Influence of Introduction of Positron Emission Tomography on Adherence to Mediastinal Staging Protocols and Performance of Mediastinoscopy

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Abstract

Purpose: In this study, we investigated the impact of implementation of [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET) in daily practice on adherence to mediastinal staging protocols and performance of mediastinoscopy in non–small-cell lung cancer (NSCLC) patients who are possible candidates for surgical resection. Institutional review board approval was obtained.

Patients and Methods: From a nonuniversity teaching hospital and three surrounding community hospitals in Eindhoven, the Netherlands, we studied data from 143 patients with NSCLC who underwent mediastinoscopy and/or thoracotomy in three consecutive periods (1, 0 to 9 months; 2, 10 to 18 months; and 3, 19 to 31 months) after introduction of PET. Mediastinoscopy was indicated in case of enlarged and/or PET-positive nodes. Adherence to these surgical mediastinal staging guidelines and the performance of PET and mediastinoscopy were investigated and compared between the three periods and with our previous study before introduction of PET.

Results and Conclusion: Guidelines for indicating mediastinoscopy were adequately followed in significantly more instances after introduction of PET (80%), compared with the period before PET (66%). Optimal yield (lymph node stations 4, right and left, and 7) of mediastinoscopy (in 27% of patients) was not significantly different from the period before PET (39% of patients). Compared with the historical data, the percentage of positive mediastinoscopies increased from 15.5 to 17.6 (not significant). We found no significant differences between the three consecutive periods with regard to adequacy of indicating and performance of mediastinoscopy. After introduction of PET, adherence to staging guidelines with respect to mediastinoscopy improved. Although fewer mediastinoscopies had an optimal yield, more proved to be positive for metastases. Nevertheless, when a mediastinoscopy is indicated, surgeons must be encouraged to reach an optimal yield because PET positive nodes might be false negative. This occurred in 5% to 6% of all patients.

Introduction

In patients presenting with non–small-cell lung cancer (NSCLC), one of the earliest and most important issues is determining resectability and operability because complete resection offers the best prospects for patients with NSCLC. Resectability depends mainly on the presence of mediastinal lymph node metastases, which are an ominous prognostic sign and generally a contraindication to primary surgical resection. Even nowadays, after introduction of [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET), mediastinoscopy remains the gold standard for detecting N2 or N3 disease.

In a former study, we found that adherence to staging guidelines and performance of mediastinoscopy in general practice is not as high as one should hope for.[1] Addition of FDG-PET to conventional testing of NSCLC patients who are possible candidates for surgical resection can be very useful in guiding mediastinal biopsy during mediastinoscopy and reduces the number of futile thoracotomies.[2] PET scanning is becoming more and more available, even in the smaller hospitals. In October 2002, FDG-PET scanning became available in our hospital. In this study, we investigated whether the nonsupervised implementation of FDG-PET in daily practice resulted in improved performance and adherence to preoperative surgical mediastinal staging procedures.

Mediastinoscopy had to be performed in case of enlarged nodes on CT scan and/or evidence of PET activity in the mediastinum. In the Netherlands, it is not the custom to perform frozen sections during the mediastinoscopy. In order to get accurate mediastinal staging, we consider that an optimal yield of a mediatinoscopy contains at least lymph node sampling of lymph node stations 4 (right and left) and 7. We compared these results with our previous study before introduction of PET, regarding adherence to protocol.[1] We studied, in patients who were upstaged postoperatively, whether upstaging might have been prevented in case preoperative staging protocols would have been followed correctly.

Patients and Methods

Study Design

Data of all patients with proven malignancy (NSCLC) who had mediastinoscopy and/or thoracotomy were collected. From a nonuniversity teaching hospital and three surrounding community (nonteaching) hospitals, data from patients evaluated

between October 2002, after the introduction of FDG-PET scanning, and April 2005, were included. To find out whether the degree of adherence to staging guidelines or performance of mediastinoscopy improved as time after implementation of PET progressed, three arbitrarily chosen consecutive periods were analyzed: the first 9 months after FDG-PET became available (period 1, October 2002 to June 2003), the second 9 months (period 2, July 2003 to March 2004), and the final 13 months (period 3, April 2004 to April 2005). Accessibility to PET was made known to physicians at its introduction and repeatedly mentioned during the weekly treatment planning conference of physicians involved in the treatment of lung cancer patients. The described staging procedures were not changed during the investigated period.

Preoperative computed tomography (CT) scans in the nonuniversity teaching hospital were prospectively reviewed by two independent radiologists (A.D.G., A.D.R.). Presence of pathologically enlarged mediastinal lymph node stations, defined as larger than 10 mm (or $>$ 15 mm for subcarinal nodes) in short axis diameter, was systematically documented for all Naruke stations.[3] Furthermore, all preoperative PET scans were reviewed by two independent nuclear medicine physicians (M.E., D.H.) in presence of CT scans. The localization of the primary tumor on PET was classified as peripheral or central/adjacent to the mediastinum. A radiologically visual boundary from the mediastinum made a tumor peripheral. In practice, this was always in the outer two thirds of the thorax. Mediastinal lymph nodes were localized according to Naruke. Criteria for PET positivity were the presence of focally enhanced uptake versus background. No standardized uptake values were measured as they proved not to be better than a visual score.[4] Whenever radiologists or nuclear medicine physicians disagreed, scans were reviewed again until agreement was obtained, which was possible in all instances. If this had not been the case, a third specialist would have been asked to review the scanning results. Results regarding adherence to mediastinal staging procedures and performance of mediastinoscopy were compared between the three consecutive periods and with the results from our previous study.[1]

Accuracy of Surgical Mediastinal Staging Procedures

Adherence to staging management guidelines. According to staging protocols in the four hospitals, PET should be performed in all patients with (suspicious) malignant lesions that were eligible for surgical resection. In all four hospitals, at the time of this study, PET was generally used to evaluate the mediastinum and to detect distant metastases.

All four hospitals used the following guideline to decide whether to perform a mediastinoscopy: only in the case of a peripheral tumor, without evidence of mediastinal lymph node metastases on PET and CT, mediastinoscopy could be omitted. In case no PET was performed, only in patients with histologically proven clinical T1N0 squamous cell carcinomas, mediastinoscopy could also be omitted (like during the period before introduction of PET[1]). For each patient, we compared clinical practice to the corresponding guidelines.

Surgery for proven N2 or N3 disease was considered nonbeneficial as a primary treatment and therefore not performed in these patients during this study. Some of these patients with stage IIIA disease were eligible for neoadjuvant chemotherapy and restaging afterward, but they were left out of this study. There were no specific, existing guidelines concerning mediastinal lymph node sampling during thoracotomy in the participating hospitals. In general, enlarged nodes were removed. In case of upstaging, we analyzed whether preoperative mediastinal staging guidelines were adequately followed, and if not, whether upstaging could have been prevented if guidelines would have been followed correctly.

Performance of mediastinoscopy. Of all mediastinoscopies, information concerning site of biopsies and histopathologic diagnosis were registered. Locations of mediastinal lymph nodes were classified according to Naruke.[3] Frozen section was not done during mediatinoscopy, so during the procedure the surgeon could not know whether or not the sampled lymph node would contain malignant cells. Therefore, optimal yield was set on biopsy site and not on histopathology. We considered the yield of mediastinoscopy optimal, in case lymph node stations 4 (right and left) and 7 were biopsied with lymph node tissue present in all three biopsies. If these three sites were not biopsied, results were considered to be nonoptimal. In case PET showed positive mediastinal lymph nodes that were accessible for mediastinoscopy, we investigated whether these nodes were actually biopsied during mediastinoscopy

Upstaging. In case of upstaging post-thoracotomy, we investigated whether these positive mediastinal lymph nodes found during thoracotomy would have been accessible for mediastinoscopy and if so, whether this false negative staging procedure was caused by nonadherence to staging guidelines.

Statistical Analysis

We used SPSS version 13.0 (SPSS Inc, Chicago, IL) for statistical analysis. To determine accuracy of preoperative surgical mediastinal staging procedures and to compare results from this study with the ones from our previous study, we performed the χ^2 test. Statistical significance was defined at $P < .05$.

Results

From October 2002 to April 2005, 143 patients with histologically proven NSCLC undergoing mediastinoscopy and/or thoracotomy were evaluated. Mean age was 65 $\pm$ 9 years (range, 41 to 84 years) and 107 (74.8%) were men. Of 143 NSCLC patients, 46 had squamous cell carcinoma, 64 had adenocarcinoma, four had bronchioloalveolair cell carcinoma, and 28 had large cell undifferentiated carcinoma; 52 (36.4%) were analyzed in period 1, 46 (32.2%) in 2, and 45 (31.5%) in 3.

Accuracy of Surgical Mediastinal Staging Procedures

Adherence to staging management guidelines. Table 1 presents data on adherence to staging guidelines and the number of

Table 1. Adherence to Staging Guidelines and the Number of Diagnostic Procedures That Were Performed in Each Period of Time After Implementation of PET

Period	No. of Patients	PET	No. of MS Performed	OY	Guidelines		Surgery	Sampling*	Upstaged†
					CF	NFC			
1	52	Y 34	Y 18	5	16	2	Y 15	Y 12	0
			N 16		14	2	Y 16	Y 9	0
		N 18	Y 12	3	12	0	Y 9	Y 4	2
			N 6		2	4	Y 6	Y 3	1 (NFC)‡
Total %		65.4	30	8 (26.7%)	OY 84.6		46	60.9	11.5
2	46	Y 33	Y 13	5	13	0	Y 8	Y 6	1
			N 20		13	7	Y 20	Y 15	2 (FC)
		N 13	Y 7	2	7	0	Y 2	Y 1	0
			N 6		0	6	Y 6	Y 1	0
Total %		71.7	20	7 (35%)	OY 71.7		36	63.9	14.3
3	45	Y 31	Y 16	4	16	0	Y 13	Y 9	1
			N 15		13	2	Y 15	Y 8	1 (FC)
		N 14	Y 8	1	8	0	Y 6	Y 4	0
			N 6		0	6	Y 6	Y 3	0
Total %		68.9	24	5 (20.8%)	OY 82.2		40	60	10.5
Overall total	143		Y 74	27%	OY 79.7		Y 122	61.5	12.1

Abbreviations: PET, positron emission tomography; MS, mediastinoscopy; OY, optimal yield; Y, procedure performed; N, procedure not performed; FC, followed correctly; NFC, not followed correctly.

* Numbers of thoracotomies during which mediastinal lymph nodes were sampled.

† Numbers of patients diagnosed having N2 or N3 disease after thoracotomy (between brackets whether guidelines were followed correctly).

‡ Mediastinal lymph nodes that proved positive for metastases during thoracotomy were not accessible for mediastinoscopy.

diagnostic procedures that were performed in each period of time. There were no statistical differences between these three periods. Overall, guidelines for indicating mediastinoscopy were adequately followed in 80% of patients.

Mediastinal lymph nodes were sampled in 75 (61.5%) of 122 patients during thoracotomy (Table 1). Maximum time interval of 28 days between mediastinoscopy and thoracotomy was exceeded in nine patients, so data from 66 of 75 patients were available for analysis on upstaging. Mean time interval between mediastinoscopy and thoracotomy was 17.2 days (range, 7 to 26 days). Although mediastinoscopy showed no lymph node metastasis in these 66 patients, in eight patients (12.1%) one or more sampled mediastinal lymph nodes proved to be malignant. In only one of these eight patients mediastinal staging guidelines were not followed correctly (of the 66 patients [12.1%]; Table 1). The mediastinal lymph node–containing metastasis in this patient was at location N5 and therefore not accessible for cervical mediastinoscopy. So upstaging could not have been prevented in this patient if guidelines would have been adequately followed.

Performance of mediastinoscopy. In Table 2, results of PET and mediastinoscopy are presented. The number of separate mediastinal lymph nodes that were positive on PET and accessible for mediastinoscopy was 15, 13, and 3 for the three consecutive periods, respectively. There were no differences between these three periods with regard to upstaging.

We found that 20 (27%) of 74 mediastinoscopies had an optimal yield (Table 1) and 13 (18%) were positive for mediastinal metastases (Table 2). Overall, of 49 separate PET-positive nodes that were accessible for mediastinoscopy, 31 (63%) were actually biopsied (Table 2). During all 74 mediastinoscopies, a total of 163 separate mediastinal lymph node localizations were biopsied, of which 14 separate nodes (9%) proved positive for metastases (data not shown). This was not significantly different compared with the results from our previous study,[1] where a total of 981 mediastinal lymph node localizations were biopsied during 387 mediastinoscopies, of which 97 (10%) proved to be positive for metastases.

Overall, data from 66 patients could be analyzed for upstaging; PET was performed in 54 of these patients. PET appeared to be false negative for mediastinal lymph node metastases in three patients (5.6%) with PET-positive (peripherally located) adenocarcinomas (Table 2).

Comparison to Period Before Introduction of PET

In Table 3 a comparison of the results from this study with those from our previous study is presented. After the introduction of PET, adherence to guidelines in our study cohort on whether to perform mediastinoscopy increased significantly ($P = .002$) from 66% to 80%. The percentage of mediastinoscopies performed with an optimal yield decreased and the num-

Table 2. Results of PET and MS in Each Period of Time After Implementation of PET

Period	No. of Patients	PET*	No. of Separate MLN†	Accessible MLN Biopsied‡		MS	Upstaged
				No.	%		
1						P 1	—
		P 16	23	15	65.2	N 14	0
						ND 1	0
						P 0	—
	52	N 18	—	—	—	N 3	0
						ND 15	0
						P 2	—
		ND 18	—	—	—	N 10	2
						ND 6	1
2						P 3	—
		P 20	18	13	72.2	N 10	1
						ND 7	0
						P 0	—
	46	N 13	—	—	—	N 0	1
						ND 13	1
						P 4	—
		ND 13	—	—	—	N 3	0
						ND 6	0
3						P 1	—
		P 16	8	3	37.5	N 13	1
						ND 2	0
						P 0	—
	45	N 15	—	—	—	N 2	0
						ND 13	1
						P 2	—
		ND 14	—	—	—	N 6	0
						ND 6	0
Overall total	143	98	49	31	63.3	P 13	8

Abbreviations: PET, positron emission tomography; MS, mediastinoscopy; MLN, mediastinal lymph nodes; P, positive result; N, negative result; ND, not done.

* Result from PET pertaining to the mediastinum (P indicates either separate MLNs were positive or presence of a tumor adjacent to the mediastinum).

† Number of separate MLNs that were P on PET and accessible for MS.

‡ Number of separate P MLNs on PET that were actually biopsied during MS.

ber of thoracotomies where mediastinal lymph nodes were sampled increased, but this did not reach the threshold of statistical significance.

Discussion

In this study, PET scan was preoperatively performed in 69% of patients undergoing mediastinoscopy and/or thoracotomy for NSCLC. We found that in daily practice, guidelines on whether to perform mediastinoscopy were correctly followed in four of every five patients. This was significantly better compared with the period before the introduction of PET ($P = .002$). In only 27% of mediastinoscopies yield of mediastinal lymph nodes was considered optimal; however, 18% of mediastinoscopies proved to be positive for metastases. Overall, 63% of separate positive mediastinal lymph nodes on PET accessible for mediastinoscopy were actually biopsied. This fairly low percentage could be clarified by several reasons. In some instances the surgeon could not find the lymph nodes. In two specific instances, a diminished flexibility in the patients neck made it mechanically impossible to reach all desired stations. In other

Table 3. Influence of Introduction of PET on Adherence to Mediastinal Staging Protocols and Performance of MS

Variable	%		P
	Pre-PET Period (n = 569)[1]	Post-PET Period (n = 143)	
Correctly indicated MS	66.1	79.7	.002
MS with optimal yield	39.0	27.0	NS
Positive MS	15.5	17.6	NS
Thoracotomies with nodes sampled*	52.7	61.5	NS
Patients upstaged after thoracotomy	16.7	12.1	NS

Abbreviations: PET, positron emission tomography; MS, mediastinoscopy; NS, not significant.
* In case surgery was performed.

cases, it is possible that the surgeon thought he had already obtained enough lymph node samples and therefore ended the mediastinoscopy in order to prevent for possible complications from more extensive sampling.

Finally, sampling of mediastinal lymph nodes during thoracotomy was done in 62% of instances, which led to upstaging in 12% of patients. PET proved to be false negative for mediastinal lymph node metastases in 5% to 6% of patients.

In this study, we found that adherence to guidelines on whether to perform mediastinoscopy was significantly ($P = .002$) increased after the introduction of PET. Perhaps shortly after the implementation of such a promising new diagnostic imaging tool like the PET scan, clinicians are more aware of the current literature and try hard to adhere to existing guidelines. Furthermore, it is possible that these guidelines after the introduction of PET were simply easier to adhere to than before. However, in contrast to what we expected, the number of patients that underwent PET did not increase in time. Results from our study might furthermore be influenced because in one of every three patients, PET was not done, possibly due to nonacquaintance of some physicians with PET in the beginning of this study and because of problems implementing its use in practice, like long waiting lists.

Although we hypothesized that performance of mediastinoscopy would improve, because of the awareness of our previous study and the introduction of PET, the opposite appeared to be true. In fact, the number of mediastinoscopies with an optimal yield decreased, although not significantly, from 39% to 27%. This may be caused by considering the result of PET as a guide to biopsy only PET-positive nodes rather than trying to get an optimal yield during mediastinoscopy. Furthermore, we found that not all positive mediastinal lymph nodes on PET were actually biopsied during mediastinoscopy. Despite this, we found in this study a slightly higher percentage of positive mediastinoscopies (17.6%) compared with our former study (15.5%; not significant).

Herder et al[5] demonstrated that use of PET for all lung cancer patients is not better than the normal staging procedures. In contrast, it was demonstrated that the use of PET in NSCLC patients considered for surgery is cost effective.[2] Despite this proven cost-effective use, introducing a new diagnostic tool, without additional measures for optimal implementation, does not automatically result in significant change of attitude of physicians and inadequate incorporation of new guidelines in daily routine. As such this is well-known from other areas of pulmonary medicine, such as introduction of guidelines for optimal use of diagnostic techniques for pulmonary embolism.[6–9] For the introduction of new diagnostic techniques, there is no comparable standard procedure and more is needed than simply making the technique available to come to optimal use. Professional organizations should not only develop guidelines but need to evaluate use as well, and if insufficient, stimulate optimal use by supervised introduction within quality care projects.[10,11] Further, clinicians have their own responsibility to be aware of the characteristic performance of the new tool used in their institution before integrating it into diagnostic algorithms.[12] In our opinion, PET is an excellent adjuvant to the old standard staging procedure and deserves a firm place in preoperative staging. We believe that futile thoracotomies can often be prevented when staging procedures are adequately followed. In practice this means that all patients with enlarged lymph nodes on CT and/or PET positive lymph nodes must undergo mediastinoscopy. Only in the case of a negative PET and the absence of enlarged lymph nodes on CT can mediastinoscopy be omitted.

In summary, after the introduction of PET we found that: staging protocol is followed in 80% of all cases; one of three patients did not undergo a PET scan; optimal yield in mediastinoscopy occurred in only 27% of all cases; only 63% of positive PET nodes accessible for mediastinoscopy were actually biopsied; false negative PET nodes occurred in 5% to 6% of all cases; and introducing optimal use of a new diagnostic technique fails if it not actively supported. We believe that monitoring these aspects of care is extremely important, but sadly it is not performed in most hospitals.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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