Is computed tomography guided biopsy still necessary for the diagnosis of adrenal masses in patients with resectable non-small-cell lung cancer?

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Abstract

Objectives: This study was undertaken: (1) to evaluate the usefulness of unenhanced computed tomography (CT), magnetic resonance imaging (MRI) and CT guided biopsy for the characterization of adrenal masses in patients with operable non-small-cell lung cancer (NSCLC) and (2) to evaluate the situations in which CT guided biopsy is absolutely necessary before potentially curative resection of NSCLC. Methods: Consecutive patients with operable NSCLC underwent unenhanced adrenal CT with density measurements of any adrenal mass over 1 cm in diameter. An adrenal mass was considered as an adenoma when its density was below 10 Hounsfield Units and a metastasis when its density exceeded 10 Hounsfield Units. Then patients underwent MRI, the signal on the T2 weighted images from the enlarged gland was classified adenoma or metastasis in comparison with that from the liver parenchyma. CT guided biopsy was performed after a pheochromocitoma was eliminated. Unenhanced CT attenuation values and signal intensity values on MRI were correlated with histopathologic results. Results: Of the 443 patients, 32 had an adrenal mass consisting of adrenal metastases in 18 cases and adenomas in 14 cases. On CT, 3/14 (21%) of the adenomas were misdiagnosed as metastases (their densities exceeded 10 Hounsfield Units) and 2/18 (11%) of the metastases were misdiagnosed as adenomas (their densities were below 10 Hounsfield Units). On MRI, none of the metastases were misdiagnosed as an adenoma (100% sensitivity) but 7/14 (50%) of the adenomas were misdiagnosed as metastases (signal superior to that of liver). Overall, a diagnostic certainty of metastasis could not be obtained in 25/32 patients (78%). CT guided biopsy with 100% sensitivity and specificity corrected all the inaccurate results of CT and MRI without any morbidity. Conclusion: Despite extensive morphological evaluation with unenhanced CT and conventional MRI, CT guided biopsy is necessary for most patients referred to surgery for an operable NSCLC and an adrenal mass. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

The strongest prognostic factor for survival in patients suffering from non-small-cell lung carcinoma (NSCLC) is whether the lesion can be completely resected. Due to the significant morbidity, mortality and cost are associated with the surgical treatment of lung cancer, it is important to identify those patients who will not benefit from resection. Computed tomography (CT), performed to assess the operability of the patients who might benefit from it, must include evaluation of the adrenal glands, because in patients with otherwise operable NSCLC, adrenal gland metastases are found in 1.62 – 3.5% of cases [1,2]. Characterization of an adrenal mass is particularly important in patients with an extra-adrenal primary malignancy when the adrenal lesion is the only site of possible metastasis. Furthermore, even in cases of extra-adrenal malignancy, many adrenal masses are benign [3]. In such cases, it is unlikely that potentially curative treatment of the primary tumor would be completed without confirmation of the nature of an adrenal lesion, thought to be the sole site of metastatic spread.
Consequently, the characterization of an adrenal mass as a likely metastasis almost always requires CT-guided biopsy (CTGB) before potentially curative surgical therapy. Recent improvements in non-invasive procedures for adrenal mass identification such as, CT scan and magnetic resonance imaging (MRI) led us to undertake a prospective study in which we compared the results of CTGB with those of CT plus MRI. The study was designed to define the situations in which CTGB is absolutely necessary before potentially curative resection of the NSCLC.

2. Patients and methods

2.1. Computed tomography

All the patients with a resectable NSCLC, referred to our institution, underwent systematic CT exploration of the adrenal glands. Five millimeter slices were obtained at 5-mm intervals through the adrenal glands. Analysis of the CT data were confined to size (in cm) and density readings in Hounsfield units (HU). Lesion size was defined as the longest diameter (in cm) in the axial plane on CT, and any lesion over 1 cm in diameter was classified as an adrenal mass eligible for entry into the study. Only unenhanced images were used for quantitative evaluation. Density readings were obtained using a region of interest within the substance of the adrenal lesion, to avoid partial volume averaging with the surrounding tissue.

On the basis of a review of threshold densities used in other studies, lesions were classified into two groups. An adrenal mass was considered as an adenoma when its density was below 10 HU, and as a metastasis, when its density exceeded 10 HU. The latter was regarded as a positive CT result when the diagnosis was confirmed.

A metastasis with a density below 10 HU was considered as a false negative result. An adenoma with a density exceeding 10 HU was considered as a false positive result.

2.2. Magnetic resonance imaging

All the patients who had an adrenal mass detected by CT underwent MRI. On MRI, the signal from the enlarged adrenal gland on the T2 weighted images was compared with that from the liver parenchyma. An adrenal mass with a signal superior to kidney signal on these images was considered as a pheochromocytoma.

An adrenal mass with a signal inferior or equal to liver signal was considered as an adenoma. If the final diagnosis was a metastasis, it was considered as a false negative result. An adrenal mass with a signal superior to liver and inferior to kidney signal was considered as a metastasis. When the diagnosis was confirmed, it was regarded as a positive result. An adenoma with a signal intensity superior to liver signal was considered as a false positive result.

2.3. CT guided biopsy

When the diagnosis of pheochromocytoma was ruled out (no biological signs and no high signal intensity on T2 weighted images), patients underwent CTGB of this mass. They were biopsied in the prone position under conscious sedation, thus allowing a posterior or postero-lateral approach to the mass.

The mass was analyzed with 5 mm axial sections and needle position documented by repeated 5 mm axial sections. The approach was direct in most cases, but was sometimes trans renal or trans hepatic. The 19 or 22 gauge needles were used. In cases of bilateral adrenal gland enlargement, both masses were biopsied. After the biopsy, CT sections were obtained to check for hemorrhage and 1 h after biopsy, chest radiography was performed to check for the absence of pneumothorax.

CTGB interpreted the results of CT and MRI. CT scan, MRI and CTGB data were summarized in order to define the cases in which CTGB was absolutely necessary to obtain a diagnosis affecting the patient’s therapeutic management.

2.4. Therapeutic management and follow up according to histological data

In the case of solitary adrenal gland metastasis homolateral to the NSCLC, adrenalectomy was performed synchronously with lung resection. In case of solitary adrenal gland metastasis controlateral to the NSCLC, an adrenalectomy was performed 3 months after lung resection [2]. Patients with bilateral adrenal metastatic spread were treated by chemotherapy and/or radiotherapy. Those with adenoma, underwent potentially curative lung resection. In each group, follow-up consisted of a thoracic CT examination including the adrenals, every 6 months.

3. Results

Thirty-two out of the 443 patients with operable NSCLC referred to our institution from 1 July 1991 to 1 July 1997 (7.22%), had an adrenal gland mass. They comprised 30 men and two women, aged from 43 to 74 years. The mean follow-up period was 36 months (range 7 to 84 months). The histological type and the TNM classification of the primary lung cancer of the 32 patients are given in Table 1. The final diagnoses for the adrenal masses according to the 100% accuracy of the CTGB results (confirmed by sur-
surgery and follow up) were 18 metastases (4% of all the patients) and 14 adenomas (3% of all the patients).

3.1. Computed tomography

None of the lesions with a density exceeding 10 HU were less than 3 cm in diameter and no lesion with a density below 10 HU was more than 3 cm in diameter.

Nineteen lesions had a density above 10 HU. They comprised 16 metastases and three adenomas. Consequently, there were three false positive results of CT scan and 21% (3/14) of the adenomas were misdiagnosed as metastases.

Thirteen lesions had a density below 10 HU; they comprised two metastases and 11 adenomas. Consequently, there were two false negative results of CT scan and 2/18 (11%) of the metastases were misdiagnosed as adenomas.

3.2. Magnetic resonance imaging

There was no lesion with a signal superior to kidney signal. The seven lesions with a signal inferior or equal to liver signal comprised seven of the 14 adenomas according to the final diagnosis. There were no false negative results of MRI, as none of the metastases were misdiagnosed as an adenoma.

Twenty-five lesions had a signal superior to that of the liver. They included all the 18 metastases and seven of the 14 adenomas. There were seven false-positive results of MRI and 7/14 (50%) of the adenomas were misdiagnosed as metastases.

3.3. CT + MRI

The seven lesions with a signal inferior to liver signal had a diameter below 3 cm and a density below 10 UH on CT. When MRI and CT criteria were taken together to diagnose adenoma, a precise diagnosis was obtained for seven patients without false negative results. The six remaining lesions classified as adenomas by CT (two metastases and four adenomas according to final diagnosis) were classified metastasis by MRI. To diagnose a metastasis, the most specific examination was CT, with 16 accurate results for the 18 patients with adrenal gland metastasis, and three false-positive results (adenomas) not corrected by MRI, which also classified these three adenomas as metastases. Among the 25 adrenal masses classified as metastases by MRI (18 metastases and seven adenomas according to final diagnosis), four adenomas were correctly classified by CT, and three others were incorrectly classified as metastases. Overall, MRI never corrected the CT data, and was only specific for the diagnosis of adenomas.

3.4. CT guided biopsy and therapeutic management

The diagnosis material of tissue cylinders was, in all cases, enough to make a certain pathological. The morbidity was nil, and a precise histological diagnosis was obtained for all 32 patients. The 14 patients with adenoma underwent potentially curative lung resection and their follow-up, mean 44 months (range:12 to 84) confirmed the diagnosis of adenoma in all cases. Among the 18 patients with adrenal gland metastasis, nine had a metastatic spread in other sites. The remaining nine patients (2% of the original cohort of 443) underwent lung and adrenal resection with confirmation of their metastatic diagnosis [2]. Eight of them died from their recurrent lung cancer respectively, 4, 6, 8, 10, 13, 14, 19 and 24 months after surgery. One patient is still alive 78 months after surgery. In the nine patients with adrenal metastases and metastatic spread in other sites who were not operated on (all the other patients underwent surgery), follow up, mean 6 months (range 2 to 15) confirmed the diagnosis.

The sensitivity and specificity of CT, MRI, CT + MRI and CTGB are given in Table 2.

4. Discussion

Despite the early enthusiasm for non-enhanced CT measurement and conventional MRI of the adrenal gland to differentiate benign from metastatic lesions, we have been unable to predict consistently whether an adrenal mass was malignant or benign and 78% of the patients had to be biopsied because these examination lacked specificity. The typical imaging features of an adrenal adenoma on CT are those of a small and usually homogeneous mass,
with a smooth rounded appearance [3,4]. Despite the fact that on CT, metastases tend to be larger than adenomas, less well defined and of inhomogeneous density, the imaging features of adrenal metastases are non-specific. Small metastases are often homogeneous, but large ones often have heterogeneous appearance due to hemorrhage or central tumor necrosis [3,4]. Assessment of size is of interest because adrenal masses larger than 3 cm are malignant in 90–95% of the cases (84% in our study) and masses less than 3 cm in diameter are benign in 78–87% of cases (85% in our study) [5–7]. However in our series, using size alone as a diagnostic criterion would have misclassified two malignant lesions which had a maximum diameter of less than 3 cm and three benign lesions which had a maximum diameter superior to 3 cm. Consequently, size alone is not a sufficient parameter for discriminating between adenomas and non-adenomas and its interpretation must be corrected by CT attenuation values [5] which indicate the amount of histological lipids in the lesion [6]. Various authors have examined the value of CT density in classifying adrenal masses. The data from many of these studies are difficult to pool, since the studied populations and the techniques used differed considerably [5–8]. Korobkin et al. demonstrated that for CT attenuation values of less than 10 HU on a non-enhanced scan, the diagnosis of adenoma was 100% specific, with a sensitivity of 85% [6]. Van Erkel et al. confirmed these results and recommended a threshold of 16.5 HU units with a sensitivity of 100% and a specificity of 95% for an adenoma when applied retrospectively to their series [7]. In our study, we misdiagnosed two metastases using 10 UH as cutoff point pointing out that an adrenal lesion should not be diagnosed as benign on the basis of attenuation measurement alone.

Recently, very encouraging results have been published about the usefulness of delayed contrast enhanced CT [9–11]. Szolar et al. demonstrated that delayed enhanced CT scans obtained 10 and 30 min after the start of contrast material injection have higher sensitivity and specificity for the differentiation of adenomas and non-adenomas than do unenhanced CT scans. One of the potential advantages of delayed enhanced CT densitometry compared with unenhanced CT scans is the opportunity to detect the lipid poor adenomas that result in an unenhanced attenuation value of greater than 10 UH [10]. Nevertheless, in the same field Boland [9] and Korobkin [10] point out that a larger number of patients have to be included to substantiate their results and to predict the exact modalities of delayed-contrast enhanced-CT in the evaluation of the adenals to make it reproducible in various institutions.

Several different MRI techniques like conventional spin-echo-imaging, and chemical shift MRI [8,12–16] have been used to distinguish benign adenomas from metastases. On MRI, low signal intensity below or equal to that of the liver signal on T2 weighted images is highly suggestive of benign signal on T2 weighted images. Very high signal intensity, above that of the kidney signal is highly suggestive of pheochromocytoma, but moderate high signal intensity above that of the liver signal but below that of the kidney signal has no specificity as shown in our series.

Chemical shift MRI is based on the decrease in signal intensity on opposed phase images when lipid is present in an adrenal mass. Schwartz et al. recently showed that chemical shift MRI can obviate the need for CTGB in 55% of patients with operable NSCLC and an adrenal mass. Their study mainly demonstrates that chemical shift MRI is interesting to ascertain the diagnosis of adenoma (100% specificity), but CTGB is still required to ascertain the diagnosis of metastasis [15]. Consequently, chemical shift MRI is no more conclusive than CT attenuation measurements, because, both methods gave indeterminate values for a similar subset of benign lesions [16].

Recently, PET with F-Fluorodeoxy-glucose (FDG) has been used to differentiate between benign and malignant adrenal masses in patients with bronchogenic carcinoma [17]. A study by Erasmus et al. revealed that 80% of patients with lung cancer and increased FDG activity in an adrenal mass had metastatic disease. Furthermore, all adrenal lesions that exhibited normal FDG activity were benign [17]. The most obvious problem related to PET are its limited availability and the nature of FDG itself, leading to non-specific imaging in cases of non-specific inflammation or acute infection [18]. Consequently, the sensitivity of PET with FDG for the detection of adrenal gland metastases is high, but its specificity is still unacceptable as a basis for withholding a potentially curative treatment of the primary lesion.

Our evaluation of imaging technics could be criticized since we did not employ the most up-to-date imaging protocols, i.e. delayed contrast-enhanced CT and MRI chemical shift imaging. However, according to literature data, further studies about these are necessary to demonstrate enough specificity for the diagnosis of adrenal metastases in patients with resectable NSCLC and density measurements on non enhanced CT is still the ‘gold standard’ and cost effective imaging protocol to evaluate the adrenals.

In our study, CTGB proved to be a perfect standard of reference with 100% sensitivity and specificity. These results are substantiated by a large world-wide experience reporting mainly minor complications (pneumothorax) in 3–9% and only two cases of needle tract metastases [19–21].
We therefore, propose the following strategy, only designed for cases in which diagnosis of a metastatic adrenal mass will alter the surgical management.

The first step is to measure the density of the mass by non-contrast CT. If it is less than 10 HU, MRI should be the next step. If the signal intensity on T2 weighted images is below or equal to liver signal, the lesion can be classified as an adenoma and no further investigation is required. Follow-up by non-contrast CT is required every 6 months. Except for pheochromocytoma, all other lesions with signal superior than liver signal should be biopsied.

If the lesion density is superior to 10 UH on non-enhanced CT, CTGB must be performed after a pheochromocytoma has been eliminated.

References