The Impact of PET on the Management of Lung Cancer: The Referring Physician's Perspective

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^{18}F-FDG PET is a molecular whole-body imaging modality that is increasingly being used for diagnosing, staging, and restaging cancer. The objective of this study was to determine referring physicians' perspectives on the impact of ^{18}F-FDG PET on staging and management of lung cancer. **Methods:** A questionnaire was sent to the 292 referring physicians of 744 consecutive patients with known or suspected lung cancer who were evaluated with PET. Questionnaires on 274 patients were returned (response rate, 37%). Management changes were categorized as intermodality (e.g., surgery to medical, surgery to radiation, and medical to no treatment) or intramodality (e.g., altered medical, surgical, or radiotherapy approach). **Results:** The primary reasons for PET referral were staging of lung cancer in 61% of patients, diagnosis in 20%, and monitoring of therapy or the course of disease in 6%. Physicians reported that PET caused them to change their decision on clinical stage in 44% of all patients: The disease was upstaged in 29% and downstaged in 15%. PET resulted in intermodality management changes in 39% of patients, whereas 15% had an intramodality change. **Conclusion:** This survey-based study of referring physicians suggests that PET has a major impact on staging and management of lung cancer.

Key Words: ^{18}F-FDG PET; lung cancer staging; questionnaire

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Over the past several years, ^{18}F-FDG PET has emerged as an important clinical tool for diagnosing, staging, and monitoring the therapy of cancer (*1,2*). PET is a molecular whole-body imaging modality that allows one to noninvasively image biologic processes such as glucose use by tumors. The utility of ^{18}F-FDG PET in tumor imaging is based on the observation first made by Warburg et al. (*3*) more than 70 y ago that many types of malignant tumors have an accelerated rate of glycolysis. This amplification is necessary because oxidative metabolism is markedly reduced in tumor cells, which therefore rely on adenosine triphosphate generated from anaerobic glycolysis. Glucose metabolism needs to be amplified dramatically to meet the energy requirements of rapidly growing tumor cells. In addition, accelerated rates of the hexose monophosphate shunt provide the carbon backbone for DNA and RNA synthesis in growing tumors (*4,5*). Glucose transport across tumor cell membranes and expression of hexokinase are also accelerated (*6,7*). These alterations of cellular metabolism are common to all neoplastic cells.

The glucose analog ^{18}F-FDG is taken up by tumor cells and phosphorylated by hexokinase to ^{18}F-FDG-6-PO4. Unlike glucose-6-PO4, ^{18}F-FDG-6-PO4 cannot be metabolized in the glycolytic pathway and remains trapped intracellularly. Thus, the distribution of ^{18}F-FDG-6-PO4 in normal and abnormal tissue can be imaged with PET.

Numerous studies have shown that ^{18}F-FDG PET is highly accurate for diagnosing and staging lung cancer (*8*). ^{18}F-FDG PET provides diagnostic information beyond that obtained through standard anatomic imaging modalities such as CT or MRI. In addition, retrospective studies and modeled decision tree analyses have suggested that the information provided by ^{18}F-FDG PET affects management in 20%–40% of all cases of cancer (*9,10*). Because reimbursement by public and private insurance organizations is now readily available, ^{18}F-FDG PET is rapidly gaining acceptance in the medical community and is being incorporated into the staging and treatment algorithms used by medical, surgical, and radiation oncologists.

Several groups have reported that ^{18}F-FDG PET has a considerable impact on the management of lung cancer (*11–13*). However, referring physicians' perspectives on the impact of ^{18}F-FDG PET on staging and management of lung cancer are unknown.

We recently reported that referring physicians altered their decision on clinical stage in 42%, 44%, and 31% of patients with colorectal cancer, lymphoma, and breast cancer, respectively, because of PET findings. Further, management changes were prompted in response to clinical PET findings in 50% of patients (*14–16*). The aim of the current study was to determine referring physicians' perspectives

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on the impact of ^{18}F-FDG PET on staging and management of lung cancer.

MATERIALS AND METHODS

Questionnaire Survey

During 13 mo between November 1998 and December 1999, questionnaires were faxed to the 292 referring physicians of 744 consecutive lung cancer patients for whom an ^{18}F-FDG PET scan was clinically ordered. Forty-eight percent of the referring physicians responded to the questionnaire for 37% of the patients. The questionnaire contained 2 sections, as described previously (*14*). The first section queried referring physicians on their reason for ordering the PET scan and their choice of management before the PET evaluation (pre-PET section). The second section queried physicians on whether the PET scan changed their decision on clinical stage and subsequent management (post-PET section). Both the pre-PET and the post-PET sections were faxed under separate cover within 1 wk after the PET scan. Questionnaires were received within 4 wk of the PET scan.

The questionnaire was considered completed if both the pre-PET and the post-PET sections were returned. The questionnaire was considered completed regardless of whether every question had been answered. Unanswered questions were identified as "no answer" in the tabulated results. If either the pre-PET or the post-PET section was not returned, the questionnaire was classified as incomplete and was excluded from further analysis. A web-based data management system was used for data collection and analysis (*17*).

Management changes were grouped into intermodality and intramodality categories. An intermodality change consisted of a management change between treatment modalities (e.g., surgery to medical treatment), and an intramodality change consisted of a management change within a treatment modality (e.g., change in chemotherapy regimen).

Image Acquisition and Reconstruction

Patients were scanned at 1 of 2 clinical PET centers: UCLA Medical Center ($n = 278$) or the Northern California PET Imaging Center (NCPIC; $n = 466$). Each PET scan was obtained on a high-resolution dedicated system (ECAT EXACT or ECAT HR+; CTI, Knoxville, TN/Siemens Medical Systems, Inc., Hoffman Estates, IL). The resolution for reconstructed images ranged from 8 to 12 mm. The characteristics of these scanners have been described previously (*18,19*). At UCLA Medical Center, non–attenuation-corrected images were reconstructed using standard filtered backprojection; at the NCPIC, iterative image reconstruction of attenuation-corrected images was performed (*20,21*).

All patients fasted for at least 6 h before receiving an intravenous injection of 370–555 MBq ^{18}F-FDG. A standard whole-body imaging protocol commencing 30–60 min after injection was used at both sites. Referring physicians received by mail a written report of the PET scan within 1 wk of the scan date.

Statistical Analysis

Data were analyzed using the χ^2 test for homogeneity of proportions, with $P < 0.05$ as the criterion for significance. χ^2 goodness-of-fit tests were performed to assess the similarity of the distributions of responses (*22*).

RESULTS

The number of completed questionnaires, subsequently referred to as respondents, received during the study period was 274, for an overall response rate of 37%. The response rate did not differ between physicians referring patients to UCLA Medical Center and physicians referring patients to the NCPIC. The medical specialties of the referring physicians are shown in Table 1. The distribution of specialties did not statistically differ between respondents and nonrespondents. Further, the specialties of referring physicians did not differ between physicians referring to the NCPIC and those referring to UCLA Medical Center.

PET Indications and Pre-PET Management

The primary reason for PET referral was more accurate staging of lung cancer in 61% of all patients, more accurate diagnosis in 20%, and monitoring of therapy or the course of disease in 6%. A combination of 2 indications—specifically, more accurate staging and more accurate diagnosis of lung cancer—was stated by 9% of the respondents, and the remaining 4% stated other unspecified indications for PET.

The management plan before PET consisted of surgery in 54% of lung cancer patients, medical treatment in 15%, radiation treatment in 6%, and no treatment in 10%. Only 2% of the respondents did not answer this question, and 4.5% stated that they had followed another, unspecified, pre-PET management plan. A combination of 2 or more of the management options was indicated by 8.5% of the physicians.

PET Influence on Clinical Stage

PET resulted in a change in the decision on clinical stage in 44% of all patients. The disease was upstaged in 29% and downstaged in 15%. In 51%, the clinical stage was not changed (5% of respondents did not answer the question). PET tended to have a greater impact on stage at 1 study site (NCPIC) (Table 2), for unclear reasons. However, differences in patient population between a community PET center and an academic PET center may account for this observation.

PET Influence on Management

PET resulted in an intermodality management change in 39% of all patients, an intramodality change in 15%, a

TABLE 1
Specialty of Referring Physicians

Specialty	Percentage		
	All referrals ($n = 744$)	Respondents ($n = 274$)	Nonrespondents ($n = 470$)
Medical oncology	33	39	30
Surgery	30	30	30
General practice	19	15	20
Pulmonary medicine	13	9	16
Radiation oncology	4	5	3
Other/not specified	1	2	1

TABLE 2
Influence of PET on Clinical Stage

Effect	UCLA Medical Center (n = 133)	NCPIC (n = 141)	P	Total (n = 274)
Upstaged	31 (23)	48 (34)	0.07	79 (29)
Downstaged	17 (13)	25 (18)	0.34	42 (15)
No change in stage	80 (60)	59 (42)	0.004	139 (51)
Question not answered	5 (4)	9 (6)	0.48	14 (5)

Probability value indicates difference in distribution of stage changes between referring physicians at the 2 institutions. Values in parentheses are percentages.

combination of inter- and intramodality changes in 2%, and no management change in 37%. Seven percent of respondents reported another, unspecified, management change or did not answer the question (Table 3). The tendency of PET to have a more substantial impact on clinical stage at the NCPIC resulted in a trend toward a greater impact on patient management at that site ($P = 0.0502$). Further, that tendency resulted in a lower number of patients for whom PET did not cause a management change ($P = 0.0005$) (Table 3).

When the type of management was grouped according to the reported change in clinical stage, intermodality management changes occurred for 76% of patients whose disease was upstaged by PET, 54% whose disease was downstaged, and 21% whose clinical stage was not changed. Intramodality management changes occurred for 24% of patients whose disease was upstaged by PET, 14% whose disease was downstaged, and 9% whose clinical stage was not changed. No change in management occurred for 10% of patients whose disease was upstaged, 3% whose disease was downstaged, and 63% whose clinical stage was not changed.

The specific types of inter- and intramodality changes in lung cancer management indicated by respondents are shown in Table 3. For 18% of respondents, PET led to a management change from surgery or radiation therapy to medical or no treatment, whereas for 9% of respondents, PET led to a management change from medical or no treatment to surgery or radiation therapy.

DISCUSSION

Guidelines for the staging of lung cancer have been established by Mountain (*23*). The current study was not designed to determine referring physicians' compliance with these guidelines. Rather, we sought insight into how referring physicians respond to the information provided by a relatively new imaging modality.

This survey of referring physicians showed that ^{18}F-FDG PET has a major impact on the management of lung cancer. To our knowledge, this was the largest systematic survey of referring physicians' attitudes on the value of PET for their lung cancer patients. Kalff et al. (*13*) used a similar approach to evaluate the impact of ^{18}F-FDG PET on the management of lung cancer. They used physician interviews rather than questionnaires, and ^{18}F-FDG PET resulted in a management change in 67% of patients with non–small cell lung cancer.

Our survey showed that PET led to a change in the decision on clinical stage in 44% of patients and an intermodality management change in 39%. These results did not differ between referrals made to the university imaging center and referrals made to the community-based imaging center. PET led to a treatment change from surgery or radiation therapy to medical or no treatment in 18% of patients and from medical or no treatment to surgery or radiation therapy in 9%. Of those patients for whom surgery was listed as the initial (pre-PET) treatment choice, 17% had a reported treatment change away from surgery (to

TABLE 3
Specific Intermodality Management Changes Resulting from PET

Change	UCLA Medical Center (n = 133)	NCPIC (n = 141)	Total (n = 274)
Intermodality*	44 (33.1)	64 (45.4)	108 (39.4)
Surgery to medical	15 (11.3)	13 (9.2)	28 (10.2)
Surgery to radiation	3 (2.3)	1 (0.7)	4 (1.5)
Surgery to no treatment	5 (3.8)	10 (7.1)	15 (5.5)
Medical to surgery	6 (4.5)	8 (5.7)	14 (5.1)
Medical to radiation	1 (0.8)	4 (2.8)	5 (1.8)
Medical to no treatment	2 (1.5)	3 (2.1)	5 (1.8)
Radiation to surgery	1 (0.8)	3 (2.1)	4 (1.5)
Radiation to medical	0 (0)	3 (2.1)	3 (1.1)
Radiation to no treatment	0 (0)	2 (1.4)	2 (0.7)
No treatment to surgery	2 (1.5)	3 (2.1)	5 (1.8)
No treatment to medical	5 (3.8)	3 (2.1)	8 (2.9)
No treatment to radiation	2 (1.5)	0 (0)	2 (0.7)
Combination of changes	2 (1.5)	11 (7.8)	13 (4.7)
Intramodality†	16 (12.0)	25 (17.7)	41 (15.0)
Change in surgical approach	7 (5.3)	13 (9.2)	20 (7.3)
Change in medical approach	8 (6.0)	7 (5.0)	15 (5.5)
Change in radiation approach	1 (0.8)	5 (3.5)	6 (2.2)
Combination of inter- and intramodality‡	1 (0.8)	4 (2.8)	5 (1.8)
None§	64 (48.1)	38 (27.0)	102 (37.2)
Other/not specified	8 (6.0)	7 (5.0)	15 (5.5)
Question not answered	0 (0)	3 (2.1)	3 (1.1)

*$P = 0.05$ (NS) for distribution between UCLA Medical Center and NCPIC.

†$P = 0.25$ (NS) for distribution between UCLA Medical Center and NCPIC.

‡$P = 0.43$ (NS) for distribution between UCLA Medical Center and NCPIC.

§$P = 0.0005$ for distribution between UCLA Medical Center and NCPIC.

NS = not statistically significant.

Values in parentheses are percentages.

radiation, medical, or no treatment). This finding was in keeping with several reports suggesting that PET reduced the number of surgical interventions in patients with lung cancer, thereby significantly improving patient management and reducing health care expenditures (*24*,*25*).

A simple, straightforward survey with short and relatively few questions was used to determine the impact of PET on disease stage and management. We recognize the shortcomings of the current approach. Stage has different meanings and implications for different types of cancer. For instance, the number of metastatic lesions in lung cancer does not affect the clinical stage, whereas the number of metastatic lesions may well alter the treatment modality. Thus, in some patients PET may have caused the decision on disease extent to be changed but not the decision on stage. This possibility may, in part, account for the observation that 21% and 9% of patients with reported inter- and intramodality changes, respectively, had no reported change in clinical stage. Other possible explanations for this discrepancy are that PET confirmed the absence or presence of disease that was suspected but not confirmed by other diagnostic tests. Another possibility is that some physicians incorrectly answered the questions on changes in staging or management.

Wagner (*26*) provided another explanation for the lack of management changes in some patients whose clinical stage was changed after PET. Physicians, before obtaining the PET results, might have been biased toward a management option that contradicted the work-up conclusions.

Another consequence of the use of a simple survey was that some questions remained unanswered (Tables 2 and 3), likely because the questionnaire did not address certain problems specific to lung cancer. However, these concerns had to be weighed against the advantages of a straightforward format that was likely to result in higher response rates.

The current study had some limitations. First, the surveyed physicians were all users of PET. The reported impact on management may therefore have been biased toward favoring PET. It is likely that many physicians across a range of specialties are not fully educated about the indications for PET or are not convinced from the existing literature that PET adds useful information to that obtained from anatomic imaging.

The 37% response rate raises the possibility of respondent bias. Response rates among health care professionals have been reported to be affected by various factors, including physician appreciation of the scientific purpose and clinical value of a trial, the simplicity of a study protocol and questionnaires, ethical aspects, the quality of communication with the trial center, and financial incentives for the referring or participating physicians (*27*–*29*). These factors may also explain why PET tended to have a greater impact on staging and management of lung cancer at 1 of our 2 study sites (NCPIC). Management changes occurred more frequently when disease was upstaged by PET than when it was downstaged (76% vs. 54%; $P = 0.03$). A probable explanation is that patients whose disease was downstaged by PET after treatment likely remained on the successful regimen, whereas those whose disease was upstaged required a management change.

A worst-case scenario is that only supporters of PET responded. Other parameters that may introduce a respondent bias relate to the type of cancer evaluated and the physician's level of specialization and interest in research. Varying levels of interest in the survey, the time required for a response, and other parameters affect response rates (*27*). In addition, better-informed physicians tend to respond more frequently to questionnaire studies.

The validity of the current results is nevertheless supported by several factors. First, respondents and nonrespondents did not significantly differ with regard to specialty. Second, the 2 participating institutions did not significantly differ with regard to response rate. Third, the respondents at both sites reported that PET had a considerable impact on staging and management decisions, indicating that physician attitudes toward PET are not unique to a single institution at a single geographic location. Fourth, even assuming a worst-case scenario in which all nonrespondents believed that PET did not alter staging decision or management, PET would still have resulted in changes in staging decision and management in 16% and 23% of patients, respectively. However, some respondents might have made the wrong clinical management decision on the basis of the PET findings.

It was beyond the scope of the current study to determine whether changes in treatment as a result of PET improved patient outcome. We can, however, infer from the published literature that management changes based on PET are justified by the high accuracy of this test for many indications. A large body of evidence showing the accuracy of PET for diagnosing and staging cancer supports referring physicians' confidence in this technology. For example, a recent metaanalysis compared the accuracy of PET and CT for staging mediastinal lymph nodes in patients with non–small cell lung cancer (*30*). The authors reviewed 33 studies, which included 514 patients studied with PET and 2,226 patients studied with CT. They concluded that both sensitivity (79% vs. 60%) and specificity (91% vs. 77%) were higher for PET than for CT. This and several other studies on various types of cancer support management changes guided by PET results (*31*,*32*). A rigorous decision tree sensitivity analysis for the cost-effectiveness of ^{18}F-FDG PET has shown that combining PET and CT for the staging of lung cancer is more economical than is the conventional strategy of staging through CT alone (*25*).

This evidence and the recent approval for reimbursement for 5 major oncologic indications by the Health Care Financing Administration and by many private insurance companies have led to the increased use and acceptance of PET by physicians. As PET technology becomes more readily available at community medical centers, it is important to understand the influence of PET on the routine

clinical management of cancer. Previous investigations of the impact of PET on management have primarily been retrospective and have included few patients. Weng et al. (*33*) reported a higher diagnostic accuracy for the combined use of PET and CT than for the use PET or CT alone for staging lung cancer. To determine PET-based clinical management changes, Weng et al. also performed a retrospective analysis of medical records and images. That analysis suggested that PET altered management in 12 of 50 patients (24%). Saunders et al. (*34*) reported that mediastinal lymph node staging is more accurate by PET than by CT. In their study of 97 patients with lung cancer, PET correctly altered the decision on clinical stage in 27% of patients and detected distant unknown metastases in 13%. PET resulted in clinical management changes in 37% of patients: For 15 patients, surgery was cancelled; for 11, surgery was performed because suspected metastatic disease was correctly excluded; for 4, surgery was performed because the diagnosis of lung cancer was suggested by PET; and for 6, further evaluation was required. Pieterman et al. (*35*) recently reported that ^{18}F-FDG PET altered the clinical stage in 60% of their lung cancer patients. Unknown distant metastases were detected in 11% of the patients. Thus, the impact of ^{18}F-FDG PET on the decision on the clinical stage of lung cancer was even more pronounced in a prospective study than in the current survey.

CONCLUSION

The results of the current survey indicated that PET findings were accepted as likely correct by referring physicians and led to changes in the decision on disease stage in >40% of lung cancer patients and to changes in management in approximately 55%.

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