Anti-CEA immunoscintigraphy and computed tomographic scanning in the preoperative evaluation of mediastinal lymph nodes in lung cancer

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Abstract

Background – Thoracic computed tomography (CT) provides most of the staging information needed before operation for lung cancer and can reduce the number of exploratory thoracotomies. In recent years a new immunoscintigraphic technique with anti-carcinoembryonic antigen (CEA) monoclonal antibodies has been shown to be effective in lung cancer staging. This study compares the yields of CT scans and immunoscintigraphy in the preoperative evaluation of the mediastinal lymph nodes of patients with non-small cell lung cancer.

Methods – One hundred and thirty one patients believed on clinical grounds to have an operable non-small cell lung cancer were photoscanned with the indium-111 labelled F(ab')2 fragments of the antibody FO23C5. Both planar and single photoemission computed tomography (SPECT) thoracic views were recorded. CT scans of the thorax, abdomen, and brain were obtained in all patients. Seventy of the patients eventually underwent surgery, an additional seven underwent mediastinoscopy or mediastinotomy, and a further 10 had both cervical exploration and thoracotomy. Pathological evaluation of the mediastinal nodes was available in all 87 patients, but in only 80 of them was the diagnosis of lung cancer eventually confirmed.

Results – The diagnostic accuracy of planar immunoscintigraphy, SPECT immunoscintigraphy, and CT scanning for N2 disease was 76%, 74%, and 71%, respectively. The corresponding sensitivity and specificity rates were 45%, 77%, 64% and 88%, 72%, and 74%. These were not significantly different.

Conclusions – This study shows that anti-CEA immunoscintigraphy has no advantage over conventional CT scanning in assessing mediastinal lymphoadenopathy in patients with lung cancer. CT scanning remains the gold standard test in these patients.

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Advances in immunology over the last decades have led to improved methods for producing radiolabelled antibodies that target tumour antigens in vivo.[1] In patients with lung cancer several studies have shown that immunoscintigraphy may detect the primary tumour and the possible presence of regional and distant metastases.[2-18] In 13 of 17 clinical investigations so far available for evaluation, tumour targeting was attempted with anti-carcinoembryonic antigen (CEA) antibodies,[2-4 6-10 12 14-17] and anti-CEA immunoscintigraphy can be regarded as the standard for immunoscintigraphic diagnosis. In a recent review of studies of anti-CEA immunoscintigraphy in lung cancer[19] the average detection rates for primary, mediastinal, and distant tumour metastases were 87% (216 of 248 patients), 70% (49 of 70), and 84% (109 of 130), respectively. In the same analysis corresponding specificities were 54% (13 negative scans of 24 benign lesions), 80% (103 of 129), and 84% (109 of 130).

Clinical studies using indium-111 labelled F(ab')2 fragments of the anti-CEA monoclonal antibody FO23C5 have been carried out by our group since November 1987.[7 10 12] We aimed to evaluate the role of planar and single photoemission computed tomography (SPECT) immunoscintigraphy images in the thoracic assessment of resectability. The present report focuses on the preoperative evaluation of mediastinal lymph nodes which, based on our earlier studies, seemed the most fruitful field of application for immunoscintigraphy.

Methods

PATIENTS AND STUDY DESIGN

Eligible patients either had histologically proved lung cancer or were so strongly suspected of having lung cancer to be offered a diagnostic and possibly curative thoracotomy. All were considered operable after a preliminary evaluation based on history, physical examination, blood chemistry and haematological counts, bronchoscopy, lung function tests, chest radiographs and other tests, as required by the results of the above evaluation. Registered patients underwent additional mandatory investigations including anti-CEA immunoscintigraphy (both planar and SPECT images), technetium-99 labelled methylene diphosphonate bone scan, and CT scans of the thorax, upper abdomen, and brain. Other

Table 1 Patient characteristics

	Registered patients (n = 131)	Assessable patients (n = 87)	Assessable patients with lung cancer (n = 80)
Mean (95% CI) age (years)	62·28 (60·93 to 63·63)	61·48 (59·78 to 63·17)	61·54 (59·79 to 63·30)
Sex (male/female)	112/19	73/14	69/11
Karnofsky performance status (70/80/90/100)	38/30/42/21	19/19/29/20	19/18/26/17
Weight loss in 6 months (%) (95% CI)	3·1 (2·25 to 3·94)	1·93 (1·16 to 2·69)	1·88 (1·09 to 2·77)
Serum carcinoembryonic antigen (ng/ml) (95% CI)	9·01 (3·49 to 14·53)	5·43 (3·11 to 7·76)	5·69 (3·21 to 8·17)
Histology (E/A/S/L/U/O/B)	67/27/11/8/11/1/6	43/26/3/6/2/1/6	43/26/3/6/2
Tumour location (central/peripheral)	85/46	61/26	57/23
Disease extent (best assessment, TNM category)			
T1–2/T3/T4	91/17/23	63/9/8	63/9/8
N1/N2/N3	57/13/49/5	49/9/19/3	49/9/19/3
M0/M1	115/16	76/4*	76/4*
Immunoscintigraphy technical notes (95% CI)			
Dose of immunoreagent (µg)	277·82 (257·79 to 297·84)	271·95 (247·14 to 296·76)	272·17 (245·79 to 298·55)
Total radioactivity (mCi)	4·85 (4·62 to 5·07)	4·75 (4·58 to 4·93)	4·71 (4·54 to 4·88)
Labelling efficiency (%)	92·65 (90·22 to 95·07)	94·42 (91·96 to 96·87)	94·18 (91·54 to 96·82)

E = epidermoid carcinoma; A = adenocarcinoma; S = small cell carcinoma; L = large cell carcinoma; U = undefined cell type or mixed histology; O = cancer other than bronchial carcinoma, B = pulmonary benign disease.
* Pulmonary micromestases discovered at thoracotomy.

imaging studies such as bone radiographs and CT scans or ultrasonographic studies of the abdomen were done to support a diagnosis or to guide needle aspirations and biopsies. All staging tests were obtained within a 3–4 week period and surgery was performed within 30 days of the first hospital admission or outpatient visit. Tumour cell type and stage of disease were classified according to internationally adopted criteria.[20][21]

Patients were informed of the nature, aim, potential risks, and benefits of both immunoscintigraphy and iodine contrast CT scanning and gave their consent before entering the study. Anthropometric and clinical characteristics of all eligible patients including age, sex, Karnofsky performance status, weight loss, serum CEA level, histological type, endobronchial tumour location, and disease extent are summarised in table 1.

IMMUNOSCINTIGRAPHY
Anti-CEA FO23C5 F(ab')2 fragments supplied as an instant labelling kit (Indomab-k2) are licensed to Sorin Biomedica (Saluggia, Italy). The kit contains 0·3 mg of a lyophilised preparation of monoclonal antibody fragments previously conjugated to the bifunctional chelating agent diethylenetrionine-pentaacetic acid (DTPA). Details concerning the production and properties of the whole antibody and its derived fragment have been previously reported.[4][10]

Radiolabelling was obtained following the manufacturer's instructions and its quality verified by gel chromatography column scanning.[4][10] The final solution was administered within two hours of being prepared. Characteristics of the injected radiopharmaceutical (dose of antibody fragments, total radioactivity, and radiolabelling efficiency) are shown in table 1.

Planar spot images (anterior and posterior views of the thorax and abdomen, anterior and lateral views of the head) were acquired by a large field of view gamma camera (GE 400 ACT, General Electric, Milwaukee, Wisconsin,

USA) fitted with a medium energy parallel hole collimator using a dual energy window (173–274 keV). Views were stored in a 128 × 128 matrix. At least one scintigraphic series, acquired 120 hours after the radio compound injection, was obtained. At each scanning time a 1500 K anterior view of the thorax was recorded while the other images were recorded for a preset time. After planar imaging SPECT views of the thorax were obtained. The patient was positioned supine with arms above the head and the thorax was centred underneath the camera. Sixty four planar images were collected around 360° with a 64 × 64 word mode matrix. The acquisition time for each plane was 20–25 seconds. The 64 planar projections were reconstructed to transverse slices with the use of a Butterworth filter (cutoff frequencies 0·3–0·4 cyles/cm, power factor 20) at a two pixel thickness for each transverse (12·8 mm thick) slice. A value of 0.04 cm^{-1} was used as attenuation coefficient. Transverse sections were reorientated into the sagittal and coronal planes.

The criteria for the interpretation of immunoscintigraphic images have already been described in detail.[10][12] Mediastinal lesions were assigned to a definite nodal station according to topographical criteria and the ATS node mapping scheme.[22] All immunoscintigraphy scans were interpreted by a specialist in nuclear medicine (A.B.) without the benefits of clinical information.

THORACIC COMPUTED TOMOGRAPHY
All thoracic CT scans were performed with a GE 9800 scanner (General Electric, Milwaukee, Wisconsin, USA). Sections 10 mm thick were obtained at 1 cm intervals during suspended inspiration from the lung apices to the upper abdomen. In selected cases 5 mm thick sections were obtained at 5 mm intervals through the region of interest. Iodinated intravenous contrast medium (150 ml bolus and 100 ml in slow infusion) was injected before all studies. Appropriate windows were used for viewing both lungs and soft tissues. Mediastinal

nodes were labelled as abnormal if they were 1 cm or larger (short axis) and/or 1·5 cm or longer (long axis) on the transverse plane images. Enlarged mediastinal lymph nodes were ascribed to a definite nodal station by the American Thoracic Society (ATS) classification.[22] All CT scans were blindly reviewed by an experienced radiologist (A.L.).

SURGICAL SAMPLING AND PATHOLOGICAL EXAMINATION

At surgery all nodal stations that were positive on either CT or SPECT images were carefully inspected and sampled, even when lymph nodes appeared macroscopically normal. All enlarged, palpable, or visible nodes were totally removed. In apparently normal mediastinums with negative preoperative studies a minimum sampling of three node stations was required to reject the hypothesis of N2 disease. Mediastinoscopies (and, in one case, left anterior mediastinotomy) were performed when CT or immunoscintigraphy studies were positive for accessible lymph nodes in otherwise operable patients. Removed lymph nodes were fixed separately in 10% neutral buffered formalin and labelled according to the ATS criteria.[22]

STATISTICAL ANALYSIS

Immunoscintigraphy can be done using either a planar imaging technique, a SPECT technique, or both. In this study both techniques were used which gave us the opportunity to obtain (and compare) two different results for one immunoscintigraphic series. With reference to the pathological data, the results of planar immunoscintigraphy, SPECT immunoscintigraphy, and CT scanning were designated true positive, false positive, true negative, and false negative for N2 metastases. Values for sensitivity, specificity, accuracy, and predictive capabilties were calculated according to the formula of Galen.[23] Proportions were furnished with their 95% confidence interval.[24] Differences in proportions observed in the same patients were tested statistically using the MacNemar test.[25] The χ^2 test was used for other comparisons between proportions.[25] The statistical significance level was set at 5%, all tests being two tailed.

Results

CHARACTERISTICS OF PATIENTS

Between November 1987 and October 1994 131 eligible patients (112 men) were registered (table 1). The final diagnosis was squamous cell carcinoma in 67 patients, small cell lung cancer in 11, adenocarcinoma in 27, large cell anaplastic carcinoma in eight, undefined cell type or mixed histology lung cancer in 11, Hodgkin's disease in one, and non-malignant lung lesions in six including one hamartochondroma, one fibrocaseous tuberculosis, two sclerosing bronchiectasis, and two persistent foci of pneumonitis with features of interstitial alveolitis and fibrosis. All patients had a Karnofsky score[26] of 70–100 and no other contra-

indication to radical surgery. At the end of presurgical staging 27 patients were judged inoperable based on unequivocal CT findings, nine withdrew their consent to a probably non-curative thoracotomy, and eight were found to have small cell lung cancer after enrollment and were given chemotherapy. Of the remaining 87 patients 70 underwent a resection, seven underwent mediastinoscopy or mediastinotomy alone, and 10 had both cervical or (parasternal) exploration and a thoracotomy. Seven had benign lesions and, histologically, the most frequent tumour cell type was squamous (43 of the 80 assessable patients with cancer). Fifty seven of these 80 lung tumours were in the distal bronchi. Table 1 summarises the clinical, scintigraphic, and pathological characteristics of the three groups of patients (131 registered, 87 assessable, and 80 with cancer).

DETECTION OF MEDIASTINAL LYMPH NODE INVOLVEMENT

Table 2 shows the main findings of the study. True positive, true negative, false positive, and false negative results, along with the corresponding values (and 95% confidence interval) for sensitivity, specificity, and accuracy, are listed. Data refer to the two groups of patients – that is, all the assessable and those assessable with cancer – and to the three types of investigation – that is, planar immunoscintigraphy, SPECT immunoscintigraphy, and CT scanning. In patients with cancer, tumour lymph node extension to the mediastinum was equally detectable by all three techniques. Diagnostic accuracy was 76%, 74%, and 71% for planar immunoscintigraphy, SPECT immunoscintigraphy, and CT scanning, respectively; sensitivity ranged from 77% with SPECT immunoscintigraphy to 45% with planar immunoscintigraphy and specificity from 88% with planar immunoscintigraphy to 72% with SPECT immunoscintigraphy. There were no statistically significant differences with the MacNemar test. Planar immunoscintigraphy and SPECT immunoscintigraphy was the best matched combination since the first technique was the most specific and the latter the most sensitive. CT images retained intermediate status. All staging techniques shared a high negative predictive capability, with SPECT immunoscintigraphy approximating 90%. Overall, similar figures were obtained when the seven patients without lung cancer were included in the computation (table 2). However, most findings in this subgroup of seven patients were falsely positive, particularly with SPECT immunoscintigraphy.

Discussion

Surgery remains the only prospect of cure in patients with non-small cell lung cancer.[27] Ideally, the preoperative assessment of the mediastinum should save patients from futile surgery. On the other hand, patients should be offered a surgical cure if appropriate. The final evaluation of the mediastinum often depends on surgical staging procedures such as media-

Table 2 Diagnostic formulae: N2 disease by technique of evaluation

	TP	TN	FP	FN	Total	Sensitivity	Specificity	Accuracy	PPV	NPV
Assessable patients										
Planar immunoscintigraphy	10	57	8	12	87	45% (25% to 66%)	88% (80% to 96%)	77% (68% to 86%)	56% (33% to 79%)	83% (74% to 92%)
SPECT immunoscintigraphy	17	46	19	5	87	77% (60% to 95%)	71% (60% to 82%)	72% (63% to 82%)	47% (31% to 64%)	90% (82% to 98%)
Thoracic CT scanning	14	49	16	8	87	64% (44% to 84%)	75% (65% to 86%)	72% (63% to 82%)	47% (29% to 65%)	86% (77% to 95%)
Assessable patients with lung cancer										
Planar immunoscintigraphy	10	51	7	12	80	45% (25% to 66%)	88% (80% to 96%)	76% (67% to 86%)	59% (35% to 82%)	81% (71% to 91%)
SPECT immunoscintigraphy	17	42	16	5	80	77% (60% to 95%)	72% (61% to 84%)	74% (64% to 83%)	52% (34% to 69%)	89% (81% to 98%)
Thoracic CT scanning	14	43	15	8	80	64% (44% to 84%)	74% (63% to 85%)	71% (61% to 81%)	48% (30% to 66%)	84% (74% to 94%)

TP = true positive; TN = true negative; FP = false positive; FN = false negative; PPV = positive predictive value; NPV = negative predictive value; SPECT = single photoemission computed tomography; CT = computed tomography.
Values are percentages with 95% confidence intervals.

stinoscopy and anterior mediastinotomy.[27–31] Cervical mediastinoscopy detects gross, usually widespread, disease of the nodes in the superior mediastinum[28–30] and, when positive, prevents a useless operation.[27] In the same way, anterior mediastinotomy has a particular role in suspected para-aortic and subaortic lymphoadenopathy.[31] These intermediate surgical techniques require skill and carry potentially serious complications[30] and additional hospital costs.

Thus, a reliable non-invasive test might be useful in limiting mediastinoscopy by selecting subgroups of patients with various probabilities of mediastinal involvement. Using such a test as a filter, patients with a low likelihood of mediastinal lymphoadenopathy could go straight to thoracotomy while others would receive a prior mediastinoscopy.[27] Besides an acceptable rate of overall accuracy, this strategy requires the "filter-test" to have low rates of false negative results, possibly less than 10%, to reduce the incidence of unexpected N2 disease found at thoracotomy. CT scanning is usually used for this purpose.[28] A meta-analysis of 42 early studies on CT scanning published in 1990 documented an average accuracy of 80%.[32] However, more recent estimates have suggested more prudent figures of 50–60% in the USA and 60–70% in Europe and Japan.[33 34] These figures suggest that thoracic CT scanning may not therefore have the accuracy needed for an ideal filter test.

Several studies have evaluated anti-CEA immunoscintigraphy in the diagnosis of lung cancer.[2–4 6–10 12 14–17] Less information is available, however, concerning the staging potential of this technique.[8 10 12 14–17] Excluding the data shown in the current report, all available information is restricted to about 100 patients and is limited by the inhomogeneity of studies.[8 14–17] For example, different commercially available immunoreagents (including the F(ab′)2 fragments of the F6 antibody,[15] the F(ab′)2 fragments of BW431/31,[14] and the intact BW431/26[8 14 15]) have been used and labelled to different radionuclides (indium-111,[14 16] technetium-99,[8 14 15] and iodine-131[17]). Furthermore, the clinical target has varied in the different studies up to the extreme in the study of MacMillan *et al*[15] who only considered patients with small cell lung cancer, and no separate analysis has been made for lymphatic

spread and direct invasion of mediastinum.[8 14 15] Above all, SPECT images were not always obtained.[8 14 15] This has caused inconsistent results with sensitivities in the range 40–75% and specificities in the range of 33–81%.[8 14–17] Because of these inconsistencies we believe that the results of our study on the value of anti-CEA immunoscintigraphy in the preoperative mediastinal assessment are important.

In a previous report of 63 patients with lung cancer,[10] where we investigated the diagnostic yield of total body scintigraphy with ^{111}In labelled F(ab′)2 fragments of the anti-CEA monoclonal antibody FO23C5, the diagnosis of mediastinal lymph node metastases was correct in about 85% of patients using both the clinical and the pathological reference criteria. We then decided to perform a formal comparison between diagnostic yields of CT scanning and anti-CEA immunoscintigraphy. A preliminary report of this comparison was published two years ago.[12] In the present study we report more mature data that are not substantially different. Current accuracy rates for N2 disease in pathologically documented cases are, respectively, 76% for planar immunoscintigraphy, 74% for SPECT immunoscintigraphy, and 71% for CT scanning. However, the gain in accuracy appears negligible, and the accuracy of the three techniques and the predictive values of a negative test (81%, 89%, and 84%, respectively, for planar immunoscintigraphy, SPECT immunoscintigraphy, and CT scanning) are not significantly different and all are within the lowest boundary of an acceptable "filter test". It must be remembered also that the search for nodal metastases was the most promising application of anti-CEA immunoscintigraphy in lung cancer staging[12] and that immunoscintigraphy is a time consuming and very expensive technique. For all these reasons, we now feel that there is no justification to prefer anti-CEA immunoscintigraphy to standard CT scanning of the thorax.

In conclusion, we believe that in lung cancer the ideal non-invasive preoperative test is not yet available and thoracic CT scanning remains the standard test for large and/or central tumours.

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1 Epenetos AA, Kosmas C. Monoclonal antibodies for imaging and therapy. *Br J Cancer* 1989;**59**:152–5.
2 Riva P, Paganelli G, Callegaro L, Bartoli MG, Turci D, Benini S, *et al*. Immunoscintigraphy of adenocarcinomas by means of 111In-labelled F(ab')2 fragments of anti-CEA monoclonal antibody FO23C5. *Nucl Med Commun* 1988;**9**:577–89.
3 Riva P, Moscatelli G, Paganelli G, Benini S, Siccardi A. Antibody-guided diagnosis: an Italian experience on CEA-expressing tumours. *Int J Cancer* 1988;**42**(Suppl 2):114–20.
4 Siccardi AG. *Studio multicentrico sulla immunoscintigrafia degli adenocarcinomi CEA secernenti. Valutazione dell'efficacia diagnositca di frammenti F(ab')2 radiomarcati dell'anticorpo monoclonale FO23C5 anti-CEA condotto in 11 Centri di Medicina Nucleare su 509 pazienti portatori di adenocarcinomi.* Consiglio Nazionale delle Richerche, Progetto Finalizzato Tecnologie Biomediche e Sanitarie, Sottoprogetto 11. Roma: Consiglio Nazionale delle Ricerche (CNR), 1989; 1–155.
5 Bourget P, Dazord L, Desrues B, Collet B, Ramee MP, Delaval P, *et al*. Immunoscintigraphy of human lung squamous cell carcinoma using an iodine-131 labelled monoclonal antibodies (Po66). *Br J Cancer* 1990;**61**:230–4.
6 Krishnamurthy S, Morris JF, Antonovic R, Ahmed A, Galey WT, Duncan C, *et al*. Evaluation of primary lung cancer with Indium-111 anti-carcinoembryonic antigen (type ZCE-025) monoclonal antibody scintigraphy. *Cancer* 1990;**65**:458–65.
7 Biggi A, Buccheri GF, Ferrigno D, Viglietti A, Farinelli MC, Comino A, *et al*. Detection of suspected primary lung cancer by scintigraphy with indium-111 anti-carcinoembryonic antigen monoclonal antibodies (type FO23C5). *J Nucl Med* 1991;**32**:2064–8.
8 Leitha T, Walter R, Schlick W, Dudczak R. 99mTc-anti-CEA radioimmunoscintigraphy of lung adenocarcinoma. *Chest* 1991;**99**:14–9.
9 Torres M, Jimenez-Heffernan A, Valverde A, Gonzel FM, Latre JM, Llamas JM, *et al*. Immunoscintigraphy of lung cancer using ¹¹¹In-labelled antiCEA FO23C5-F(ab')2. *Nuclear Med Commun* 1991;**12**:937–50.
10 Buccheri GF, Biggi A, Ferrigno D, D'Angeli B, Vassallo G, Leone A, *et al*. Imaging lung cancer by scintigraphy with Indium-111 labeled F(ab')2 fragments of the anti-carcinoembryonic antigen monoclonal antibody FO23C5. *Cancer* 1992;**70**:749–59.
11 Perkins AC, Pimm MV, Morgan DAL, Wastie ML, Reynolds JR, Baldwin RW. ¹³¹I and ¹¹¹In-labelled monoclonal antibody imaging of primary lung carcinoma. *Nucl Med Commun* 1992;**7**:729–39.
12 Buccheri G, Biggi A, Ferrigno D, Leone A, Taviani M, Quaranta M. Anti-CEA immunoscintigraphy might be more useful than computed tomography in the preoperative thoracic evaluation of lung cancer. *Chest* 1993; **104**:734–42.
13 Colombo P, Paganelli G, Magnani P, Songini C, Facio F, Faglia G. Immunoscintigraphy with anti-chromogranin A antibodies with endocrine/neuroendocrine tumors. *J Endocrinol Invest* 1993;**16**:841–3.
14 Kairemo KJA, Aronen HJ, Liewendahl K, Paavonen T, Heikkonen JJ, Virkkunen P, *et al*. Radioimmunoimaging of non-small cell lung cancer with ¹¹¹In- and ⁹⁹ᵐTc-labeled monoclonal anti-CEA-antibodies. *Acta Oncol* 1993;**32**: 771–8.
15 Macmillan CH, Perkins AC, Wastie ML, Leach IH, Morgan DAL. Immunoscintigraphy of small-cell lung cancer: A study using technetium and indium labelled anti-carcinoembryonic antigen monoclonal antibody preparations. *Br J Cancer* 1993;**67**:1391–4.
16 Vuillez J-P, Moro D, Brambilla E, Brichon P-Y, Ferretti G, Saccavini JC, *et al*. Immunoscintigraphy using ¹¹¹In-labelled F(ab')2 fragments of anti-carcinoembryonic antigen (CEA) monoclonal antibody for staging of non-small cell lung carcinoma. *Eur J Cancer [A]* 1994;**30A**:1089–92.
17 Boilleau G, Pujol JL, Ychou M, Faurous P, Marty-Ane C, Michel FB, *et al*. Detection of lymph node metastases in lung cancer: comparison of ¹³¹In-anti-CEA-antiCA19-9 immunoscintigraphy versus computed tomography. *Lung Cancer* 1994;**11**:209–19.
18 O'Byrne KJ, Ennis JT, Freyne PJ, Clancy LJ, Prichard JS, Carney DN. Scintigraphic imaging of small-cell lung cancer with [¹¹¹In]pentetreotide, a radiolabelled somatostatin analogue. *Br J Cancer* 1994;**69**:762–6.
19 Buccheri G, Biggi A, Ferrigno D. Anti-CEA monoclonal antibody scintigraphies in lung cancer. *Lung Cancer* 1994; **11**(Suppl 2):86–7.(Abstract)
20 World Health Organization. *International histological classification of tumours.* Berlin: Springer-Verlag, 1991.
21 UICC. *TNM Classification of malignant tumours.* Berlin: Springer-Verlag, 1987:69–73.
22 American Joint Committee on Cancer. Purposes and principles of staging. In: Beahrs OH, Earl Henson D, Hutter RVP, Myers MH, eds. *Manual for staging of cancer.* Philadelphia: Lippincott, 1988:3–10.
23 Galen RS. Predictive values of laboratory tests. *Am J Cardiol* 1975;**36**:536–8.
24 Bulpitt CJ. Confidence intervals. *Lancet* 1987;**i**:494–7.
25 Siegel S. *Nonparametric statistics for the behavioural sciences.* New York: MacGraw Hill, 1956.
26 Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: Macleod CM, ed. *Evaluation of chemotherapeutic agents.* New York: Columbia University Press, 1949:199–205.
27 Goldstraw P. The practice of cardiothoracic surgeons in the perioperative staging of non-small cell lung cancer. *Thorax* 1992;**47**:1–2.
28 Unruh H, Chu-Jeng Chu CR. Mediastinal assessment for staging and treatment of carcinoma of the lung. *Ann Thorac Surg* 1986;**41**:224–9.
29 Ginsberg RJ. Evaluation of the mediastinum by invasive techniques. *Surg Clin North Am* 1987;**67**:1025–35.
30 Foster ED, Munro DD, Dobell ARC. Mediastinoscopy: a review of anatomical relationships and complications (collective review). *Ann Thorac Surg* 1972;**13**:273–86.
31 Bowen TE, Zajtchuk R, Green DC, Brott WH. Value of anterior mediastinotomy in bronchogenic carcinoma of the left upper lobe. *J Thorac Cardiovasc Surg* 1978;**76**: 269–71.
32 Dales RE, Strak RM, Raman S. Computed tomography to stage lung cancer. Approaching a controversy using meta-analysis. *Am Rev Respir Dis* 1990;**141**:1096–101.
33 Armstrong P. Preoperative computed tomographic scanning for staging lung cancer. *Thorax* 1994;**49**:941–3.
34 Mori K, Yokoi K, Saito Y, Tominaga K, Miyazawa N. Diagnosis of mediastinal lymph node metastases in lung cancer. *Jpn J Clin Oncol* 1992;**22**:35–40.