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FDG-PET-Detected Extracranial Metastasis in Patients with Non-Small Cell Lung Cancer Undergoing Staging for Surgery or Radical Radiotherapy

Survival Correlates with Metastatic Disease Burden

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The prognostic significance of extracranial distant metastasis detected by positron emission tomography (PET) was investigated in patients with non-small cell lung cancer (NSCLC). Forty-two patients staged with ^{18}F-fluorodeoxyglucose-PET-detected distant metastasis before planned surgery (n = 7) or radical radiotherapy (RT)/chemoradiotherapy (n = 35) for NSCLC were identified from a prospective database. The influence of metastasis number and other prognostic factors was investigated using Cox's regression analysis. Treatment after PET included surgery (n = 2), radical RT (n = 5), palliative RT (n = 25), chemotherapy (n = 8) or supportive care (n = 2). All but 4 patients had died by the last follow-up. Median survival was 9 months overall, 12 months for 27 patients with single PET-detected metastasis and 5 months for 15 patients with >1 metastasis ($p = 0.009$). It was found that the Eastern Cooperative Oncology Group performance status ($p = 0.027$) but not pre-PET stage, weight loss or metastasis site correlated with survival. PET-detected metastatic tumor burden appeared to influence survival and should be evaluated as a prognostic factor in NSCLC.

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Positron emission tomography (PET) is becoming widely used in the staging of patients with non-small cell lung cancer (NSCLC) who are candidates for curative therapy with surgery (1–4) or radical radiotherapy/chemoradiotherapy (5). PET scanning, using F-18-fluorodexyglucose (FDG) as a tracer, often gives rise to stage migration from local to locoregional disease, because of its greater sensitivity and specificity in staging the intrathoracic lymph nodes. PET is also more sensitive than conventional staging in the detection of distant metastases in NSCLC. There are many reports of upstaging by PET of patients with limited or locoregional disease to stage IV (6,7). PET may detect metastasis in adrenal (8), bone (9) or other distant sites despite the presence of apparently limited disease on conventional staging workup. We have previously reported that the probability of distant metastasis being detected by PET scanning increases with increasing 'apparent disease stage' on non-PET staging (7). Therefore the rate of detection of unsuspected metastasis is lowest in 'pre-PET' stage I (7%) and highest in 'pre-PET' stage III (22%). Evidence of distant metastasis on PET was powerfully correlated with verifiable disease progression at sites of PET positivity (7), but the influence of PET-detected metastasis on survival was not addressed in that study. The exclusion of patients with PET-detected advanced disease from radical radiation therapy, either because of distant metastasis or locoregional disease unsuitable for radical irradiation, has been the major factor in achieving an increase in median survival from 16 to 31 months for radically irradiated patients at our center, (patients with ECOG 0-1 and $<10\%$ weight loss (10)).

More effective patient selection for radical therapies with PET has given rise to a new class of patients; those with PET-detected extensive disease who are denied radical treatment as a consequence. Very little information exists about the fate of these patients. It might be considered that

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patients with PET-detected stage IV disease would have a superior survival compared with patients with conventionally detected metastasis, if only because of the lead-time bias associated with diagnosis by a more sensitive screening test.

FDG-PET almost certainly provides a more accurate indication of the true tumor burden than any previously available investigation or combination of investigations. Determination of disease extent by PET does not rely on synthesis of disparate pieces of information gained from other investigations of varying sensitivity and specificity such as radionuclide bone scanning or computed tomography. Because PET is likely to give a more accurate estimate of the true disease extent, we advanced the hypothesis that new prognostic factors could become apparent in patients with 'PET-detected stage IV' disease.

In this study we report on the survival for patients who were candidates for radical local or locoregional therapies (radical surgery or radiation therapy/chemoradiation) but who were found to have distant extracranial metastasis on PET. We have investigated the influence on survival of both the number of metastases detected by PET and the sites of those metastases. The relationship between PET-detected metastasis and other known prognostic factors, including performance status and weight loss, has also been investigated (11).

MATERIAL AND METHODS

FDG-PET scanning was performed as part of a prospective study of the value of functional imaging in NSCLC at the Peter MacCallum Cancer Institute. The institutional clinical research and ethics committees approved this study. Those eligible for the analysis reported in this paper were consecutive patients with NSCLC who had undergone PET staging as part of an evaluation for potentially curative therapy with surgery or radical radiotherapy between November 1996 and June 1999 and who were reported to have distant metastasis on their PET scans.

Initial pretreatment staging procedures, in addition to PET scanning, included a recent high-quality CT scan of the chest and upper abdomen and, in almost all cases, a bone scan. Patients with adenocarcinoma, large cell carcinoma and/or lymph node metastasis routinely underwent brain CT or MRI scanning. On the basis of conventional imaging studies, patients were allocated a 'Pre-PET' stage using the 1997 revision of the international staging system (12). Imaging studies were reviewed at weekly multidisciplinary lung cancer meetings. Where possible, biopsies or further imaging studies were performed to resolve discrepancies between imaging modalities before treatment was commenced. In the first year of the study, extensive disease that was apparent on a PET scan but unsupported by other evidence did not preclude an attempt at radical treatment. With confirmation of the high accuracy of PET scanning at our institution, it was subsequently considered unethical to proceed with radical therapy for patients with previously unsuspected extensive locoregional disease or distant metastasis clearly apparent on PET scanning, and such patients received palliative therapies.

Treatment policy

Medically fit patients with stage I-II NSCLC were offered radical surgery. All other patients, with stage I-III disease who had tumors that could be encompassed within a tolerable radiotherapy target volume and had ECOG performance status < 2 and weight loss $< 10\%$ were offered radical RT or chemoRT. Otherwise favorable patients with ECOG 2 or weight loss $> 10\%$ could also be considered for radical RT. Radical RT was routinely given with concurrent platinum-based chemotherapy, usually carboplatin (13), provided the patient consented and renal function was adequate.

Patients considered as having locoregional disease that was too extensive for radical RT or with evidence of distant metastasis after PET staging were usually offered palliative radiotherapy as initial therapy, particularly if there were locoregional disease symptoms. Selected patients with distant metastasis and without significant locoregional symptoms received initial chemotherapy.

PET scanning acquisition and processing

PET scans were acquired 60 min after intravenous administration of F-18 FDG. All patients were requested to fast for 6 h prior to the scan. Imaging was performed on a dedicated PET scanner (GE Quest 300-H scanner, UGM Medical Systems Inc., Philadelphia, PA, USA) (14) and emission data were processed using iterative reconstruction both with and without measured attenuation correction. The scan encompassed the lower neck, thorax and upper abdomen. Once issued, the PET scan reports were recorded and entered into a database. They were not reinterpreted in the light of subsequent clinical information. The site and number of all distant metastases apparent on each patient's PET scan were recorded, unless metastases exceeded 6 in number, in which case they were recorded as 7 or more in the database.

Statistics

Survival was measured from the date of the staging PET scan to the date of death from any cause. A closeout date for analysis was taken to be September 12 2001, the earliest date of last contact with patients still known to be alive and not lost to follow-up. Patients who were still alive at the closeout date had their survival censored at that date; i.e., any follow-up beyond this date was ignored in order to minimize bias that might arise from selective reporting of death. Median follow-up time is calculated as the median potential follow-up time. Potential follow-up time for each

patient is the time from PET scan to the closeout date (or date lost to follow-up).

Single prognostic factors were assessed using the logrank test and Cox's regression analysis. Exact p-values were used when comparing two groups. Prognostic factors were assessed simultaneously using Cox's regression. The prognostic significance of 'number of metastases' was assessed by coding the variable in two ways: (i) grouping this variable into single versus multiple metastases; and (ii) using the ungrouped data. Henceforth, these variables will be referred to as 'multiple metastases' and 'number of metastases', respectively. In analyses of 'number of metastases', because patients with 7 or more metastases were coded simply as '$\geq$ 7', the 'ranks' (1 to 42) of the number of metastases have been used (ranks being averaged for tied data). Data were also analyzed using the value 7 for patients with 7 or more metastases and analyzing the number of metastases as their logarithm, but any conclusions remained unaltered. Ninety-five percent confidence intervals (95% CI) were given for median survival times and hazard ratios. All p-values were two-sided.

RESULTS

Forty-two patients (26 male, 16 female, median age 65 years) had PET-detected distant metastases. Histology was squamous cell carcinoma (n = 21), adenocarcinoma (n = 11), large cell carcinoma (n = 6), mixed NSCLC (n = 1) or other carcinoma (n = 3) Details of other baseline patient characteristics are given in Table 1. Seven of the patients were candidates for surgery before PET and the remaining 35 were candidates for radical RT/chemoRT. One patient had a metachronous, apparently solitary, lung metastasis evident on CT and was being considered for surgical resection of this lesion; PET showed that this patient had other sites of metastasis. All other patients had local or locoregional disease, with stage I-III on conventional assessment.

Metastases were detected by PET scanning in the following sites: lung 16 patients (38%), bone 9 patients (21%), adrenal gland 8 patients (18%), lymph node 6 patients (14%), liver 4 patients (9%), other abdominal sites 4 patients (9%), pleura 3 patients (7%), skin 1 patient, kidney 1 patient. Patients frequently had more than one site of PET-detected metastatic disease. In 27 cases there was a single metastasis and in 15 cases multiple metastases.

Initial patient management strategies chosen following the staging PET scan were as follows; radical surgery n = 2, radical RT/chemoRT n = 5, palliative chemotherapy n = 8, palliative RT n = 25, in 1 case given with concurrent chemotherapy and supportive care n = 2. Radical surgery was performed in 2 cases and radical RT/chemoRT given in 5 cases despite PET evidence of metastasis but which could not be confirmed by other investigations. PET therefore changed the disease management from radical to palliative therapies in 35 of the 42 patients (83%) with PET-detected metastasis. All but one of the 7 patients treated radically had evidence of progression of metastatic disease by the time of the last follow-up. Patients with disease progression after palliative chemotherapy often received palliative RT, and vice versa. A range of single and multi-agent chemotherapy regimens was implemented. The chemotherapeutic agents used included cisplatin, carboplatin, VP-16, paclitaxel, vinorelbine and gemcitabine.

There were no missing data for any variable. None of the patients was lost to follow-up. The mean potential follow-up time was 42 months (range, 27 to 57 months). No known deaths were censored beyond the closeout date. In Table 2 the distribution of the prognostic factors considered is presented, overall and according to whether metastases were single or multiple. Patients with multiple metastases tended to have a poorer performance status.

Univariate analyses of overall survival

All but four of the patients studied died. The four living patients survived for 41, 49, 53 and 58 months. For these patients, performance status was 0 (1 patient) and 1 (3 patients); weight loss was 'none' (3 patients) and '$>$ 10%' (1 patient); and pre-PET stages were I (1 patient) and III (3 patients). All four surviving patients had a single PET-detected metastasis. For all patients, the median survival time was 9 months [95% CI: (7,13)] and the 1-year survival rate 40% (standard error = 8%).

The unifactor analyses are summarized in Table 2. Poor performance status was significantly related to shorter survival ($p_{trend} = 0.027$). Neither weight loss (p = 0.56) nor pre-PET stage ($p_{trend} = 0.36$) was significantly associated with survival, but this may be related to the relatively small sample size.

The presence of multiple metastases was significantly related to survival (p = 0.009): the median survival of patients with a single metastasis was 12 months and of those with multiple metastases survival was 5 months. The hazards ratio of multiple compared with single metastases was 2.5 [95% CI: (1.3, 4.9)]; i.e. patients with multiple metastases were dying at 2.5 times the rate of those with single metastases. The number of metastases (using ranks) was also prognostically significant (p = 0.006).

Nevertheless there is little evidence to suggest that the absolute number of metastases provides a significantly stronger relationship to survival than categorizing metastasis as single or multiple. This question was analyzed in two ways: 1) By including both variables, 'multiple metastases' and 'number of metastases', in the Cox regression model—number of metastases was not statistically significant (p = 0.58) after adjusting for multiple metastases; and 2) by testing the effect of 'number of metastases' in patients with multiple metastases—the absolute number of metastases $>$ 1 was not statistically significant (p = 0.50).

Table 1

Distributions of prognostic factors by number of metastases

Factor	Levels	Single metastasis	Multiple metastases	All patients	p-value*
All patients		27	15	42	
Sex	Female	9	7	16	0.51
	Male	18	8	26	
ECOG performance status	0	7	1	8	0.073
	1	18	11	29	
	2	2	3	5	
Weight loss	None	20	8	28	0.44
	$<10\%$	4	6	10	
	$>10\%$	3	1	4	
Pre-PET stage	1	6	2	8	0.96
	2	1	4	5	
	3	20	8	28	
	4	0	1	1	
PET T stage	0	2	1	3	0.46
	1	5	1	6	
	2	8	5	13	
	3	5	3	8	
	4	7	5	12	
PET N stage	0	4	3	7	0.66
	1	0	0	0	
	2	17	5	22	
	3	6	7	13	
No. of metastases	1			27	
	2			5	
	3			4	
	4			2	
	6			1	
	7 or more			3	

* p-value for trend where appropriate.
Abbreviations: ECOG = Eastern Cooperative Oncology Group; PET = positron emission tomography.

Survival duration according to the number of metastases is plotted in Fig. 1. The overall survival curves comparing patients with single and those with multiple metastases are presented in Fig. 2.

Multifactor analysis

Number of metastases (ranks) remained significant after adjusting for both performance status ($p = 0.018$) and pre-PET stage ($p = 0.005$). Neither of these two variables was

Table 2

Unifactor analyses of association between prognostic factors and overall survival

Factor	Levels	N	Median survival (months)	Relative mortality rate (log rank)	p-value*
All patients		42	9	1.00	
No. of metastases	Single	27	12	0.77	0.009
	Multiple	15	5	1.84	
ECOG performance status	0	8	24	0.59	0.027
	1	29	9	1.10	
	2	5	5	2.03	
Weight loss	None	28	9	0.87	0.56
	$<10\%$	10	5	2.02	
	$>10\%$	4	10	0.70	
Pre-PET stage	1	8	12	0.70	0.36
	2	5	9	1.58	
	3	28	9	1.02	
	4	1	5	3.73	

* p-value is exact for No. of metastases and is for trend for the other variables.
Abbreviations: ECOG = Eastern Cooperative Oncology Group; PET = positron emission tomography.

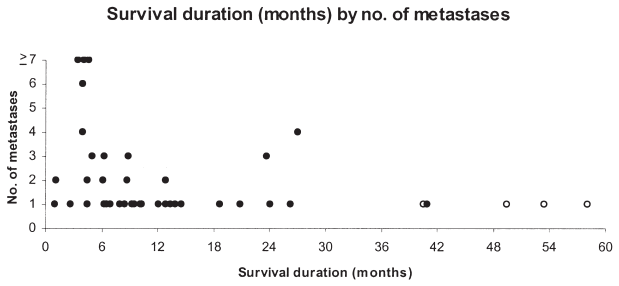

Fig. 1. Survival duration in 42 patients by number of metastases found on positron emission tomography (PET). Note three patients with 'multiple' metastases designated as '≥ 7'. Patients still alive (i.e. with censored survival times) are indicated by open circles.

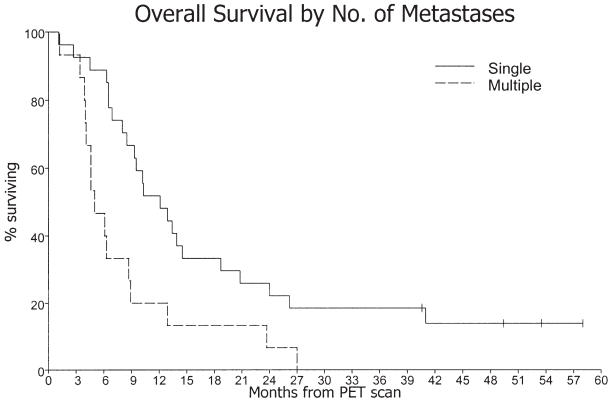

Fig. 2. Overall survival curves of patients with single (27 patients) and multiple (15 patients) metastases [p = 0.009]. Median survival times are 12 months and 5 months, respectively.

significantly related to survival in the presence of number of metastases (p = 0.077 and 0.33, respectively).

Analysis of sites of metastasis

Data on the sites of metastases are summarized in Table 3. Formal analysis of these data was not performed because of the relatively large number of sites (9) and the small numbers of patients with involvement at each site. Bone metastasis tended to be associated with multiple metastases, as were liver and pleural metastases.

DISCUSSION

In this study we found that PET-detected metastasis is powerfully correlated with early death in NSCLC. This confirms the findings of our earlier study in which we reported a very high probability of progression with metastatic disease in patients with PET-detected metastasis who did not show clear evidence of metastasis in conventional staging investigations (7). In that study, PET was highly specific in addition to being more sensitive than conventional assessment. These investigations are among the first to provide information on the clinical significance of PET-detected abnormalities interpreted by nuclear medicine physicians as distant metastases. Our results suggest that PET scan images consistent with metastasis should be given significant weight when deciding appropriate treatment strategies in individual cases. Although PET-detected metastasis was associated with high mortality, patients in this series who were found by PET to have stage IV disease had a median survival of 9 months, which is superior to the rate of survival reported in most published series of patients with stage IV NSCLC. In the recently published randomized trial from the Eastern Cooperative Oncology Group (ECOG), which compared 4 chemotherapy regimens, median survival for patients with stage IV or recurrent disease was 7.8 months and one-year survival was 32% (15). In the randomized trial confined to patients with stage IV disease reported by Ganz and colleagues, patients in the chemotherapy arm had a superior survival to those treated with palliative care but with a median of only 20 weeks' duration (16). In the MIC2 trial for patients with advanced NSCLC, survival was 6.7 months for the chemotherapy-treated patients (17). In the data from our own center, patients with predominantly stage III and IV NSCLC had a median survival of 6 months when treated with palliative RT and 6.8 months when treated with RT

Table 3

Frequencies of sites of PET-detected metastasis, with median survival times of patients with and without site involvement

Site	No. of patients with site involved	Median survival (months)		Exact p-value[1]
		Site uninvolved	Site involved	
Lung	16	9	9	1.00
Bone	9	10	5	0.24
Adrenal gland	8	9	10	0.57
Lymph node	6	9	9	0.81
Liver	4	9	6	
Abdomen	4	9	9	
Pleura	3	9	4	
Skin	1	9	3	
Kidney	1	9	6	

[1] Comparing uninvolved versus involved for that site; p-value given only when there are at least 5 patients involved with that site.

plus 5-fluorouracil (18). A median survival of >9 months has been reported in some trials of palliative chemotherapy in NSCLC, but these trials have all contained significant numbers of patients with stage-III disease. The apparently superior survival for patients with PET-detected stage IV NSCLC is consistent with the existence of a 'lead-time bias' effect in which earlier detection of a lesion may falsely give the impression of a survival benefit from a diagnostic test (19). Despite early recognition of incurable metastatic disease, such patients may be destined to die at the same point in time regardless of whether the lesion is known about or not. It is possible that only the period of survival with known stage IV disease will be increased.

This may, however, be unduly pessimistic because it is possible that in some cases, early administration of treatment, at a time of low tumor burden, could result in improved outcomes. It is known that treatment with palliative chemotherapy in advanced NSCLC is associated with a modest increase in median survival (17,20) and it is possible that earlier detection of metastatic tumor could lead to further improvements in survival.

Another striking feature of our data is the marked difference in survival between patients with a single PET-detected metastasis and patients with two or more lesions. None of the patients with 2 or more metastases survived for 2.5 years, but the estimated 4-year survival for patients with a single metastasis was approximately 25%. The difference in survival between these two groups was highly statistically significant. It is known that prolonged survival may occur following resection of solitary brain (21,22) or adrenal metastasis (23) in NSCLC but none of the patients in this series underwent surgical removal of a metastasis. Although the biggest difference in survival was between patients with a single metastasis and those with 2 or more metastases, there was a suggestion of a worsening survival time with numbers of metastatic lesions beyond 2. This effect was small but that may reflect the relatively small size of our sample of patients with multiple metastases. No effect of site of metastasis could be demonstrated, although there was a trend toward inferior survival with bone metastasis. Larger studies involving patients with conventionally detected metastases have shown a poorer survival time in patients with bone or liver disease (24,25).

Patients in this series were managed initially with a wide range of management strategies, ranging in intensity from surgical resection of intrathoracic disease to supportive care only. Most patients, however, received palliative radiotherapy or chemotherapy as initial therapies. As discussed above, it is clear from randomized trials that a small but statistically significant survival benefit may be obtained with early chemotherapy. It is unlikely that differences in treatment intensity could have accounted for the association between PET-detected metastatic tumor burden and survival.

There were two main limitations in the extent of anatomic imaging by PET in this study. The brain was not imaged because of the high background uptake of FDG by normal neural tissue, which limits the sensitivity of FDG-PET at this site. CT or MRI scanning stages the brain more effectively. At our center we routinely use CT or MRI and not PET to stage the brain in patients with adenocarcinoma or large cell carcinoma. The second limitation was a result of the shortage of available scanning time; scans extended only from the neck to below the liver and did not include the pelvis and upper femurs. It is possible that a small number of patients would have had PET-apparent metastasis outside the field of view used in the current study had a whole-body PET scan been performed and that this would have permitted an even more accurate estimate of the true disease burden.

We believe that the data presented here may have implications for the management of stage IV NSCLC. A single sensitive and specific imaging modality was used to detect all sufficiently conspicuous lesions within the field of view of the scanner. This approach is therefore likely to have provided the most accurate estimate of the true extracranial metastatic tumor burden from any currently available investigation or combination of investigations. The number of metastatic lesions appears to be an independent prognostic factor. Patients with a single metastatic lesion have superior survival and could potentially benefit from definitive therapy, such as surgery or radiation therapy, to the primary tumor and the site of metastatic disease. If these results are confirmed at other centers, it will become necessary to ensure that the use of PET for staging is reported in clinical trials and that randomization in phase III trials of systemic therapy for stage IV NSCLC is stratified by number of patients with single PET-detected metastatic lesions. There could even be a case for changing the staging system, subdividing stage IV into categories with single and multiple metastases. In the future, identification of the precise anatomic location of metastases will be greatly assisted by the new generation of combined PET/CT scanners that allow perfect image co-registration and fusion.

REFERENCES

1. Lewis P, Griffin S, Marsden P, et al. Whole-body 18-F-fluorodeoxyglucose positron emission tomography in preoperative evaluation of lung cancer. Lancet 1994; 44: 265–6.
2. Vansteenkiste JF, Stroobants SG, DeLeyn PR, et al. Lymph node staging in non-small cell lung cancer with FDG-PET scan: a prospective study on 690 lymph node stations from 68 patients. J Clin Oncol 1998; 16: 2142–9.
3. Scott WJ, Schwabe JL, Gupta NC, et al. Positron emission tomography of lung tumors and mediastinal lymph nodes using {18F} fluorodeoxyglucose. Ann Thorac Surg 1994; 58: 698–703.
4. Dwamena BA, Sonnad SS, Angobaldo JO, et al. Metastases from non-small cell lung cancer: mediastinal staging in the

1990's—meta-analytic comparison of PET and CT. Radiology 1999; 213: 530–6.
5. MacManus M, Hicks R, Ball D, et al. FDG-PET staging in radical radiotherapy candidates with non-small cell lung cancer: powerful correlation with survival and high impact on treatment. Cancer 2001; 92: 886–95.
6. Weder W, Schmid RA, Bruchhaus H, et al. Detection of extrathoracic metastases by positron emission tomography in lung cancer. Ann Thorac Surg 1988; 66: 886–92.
7. MacManus M, Hicks R, Matthews J, et al. High rate of detection of unsuspected metastases by PET in apparent stage III NSCLC: implications for radical radiation therapy. Int J Radiat Oncol Biol Phys 2001; 50: 287–93.
8. Erasmus JJ, Patz EF, McAdams HP, et al. Evaluation of adrenal masses in patients with bronchogenic carcinoma using 18F-fluorodeoxyglucose positron emission tomography. Am J Roentgenol 1997; 168: 1361–2.
9. Bury T, Barreto A, Daenen F, et al. Fluorine-18 deoxyglucose positron emission tomography for the detection of bone metastases in patients with non-small cell lung cancer. Eur J Nucl Med 1998; 15: 1244–7.
10. MacManus MP, Wong K, Hicks RJ, et al. Early mortality following radical radiotherapy (RRT) for non-small cell lung cancer (NSCLC): Comparison of PET-staged and conventionally-staged cohorts treated at a large tertiary referral center. Int J Radiat Oncol Biol Phys 2002; 52: 351–61.
11. Hilsenbeck SG, Raub WA, Sridhar HS. Prognostic factors in lung cancer based on multivariate analysis. Am J Clin Oncol 1993; 16: 301–9.
12. Mountain CF. A new international staging system for lung cancer. Chest 1997; 111: 1711–7.
13. Grossi M, Millward M, Fisher R, et al. Combined modality treatment using concurrent radiotherapy and pharmacologically guided carboplatin for inoperable and incompletely resected non-small cell lung cancer. Lung Cancer 2001; 31: 73–82.
14. Karp JS, Muehllehner G, Mankoff DA, et al. Continuous-slice PENN-PET: a positron tomograph with volume imaging capability. J Nucl Med 1990; 31: 617–27.
15. Schiller JH, Harrington D, Chandra P, et al. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. N Engl J Med 2002; 346: 92–8.
16. Ganz PA, Figlin RA, Haskell CM, La Soto N, Siau J. Supportive care versus supportive care and combination chemotherapy in metastatic non-small cell lung cancer. Does chemotherapy make a difference? Cancer 1989; 63: 1271–8.
17. Cullen MH, Billingham LJ, Woodroffe CM, et al. Mitomycin, ifosfamide, and cisplatin in unresectable non-small-cell lung cancer: effects on survival and quality of life. J Clin Oncol 1999; 17: 3188–94.
18. Ball D, Smith J, Bishop J, et al. A phase III study of radiotherapy with and without continuous infusion fluorouracil as palliation for non-small cell lung cancer. Br J Cancer 1997; 75: 690–7.
19. McIntosh MW. Instrumental variables when evaluating screening trials: estimating the benefit of detecting cancer by screening. Stat Med 1999; 18: 2775–94.
20. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Br Med J 1995; 311: 899–909.
21. Shahidi H, Kvale PA. Long-term survival following surgical treatment of solitary brain metastasis in non-small cell lung cancer. Chest 1996; 109: 271–6.
22. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 1990; 322: 494–500.
23. Luketich JD, Burt ME. Does resection of adrenal metastases from non-small cell lung cancer improve survival? Ann Thorac Surg 1996; 62: 1614.
24. O'Connell JP, Kris MG, Gralla RJ, et al. Frequency and prognostic importance of pretreatment clinical characteristics in patients with advanced non-small-cell lung cancer treated with combination chemotherapy. J Clin Oncol 1986; 4: 1604–14.
25. Finkelstein DM, Ettinger DS, Ruckdeschel JC. Long-term survivors in metastatic non-small-cell lung cancer: an Eastern Cooperative Oncology Group Study. J Clin Oncol 1986; 4: 702–9.