Hypothesis: That aggressive surgical treatment of lung cancer (LC) is justified by stage-based outcome in immunosuppressed solid organ transplant recipients.

Design: Case series.

Setting: University hospital.

Patients: Lung cancer developed in 15 patients (0.28%) among a solid organ transplant recipient population of 5400 accrued at our institution over a 25-year period.

Main Outcome Measures: Smoking prevalence, subtypes and stages of LC represented, operative morbidity, and survival.

Results: The mean time from transplantation to the diagnosis of LC was 76 months (range, 9-192 months). Eight patients received kidneys; 3, lungs; and 4, hearts. Only 11 patients (73%) had a smoking history (mean, 66 pack-years). The following carcinomas developed in our patient population: adenocarcinoma, 6 patients; squamous cell, 5; large cell undifferentiated, 2; bronchoalveolar, 1; and small cell, 1. Eight patients (53%) presented with inoperable stage IIIB or IV disease. The remaining patients presented in stages IA (n=2), IB (n=1), IIB (n=2), and IIIA (n=2); all underwent resection. No major postoperative complications occurred. All patients with stage IIB or greater disease with or without treatment died quickly (mean survival, 1.4 months; range, 0.33-3.0 months). All patients with stage IIB or less remain alive a mean of 37 months after resection. Patients with stage IIIA survived only a mean of 6.0 months despite resection.

Conclusions: Regarding LCs in transplant recipients compared with LCs in the nontransplant population, we find that (1) there is an increased incidence among nonsmokers; (2) death occurs rapidly in unresected patients; (3) resection carries a low morbidity rate; and (4) resection seems to offer a high chance of cure in those with cancers staged IIB or less.

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The prolonged immunosuppressive therapy that is required following organ transplantation carries a markedly increased risk of the subsequent development of malignant tumors. Further, once these malignancies develop, the transplant patients’ reduced natural antitumoral immune response may result in more rapid dissemination of the neoplasm. In approximately descending order of frequency, the commonly occurring malignancies in transplant patients are cancers of the lips and skin, lymphoproliferative disorders, bronchogenic carcinoma, cervical carcinoma, Kaposi sarcoma, and renal cell carcinoma. The incidence of bronchogenic carcinoma in this population, however, is likely to grow proportionally as the population of transplant recipients with risk factors for lung cancer (LC) increases (ie, heart and lung transplant recipients with histories of smoking).

Given the likely increasing incidence of these tumors, we reviewed our experience to examine the clinicopathologic characteristics of LCs that developed in solid organ transplant recipients at our institution. We were particularly interested in addressing the following hypotheses: (1) that these tumors present at a later stage and result in a poorer outcome due to suppression of the host immune response; (2) that squamous tumors would predominate, given the known association between viral infection and squamous cell carcinomas in other organs; and (3) that the tumors might occur at a greater rate in nonsmokers than they do in the nonimmunosuppressed population. Our most important goal, however, was to determine whether aggressive surgical treatment of these ma-
lignant neoplasms was justified by the outcome in this high-risk population with compromised natural antitumoral immunity.

**METHODS**

Solid organ transplant recipients in whom LC developed were identified from the University of Pennsylvania Health System’s General Thoracic Surgery database, transplantation database, or from a computerized record of hospital discharge diagnoses. Data were collected from these patients’ inpatient and outpatient medical records. The study was reviewed and granted a waiver of the requirement for informed consent by the University of Pennsylvania’s Office of Regulatory Affairs.

Between January 1, 1977, and July 31, 2002, a total of 5400 patients underwent organ transplantation at the Hospital of the University of Pennsylvania, Philadelphia. These operations included lung (n=318), heart (n=463), kidney (n=3750), pancreas (n=40), and liver (n=829) procedures. Fifteen patients (0.28%) of 5400 solid organ transplant recipients were discovered to have primary lung tumors at varying intervals after receiving the transplantations (Table 1).

The indications for lung transplantations were chronic obstructive pulmonary disease in 2 patients and idiopathic pulmonary fibrosis in 1 patient. Ischemic cardiomyopathy was the indication for heart transplantation in each of the 4 heart recipients in whom LC developed. Kidney transplant recipients spanned a wide range of lesions resulting in end-stage renal failure.

In the lung transplant group, antithymocyte globulin was used for induction therapy, and maintenance was carried out with a combination of cyclosporine, azathioprine, and prednisone. Cyclosporine levels were maintained at 250 to 400 ng/dL. Azathioprine was given at 2.5 mg/kg per day; prednisone therapy was started at the dose of 0.5 mg/kg per day and later tapered to 10 mg/d. In adverse situations, tacrolimus was substituted for cyclosporine and azathioprine was replaced with mycophenolate mofetil. In the heart transplant recipients, from the inception of the program in 1987 until 1998, immunosuppression was achieved using the same drug and dose regimens as for the lung transplant patients. With the availability of newer drugs in 1998, azathioprine was replaced by mycophenolate. Heart transplant recipients received prednisone at 1 mg/kg early postoperatively; but this was tapered off within 9 months. In the kidney transplant recipients, again similar drug regimens were used, but the combinations varied with different periods. The current combination consists of antithymocyte globulin starting intraoperatively, followed by tacrolimus with maintenance levels of 10 µg/L; mycophenolate mofetil, 500 mg twice daily; and prednisone tapered off to 5 mg/d within 1 month. Certainly, a particular patient’s clinical course dictated modifications in these regimens.

Before transplantation, all potential recipients underwent standard chest radiography, but routine preoperative chest computed tomography has been carried out only in the potential lung transplant recipients and only for the past 2 years. There has been no standardized protocol for routine radiological examination of the chest following any of the types of organ transplants except the lung transplantations. Beyond the initial postoperative period, lung transplant recipients have undergone chest radiography every 2 months for 1 year and every 3 months thereafter. Recipients of other organ transplantations have undergone chest radiography only as indicated by clinical symptoms.

**RESULTS**

Among the 15 patients with LC, 3 (0.94% of all lung transplantations) belonged to the lung transplant group, 4 (0.86% of all heart transplantations) were from the heart transplant population, and 8 (0.21% of all renal transplantations) had undergone kidney transplantations. Thus, the overall incidence of LC was highest in lung transplant recipients. Further, since lung transplantations have been performed only in more recent years, the incidence per patient-year following transplantation will be still higher in the lung transplantation group than in the other groups. Each of the malignancies in lung transplant recipients occurred in the native lung.

The ages of those patients in whom LC developed ranged from 36 to 72 years (mean, 57 years) at the time of transplantation. Thirteen were men and 2 were women. Only 11 (73%) of 15 patients had a history of cigarette smoking, ranging from 20 to 120 pack-years (mean, 66 pack-years).

The interval between undergoing transplantation and the diagnosis of the lung tumors varied over a wide range. The mean was 75 months (range, 9-192 months). The interval was much longer in kidney transplant recipients (mean, 102 months; range, 48-192 months) and considerably shorter in the lung transplant recipients (mean, 29 months; range, 9-60 months). The lung transplant recipients were found to be heavier smokers (50-120 pack-years; mean, 93 pack-years) than kidney transplant recipients (20-90 pack-years; mean, 48 pack-years).

Most patients’ conditions were diagnosed at an advanced stage of LC (Table 2). Eight (53%) of 15 patients were assigned stages IIIb or IV and their malignancies were deemed unresectable. Two patients each were classified as having IA, IIB, and IIIA, and 1 was assigned stage IB. Six (75%) of the 8 kidney transplant recipients presented at stage IIIb or higher, while, in general, the lung and heart transplant recipients presented with resectable disease. Six patients had adenocarcinoma, 5 had squamous cell carcinoma, 2 had large cell

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Smoking, Pack-years</th>
<th>Transplanted Organ</th>
<th>Interval Between Transplantation and the Diagnosis of Lung Cancer, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/58</td>
<td>50</td>
<td>Lung</td>
<td>65.2</td>
</tr>
<tr>
<td>2/M/59</td>
<td>110</td>
<td>Lung</td>
<td>13.8</td>
</tr>
<tr>
<td>3/M/62</td>
<td>120</td>
<td>Lung</td>
<td>9.2</td>
</tr>
<tr>
<td>4/M/62</td>
<td>40</td>
<td>Heart</td>
<td>29.6</td>
</tr>
<tr>
<td>5/M/72</td>
<td>Nonsmoker</td>
<td>Heart</td>
<td>60.2</td>
</tr>
<tr>
<td>6/M/63</td>
<td>90</td>
<td>Kidney</td>
<td>71.2</td>
</tr>
<tr>
<td>7/M/72</td>
<td>80</td>
<td>Heart</td>
<td>76.0</td>
</tr>
<tr>
<td>8/F/46</td>
<td>40</td>
<td>Kidney</td>
<td>20.6</td>
</tr>
<tr>
<td>9/M/51</td>
<td>Nonsmoker</td>
<td>Kidney</td>
<td>94.8</td>
</tr>
<tr>
<td>10/F/52</td>
<td>60</td>
<td>Kidney</td>
<td>47.4</td>
</tr>
<tr>
<td>11/M/61</td>
<td>90</td>
<td>Kidney</td>
<td>64.0</td>
</tr>
<tr>
<td>12/M/36</td>
<td>Nonsmoker</td>
<td>Kidney</td>
<td>153.5</td>
</tr>
<tr>
<td>13/M/66</td>
<td>Nonsmoker</td>
<td>Kidney</td>
<td>107.2</td>
</tr>
<tr>
<td>14/M/42</td>
<td>20</td>
<td>Kidney</td>
<td>202.0</td>
</tr>
<tr>
<td>15/M/59</td>
<td>30</td>
<td>Kidney</td>
<td>91.1</td>
</tr>
</tbody>
</table>

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undifferentiated carcinoma, 1 had small cell carcinoma, and 1 had bilateral bronchoalveolar carcinoma.

No major postoperative morbidities or mortalities occurred. Therapeutic procedures included anatomical resections in 7 patients and thoracoscopic pleurodesis in 1 patient with malignant pleural effusion. All resections were lobectomies with complete mediastinal lymphadenectomy. One patient with stage IIA disease underwent postoperative chemoradiotherapy. Among the other unresected patients, 1 received chemotherapy only, and 2 were treated with palliative radiotherapy. Four patients with very poor performance status and advanced stage disease received only supportive care.

The survival after the diagnosis of LC demonstrated stage-dependent variation ranging between 0.33 and 64.2 months (mean, 14 months). Patients with early-stage cancers constituting stages I and II have survived for a mean of 37.3 months (range, 3-64 months); all remain alive and free of disease. The 2 patients with stage IIA disease lived for an average of 6.2 months. Stage IIB and IV tumors showed aggressive behavior with a remarkably short mean survival time of 1.4 months (range, 0.33-3.0 months). This is in marked contrast to the patients with stage IIB or less, each of whom was alive at the last follow-up. Among the various groups, the kidney transplant recipients had considerably shorter survival (mean, 5.9 months) compared with heart and lung transplant recipients (mean, 27.6 and 24.7 months, respectively), consistent with the later stage at which the kidney transplant patients’ tumors presented.

**COMMENT**

Advances in immunosuppression management have led to prolonged survival in many transplant recipients. A by-product of this improvement, however, has been the identification of several complications of chronic immunosuppression. Among the most important of these is the substantially increased incidence of malignancies in transplant recipients. Penn and Branson were the first to report an association between malignancy and immunosuppression in transplant patients. Since then, a substantial body of literature has been published on the subject.

The lungs, compared with several other organs, however, have been underemphasized as a primary site of malignant change in this population. The most common malignancies in transplant patients arise in the lips and skin and the lymphatic system, and these sites have attracted the most attention. The series by Sheil et al of malignancies in transplant recipients, which includes cases of LCs, represents the largest group of such patients, but this series includes only kidney transplant recipients. In our study, 8 of 15 patients were kidney transplant recipients. However, only in recent years have heart and, most recently, lung transplantation become sufficiently widespread to provide a cohort of these patients for analysis. These individuals have often been heavier smokers and, thus, might be at still higher risk of developing LC with immunosuppression. We reviewed our entire solid organ transplantation population to update knowledge about the occurrence of LC following transplantation in an era that includes heart and lung transplantations and to address the specific hypotheses listed in the introduction of this article. To our knowledge, our single-institutional experience represents the largest series of LCs occurring in a group of transplant recipients that includes kidney, heart, and lung recipients.

Our incidence of LC in transplant recipients of 0.28% is virtually identical to that noted in the most recent series of LCs in transplant recipients that includes all solid organ transplant types (0.3%), but somewhat lower than an earlier such series (0.9%). Others have published incidences, following heart and lung transplantation, of between 0.64% and 4.1%. These values are consistent with our finding of a higher incidence of LC following heart and lung than following kidney transplantation.

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**Table 2. Tumor Characteristics and Survival Data**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Stage</th>
<th>Location</th>
<th>Histologic Feature</th>
<th>Treatment</th>
<th>Survival, mo</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T3 N1 M0</td>
<td>IIIA</td>
<td>LLL</td>
<td>SCC</td>
<td>Lobectomy and chemotherapy</td>
<td>8.7</td>
</tr>
<tr>
<td>2</td>
<td>T1 N0 M0</td>
<td>IA</td>
<td>RUL</td>
<td>Adenocarcinoma</td>
<td>Lobectomy</td>
<td>64.2</td>
</tr>
<tr>
<td>3</td>
<td>T4 N0 M0</td>
<td>IIB</td>
<td>MPE</td>
<td>Adenocarcinoma</td>
<td>Pleurodesis</td>
<td>2.3</td>
</tr>
<tr>
<td>4</td>
<td>T3 N2 M1</td>
<td>IV</td>
<td>RUL</td>
<td>Adenocarcinoma</td>
<td>None</td>
<td>0.3</td>
</tr>
<tr>
<td>5</td>
<td>T1 N0 M0</td>
<td>IA</td>
<td>RUL</td>
<td>Adenocarcinoma</td>
<td>Lobectomy</td>
<td>29.1</td>
</tr>
<tr>
<td>6</td>
<td>T2 N0 M0</td>
<td>IB</td>
<td>RLL</td>
<td>SCC</td>
<td>Lobectomy</td>
<td>54.5</td>
</tr>
<tr>
<td>7</td>
<td>T3 N0 M0</td>
<td>IIB</td>
<td>RUL</td>
<td>SCC</td>
<td>Lobectomy CWR</td>
<td>3.0</td>
</tr>
<tr>
<td>8</td>
<td>T3 N0 M0</td>
<td>IIB</td>
<td>RUL</td>
<td>SCC</td>
<td>Lobectomy</td>
<td>35.5</td>
</tr>
<tr>
<td>9</td>
<td>T3 N3 M1</td>
<td>IV</td>
<td>RUL</td>
<td>Small cell carcinoma</td>
<td>None</td>
<td>0.5</td>
</tr>
<tr>
<td>10</td>
<td>T3 N2 M1</td>
<td>IV</td>
<td>LUL</td>
<td>Adenocarcinoma</td>
<td>None</td>
<td>0.5</td>
</tr>
<tr>
<td>11</td>
<td>T4 N1 M0</td>
<td>IIB</td>
<td>LLL</td>
<td>Large cell undifferentiated</td>
<td>RT</td>
<td>1.0</td>
</tr>
<tr>
<td>12</td>
<td>T4 N0 M0</td>
<td>IIB</td>
<td>MPE</td>
<td>Adenocarcinoma</td>
<td>None</td>
<td>1.7</td>
</tr>
<tr>
<td>13</td>
<td>T4 N1 M1</td>
<td>IV</td>
<td>Bilateral Bronchoalveolar</td>
<td>Chemotherapy</td>
<td>2.1</td>
<td>Dead</td>
</tr>
<tr>
<td>14</td>
<td>T4 N2 M1</td>
<td>IV</td>
<td>LLL</td>
<td>Large cell undifferentiated</td>
<td>RT</td>
<td>3.0</td>
</tr>
<tr>
<td>15</td>
<td>T2 N2 M0</td>
<td>IIIA</td>
<td>RLL</td>
<td>SCC</td>
<td>Lobectomy</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Abbreviations: CWR, chest wall resection; LLL, left lower lobe; LUL, left upper lobe; MPE, malignant pleural effusion; RLL, right lower lobe; RT, radiotherapy; RUL, right upper lobe; SCC, squamous carcinoma; UICC, Union International Contre le Cancer.
Eight of the 15 patients with LCs in our series were unresectable (stage IIIB-IV) at the time of presentation. This staging at diagnosis is somewhat higher than was found in most,\textsuperscript{9,10,17,20} but not all,\textsuperscript{13,14} of the other larger series on LC in transplant recipients. Although this rate of unresectability is not dramatically different from what one might expect in a general population of patients with LC, transplant recipients represent a group receiving close medical follow-up. One might expect, if this was the only factor playing a role, that their tumors would be identified earlier in their course rather than later. When correcting for this confounding factor, we believe that it is likely that the tumors in this immunosuppressed population do, in fact, advance more rapidly before diagnosis.

Six of 8 patients with stage IIIB-IV disease were kidney transplant recipients, and this group had a prolonged interval to the discovery of the malignancy (mean, 102 months) vs the heart and lung transplant recipients (mean, 57 and 29 months, respectively). It could be argued that delayed detection of LCs in this group might have resulted from the fact that kidney transplant recipients did not receive routine follow-up chest radiographs as did lung transplant recipients. It is likely, further, that the heart transplant recipients would have had more frequent clinical indications than kidney transplant recipients for undergoing chest radiography that might discover an early LC. Another reason that kidney transplant recipients have likely had less aggressive screening than the other groups is that a higher percentage of the heart and lung transplantations have been performed in more recent years, after the recognition that late detection of LCs may easily be mistaken for one of the infectious processes that occur in transplant recipients independent of smoking, a longer period is required before genetic changes sufficient to result in cancer can accumulate independent of cigarette smoking.

CONCLUSIONS

There is little doubt that suppression of the normally protective antitumoral immune response accelerates tumor growth and metastatic spread.\textsuperscript{22} This fact may account for the remarkably short mean survival of 1.4 months in our patients with LC who presented with unresectable (stage IIIB-IV) disease. Survival of our patients with resected stage IIIA disease (mean, 6.2 months), although better than that of patients with stage IIIB-IV disease, is not promising and suggests that surgical intervention in stage IIIA is of questionable value in transplant recipients. These results would suggest that at a minimum, these patients should undergo routine mediastinoscopy, and that those with N2 disease should undergo neoadjuvant treatment prior to surgical resection if it is felt that they can tolerate such a demanding regimen.

In contrast to the poor results obtained in stages IIIA, IIIB, and IV in our series, however, it is remarkable how well the patients with stages IA-IIIB LC have done to date. This group has a mean overall survival of 37.3 months; all are alive and free of disease at the last follow-up. These results are somewhat better than those reported in other series of LC in transplant recipients,\textsuperscript{9,10,13,17,20} and at least as favorable as those published for nonimmunosuppressed patients.\textsuperscript{21} This finding suggests that if a complete resection can be performed, the increased risk resulting from immunosuppression plays no major role. This finding, in conjunction with the finding of extremely poor outcomes in patients with higher-staged carcinomas and the absence of increased operative morbidity in these patients, highlights the need for early detection of lung tumors in this population. If there exists any population in which computed tomographic-based screening is appropriate, the population of transplant recipients, particularly if they have been smokers, seems to be a well-suited group.

Regarding our hypothesis that squamous cell carcinomas might predominate, data show that, on the contrary, the different histological types are approximately normally represented among our patients. This is in contrast to 2 of the previous series\textsuperscript{2,20} that did contain a preponderance of squamous tumors among non–small cell tumors. However, the presence of 4 nonsmokers (27%) in the group is far higher than the prevalence of nonsmokers in the general population of patients with LC. Further, only 1 of the tumors in nonsmokers was a bronchoalveolar carcinoma, the histological type that is known to occur in nonsmokers. This suggests that there is some effect of immunosuppression that is independent of smoking (perhaps at the level of oncogene expression) that predisposes to bronchogenic carcinoma in these patients.

It is unclear why this series is alone among the larger series of LC in transplant recipients to identify an increased risk among nonsmokers. One possible explanation is the greater number of kidney transplant recipients in our series, many of whom have had a long duration of immunosuppression. Shell et al\textsuperscript{4} did not report on the number of nonsmokers in their article that includes LCs found in kidney transplant patients from the Australia–New Zealand transplant registry. In fact, our nonsmokers are predominately in the kidney transplant group. Further, the nonsmokers do demonstrate a longer interval before the development of LC (mean, 103 months) vs the smokers (mean, 56 months). This suggests that although immunosuppression may cause LC to occur in transplant recipients independent of smoking, a longer period is required before genetic changes sufficient to result in cancer can accumulate independent of cigarette smoking.

Bronchogenic carcinoma is among the solid organ tumors to which transplant recipients are susceptible. Although many of these cancers occur in former smokers, a higher proportion of nonsmokers develop LC in the transplant population than in the general population. The recent increase in lung transplantation, in particular, is likely to lead to a greater incidence of LC in transplant recipients. The effect of immunosuppression appears to result in the more rapid progression of these tumors to an unresectable stage. Our data suggest that patients with
stage IIIB-IV disease do very poorly and should receive only palliative care. Patients with stage IIIA disease should receive neoadjuvant therapy if their performance status permits, as resection without such therapy appears to have a poor outcome. However, the excellent results following surgical resection of patients with stage I and II disease indicates that aggressive surgical therapy should be carried out in these cases and highlights the importance of early diagnosis of LC in immunosuppressed patients. This may be an appropriate group in which to apply regular computed tomographic screening.

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Correspondence: Joseph B. Shragar, MD, General Thoracic Surgery, 4 Silverstein Bldg, Hospital of the University of Pennsylvania, 3400 Spruce St, Philadelphia, PA 19104 (jshrag@mail.med.upenn.edu).

REFERENCES


ARCHIVES OF INTERNAL MEDICINE

The Additional Diagnostic Value of Ultrasonography in the Diagnosis of Breast Cancer

Karin Flobbe, PhD; Anne Marie Bosch, MD; Alfons G. H. Kessels, MD, MSc; Gerard L. Beets, MD, PhD; Patricia J. Nelemans, MD, PhD; Maarten F. von Meyenfeldt, MD, PhD; Joseph M. A. van Engelshoven, MD, PhD

Background: The use of ultrasonography (US) in diagnostic breast imaging is increasing. Restricting US to subgroups of patients who benefit most would result in a more efficient and effective application. This study assessed the diagnostic value of US as an adjunct to mammography (MAM) and a clinical examination (CE) in the diagnosis of breast cancer and the feasibility of selecting subgroups of patients who benefit the most.

Methods: Between October 1, 1999, and August 1, 2000, all consecutive patients referred for breast imaging underwent additional US after MAM and a CE. Results were scored on a 5-point grading scale of increasing suggestion of malignancy. Pathologic results during 12 months of follow-up were used as the criterion standard. Receiver-operating characteristic curve analysis assessed the diagnostic value of US in the whole population and in subgroups of patients according to indication for referral and age.

Results: A total of 3835 breasts were examined in 2020 patients, with a 6.3% prevalence of breast cancer. Breast US detected 8 extra malignancies and correctly downgraded 332 cases from a positive to a negative diagnosis (ie, from a suggested malignancy to no malignancy). Receiver-operating characteristic curves showed a significant improvement in diagnostic value by adding US to MAM and a CE (area under the curve for CE+MAM+US vs CE+MAM, 0.99 vs 0.95; P=.002). The diagnostic yield improved significantly in patients referred for palpable breast lumps (P=.004) or referred from the National Breast Cancer Screening Program (P=.05). Less pronounced was the value in patients referred for other symptoms or for follow-up of a prior breast malignancy. When breast imaging of the contralateral breast or of asymptomatic patients referred for reassurance or follow-up of a prior benign lesion was performed, the value of additional US remained undefined because of the few malignancies found.

Conclusions: The systematic application of breast US improved the overall diagnostic yield. The diagnostic value increased most in patients with palpable breast lumps and in patients referred with abnormal screening MAM results. (2003;163:1194-1199)

Correspondence: Dr Karin Flobbe, Department of Radiology, Maastricht University Hospital, PO Box 5800, 6202 AZ Maastricht, the Netherlands (flobbe@rad.unimaas.nl).