
17. Hoh CK, Glaspy J, Rosen P, et al. Whole body FDG PET imaging for staging of Hodgkin's disease and lymphoma. *J Nucl Med*. 1997;38:343–348.
18. Meta J, Seltzer M, Schiepers C, et al. Impact of ^{18}F-FDG PET on managing patients with colorectal cancer: the referring physician's perspective. *J Nucl Med*. 2001;42:586–590.
19. Carbone PP, Kaplan HS, Mushoff K, et al. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res*. 1971;31:1860–1861.
20. Wienhard K, Dahlbom M, Eriksson L, et al. The ECAT EXACT HR: performance of a new high resolution positron scanner. *J Comput Assist Tomogr*. 1994;18:110–118.
21. Adam L, Zaers J, Ostertag H, Trojan H, Bellmann M, Brix G. Performance evaluation of the whole body PET scanner ECAT EXACT HR+ following the IEC standard. *IEEE Trans Nucl Sci*. 1997;44:1172–1179.
22. Kotzerke J, Guhlmann A, Moog F, et al. Role of attenuation correction for fluorine-18 fluorodeoxyglucose positron emission tomography in the primary staging of malignant lymphoma. *Eur J Nucl Med*. 1999;26:31–38.
23. Suissa S, Shuster J. Exact unconditional test for the 2×2 binomial table. *J R Stat Soc, Series A*. 1985;148:317–327.
24. Delbeke D, Morgan DS, Kovalsky E, et al. F18-fluorodeoxyglucose imaging with positron emission tomography for initial staging of Hodgkin's disease and lymphoma [abstract]. *J Nucl Med*. 2000;41(suppl):275P.
25. Temple-Smith M, Mulvey G, Doyle W. Maximising response rate in a survey of general practitioners: lessons from a Victorian survey on sexually transmitted diseases. *Aust Fam Physician*. 1998;27(suppl 1):S15–S18.
26. Fallowfield L, Ratcliffe D, Souhami R. Clinician's attitude to clinical trials of cancer therapy. *Eur J Cancer*. 1997;33:2221–2229.
27. Maheux B, Legault C, Lambert J. Increasing response rate in physician's mail surveys: an experimental study. *Am J Public Health*. 1989;79:638–639.
28. Shiono PH, Klebanoff MA. The effect of two mailing strategies on the response to a survey of physicians. *Am J Epidemiol*. 1991;134:539–542.
29. Everett SA, Price JH, Bedell AW, Telljohann SK. The effect of monetary incentive in increasing the return rate of a survey to family physicians. *Eval Health Prof*. 1997;20:207–214.
30. Ellis PM, Butow PN, Simes RJ, Tattersall MH, Dunn SM. Barriers to participation in randomized clinical trials for early breast cancer among Australian cancer specialists. *Aust NZ J Surg*. 1999;69:486–491.
31. Donaldson GW, Moinpour CM, Bush NE, et al. Physician participation in research surveys: a randomized study of inducements to return mailed research questionnaires. *Eval Health Prof*. 1999;22:427–441.
32. Hjorth M, Holmberg E, Rodjer S, Taube A, Westin J. Physician's attitude toward clinical trials and their relationship to patient accrual in a Nordic multicenter study on myeloma. *Control Clin Trials*. 1996;17:372–386.
33. Chauvin P, Valleron AJ. Participation of French general practitioners in public health surveillance: a multidisciplinary approach. *J Epidemiol Community Health*. 1998;52(suppl 1):2S–8S.
34. Lapela M, Leskinen S, Minn HRI, et al. Increased glucose metabolism in untreated non-Hodgkin's lymphoma: a study with positron emission tomography and fluorine-18 fluorodeoxyglucose. *Blood*. 1995;86:3522–3527.
35. Okada J, Yoshikawa K, Itami M, et al. Positron emission tomography using fluorine-18-fluorodeoxyglucose in malignant lymphoma: a comparison with proliferative activity. *J Nucl Med*. 1992;33:325–329.
36. Rodriguez M, Rehn S, Ahlstrom H, Sundstrom C, Glimelius B. Predicting malignancy grade with PET in non-Hodgkin's lymphoma. *J Nucl Med*. 1995;36:1790–1796.
37. Römer W, Hanauske AR, Ziegler S, et al. Positron emission tomography in non-Hodgkin's lymphoma: assessment of chemotherapy with fluorodeoxyglucose. *Blood*. 1998;91:4464–4471.