Prognostic significance of adrenal gland morphology at CT in patients with three common malignancies

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Objectives: To determine whether minor alterations in adrenal gland morphology at baseline CT in three common cancers indicate early metastasis.

Methods: 689 patients (237 with lung cancer, 228 with breast cancer, 224 with melanoma) underwent baseline and follow-up CTs that included the adrenals. Two readers independently scored each adrenal at baseline CT as normal, smoothly enlarged, nodular or mass-containing. Adrenals containing a mass >10 mm were excluded. The appearance of each adrenal on the latest available CT was assessed for change since baseline. Cox models were used to assess the association between adrenal morphology at initial CT and subsequent development of adrenal metastasis (defined as new mass >10 mm, corroborated by follow-up imaging). κ statistics were calculated to assess inter-reader agreement.

Results: Initial and follow-up CT evaluations were recorded for 1317 adrenals (median follow-up, 18.6 months). At initial CT, Readers 1 and 2 interpreted 1242 and 1230 adrenals as normal, 40 and 57 as smoothly enlarged, 29 and 25 as nodular, and 6 and 5 as containing masses $\leq$ 10 mm, respectively. κ -values were 0.52 (moderate) at initial CT and 0.70 (substantial) at follow-up. The hazard ratio for developing a metastasis at follow-up CT given an abnormal adrenal assessment at baseline was 0.7 [95% confidence interval (CI) 0.2–2.1; $p=0.47$] for Reader 1, and 2.0 (95% CI 0.8–4.7; $p=0.12$) for Reader 2.

Conclusion: Minor morphological abnormalities of adrenals at initial CT did not represent early adrenal metastasis in most patients in this population.

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The adrenal gland is a common site of cancer metastasis, with a reported incidence of up to 36% in post-mortem studies [1]. Adrenal metastases start as microscopic foci that are not detectable by imaging until they grow and become a discrete mass. The ability to identify an adrenal metastasis at an earlier stage, before macroscopically evident at standard imaging, would allow earlier institution of appropriate therapy and thus potentially improve patient outcomes.

Benitah et al [2] found no significant association between adrenal gland morphology at baseline CT and the subsequent development of adrenal metastasis at CT in patients with primary lung carcinoma. In addition to lung cancer, breast cancer and melanoma are two of the more common primary solid tumours that metastasise to the adrenal gland [3, 4]. Up to 50% of melanoma patients develop adrenal metastases, the majority of which are clinically silent [5]. Survival may be prolonged in patients whose adrenal metastases are resected [4]. No data regarding the prognostic significance of baseline adrenal morphology at CT in patients with melanoma or breast carcinoma have been reported, to our knowledge.

The purpose of our study was to assess whether minor changes in adrenal morphology at baseline CT represent

the presence of early adrenal metastasis in patients with lung carcinoma, breast carcinoma or melanoma.

Methods and materials

Patients

This United States Health Insurance Portability and Accountability Act-compliant retrospective study was approved by our Institutional Review Board, which waived the need for informed consent. Consecutive patients with a histopathologically confirmed diagnosis of only one cancer—lung cancer, breast cancer or melanoma—diagnosed after 1 January 2002, and who underwent both baseline CT and at least one follow-up CT that included the adrenal glands, were identified by computerised reviews of the institutional tumour registry and radiology database. This time period was chosen to provide a long clinical and radiological follow-up. Patients with any additional cancer diagnosis (other than non-melanocytic basal cell skin cancer) were excluded. If neither adrenal gland was included in the baseline scan for technical reasons, the patient was not included in the study. Patients were also excluded if an adrenal nodule measuring >10 mm was present at baseline CT. The first 237 consecutive eligible patients with lung cancer, the first 228 with breast cancer and the

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first 224 with melanoma, diagnosed after 1 January 2002, were included in the study.

CT examinations

916 CT scans were performed at our institution. 462 CT studies were performed at outside facilities and were entered into our picture archiving and communication system (PACS) prior to interpretation. Most were performed using helical scanners, collimation of 5–7.5 mm (86.9%), and after bolus administration of intravenous contrast (76.9%).

The earliest available CT for each patient that included at least one adrenal gland was considered the initial CT for this study, and the most recent available CT that included at least one adrenal gland was considered the final CT.

Image analysis

Two radiologists independently reviewed the CT studies in each patient. One reader (CPM) had completed 6 months of a body imaging fellowship, and the other (JLF) had 6 months of experience as an attending radiologist in body imaging. Prior to commencing the image analysis, both readers reviewed a training image set, comprising two representative examples of each of the adrenal gland morphological types defined in the study (Figure 1); the training images were not obtained from study patients.

CT images were reviewed on a PACS workstation (Centricity; General Electric, Milwaukee, WI), using soft-tissue window settings that the reader could manipulate, if

desired. Studies were presented to the readers in random order. The readers were aware that the patients had a histopathological diagnosis of one of the three cancers, but were unaware of other clinical and radiological findings. If multiple image series included the adrenals, contrast-enhanced images were preferentially selected for evaluation. Only axial images were interpreted.

Each reader independently scored each adrenal gland at baseline CT as normal, smoothly enlarged, nodular, containing a mass or not visible. An adrenal gland was considered to be smoothly enlarged if at least one of the limbs (measured individually) measured >6 mm in thickness. An adrenal gland was considered nodular if a surface showed one or more convex contour deformities, without a discrete mass. An adrenal mass was defined as a focal round or oval structure, of any size, within the adrenal gland. Readers measured the largest dimension of any adrenal mass, using electronic callipers. If either adrenal gland was not visible, this fact was recorded along with the assessment of the visualised contralateral gland.

At a subsequent reading session (at least 3 weeks after the first session), each reader independently directly compared the appearance of each adrenal gland at the latest available follow-up CT for each patient with its appearance at baseline CT, and any change in appearance was recorded. If changes in adrenal morphology were seen that might suggest a treatment effect, such as a decrease in adrenal size, the reader reviewed any intervening CT examinations to identify the date on which any change from baseline CT could be appreciated, and the date and nature of any such changes were recorded.

If either adrenal gland was interpreted as containing a mass >10 mm at follow-up CT, the institutional

Figure 1. Axial contrast-enhanced CT images (from training image set) showing various morphological changes in adrenal glands at CT. (a) Smooth enlargement of left adrenal gland (circle). Left medial limb measured 7 mm wide. (b) Nodular left adrenal gland. The contour of the lateral limb of left adrenal gland is focally convex (arrow) along only one surface. (c) Adrenal mass. Left adrenal gland contains a 12 mm mass (arrow).

electronic medical record was reviewed to obtain any available histopathological correlation.

Statistical analysis

Interobserver agreement for classifying adrenal gland morphology at baseline CT and at follow-up CT was evaluated using the κ statistic.

An adrenal metastasis was considered present in this study if a new mass >10 mm had developed at the last available follow-up CT. To determine whether the initial adrenal assessment was predictive of metastasis, the following three categories were combined into a "Not Normal" category because of sparse data of metastatic events: smoothly enlarged, nodular and mass (≤ 10 mm at baseline). The association between initial adrenal assessment of (Normal *vs* Not Normal) and metastases was assessed using Cox models with robust standard errors that accounted for the correlated data due to the two adrenal side measurements obtained in most patients. 95% confidence intervals (CIs) were also calculated for these estimates.

Summary statistics were performed on a per adrenal gland basis and on a per patient basis. Statistical analyses were performed using SAS, version 9.1 (SAS Institute, Inc., Cary, NC) and Stata, version 11.0 (StataCorp, College Station, TX) by two authors (ASR, CSM).

Results

1317 adrenal glands were visible and evaluated in 689 patients (231 male, 458 female) (Table 1), with median follow-up of 18.6 months (range, 0.1–153 months).

Two right and seven left adrenals were not identified by Reader 1 at baseline, and five right and eleven left adrenals by Reader 2. At follow-up CT, four and two right, and six and three left adrenals were not identified by Readers 1 and 2, respectively. In those cases, no mass was evident in the adrenal bed.

Metastasis subsequently developed at follow-up CT in 72 of 1242 (5.80%) and 51 of 1230 (4.15%) adrenal glands characterised as normal by Readers 1 and 2, respectively, at initial CT (Table 2). Metastasis subsequently developed at follow-up CT in 3 of 69 (4.3%) and 6 of 82 (7.3%) adrenal glands characterised as Not Normal by Readers 1 and 2, respectively, at initial CT (Figures 2 and 3). The median time to the first follow-up CT that showed adrenal metastasis was 5.5 months (range, 3–8 months) for Reader 1 and 3 months (range, 1–24 months) for Reader 2. All metastases were in patients with lung

cancer, except for in one patient with melanoma. The metastases ranged in size from 1.7 to 3.1 cm. Histopathological verification of metastasis was available in only one adrenal gland classified as containing a (new) mass >10 mm at follow-up CT; all others were presumed based on typical changes in size at follow-up CT.

There was no significant association between the initial adrenal assessment by Reader 1 or 2 and the subsequent development of adrenal metastasis ($p=0.47$ and $p=0.12$, respectively); the hazard ratios for development of an adrenal mass >10 mm at follow-up were 0.7 and 2.0, respectively (95% CIs, 0.2–2.1 and 0.8–4.7, respectively).

Interobserver agreement for right and left adrenal glands combined at initial CT was moderate ($\kappa=0.52$), and substantial ($\kappa=0.70$) at follow-up (Table 3).

In the 10 patients with adrenal masses classified as ≤ 10 mm at initial CT (5 by Reader 1, 6 by Reader 2, with 1 patient classified the same by both readers), none of those adrenals showed change at follow-up imaging. In two of these, MRI scans showed signal changes typical of adrenal adenoma at chemical shift imaging.

Discussion

Soon after the clinical introduction of CT, Montagne et al [6] reported good correlation between adrenal length, width and thickness as measured at CT and as previously reported at autopsy in patients without clinical evidence of adrenal disease. In 22% of those patients studied, visualisation of at least one adrenal gland was deemed inadequate, at least partly because measurements were made on film, and the CT sections were 10 mm thick and subject to motion artefacts. The two most frequent configurations for the right adrenal gland were linear (87%) and V-shaped; for the left adrenal gland, the three most common configurations were V-shaped (50%), Y-shaped (32%) and triangular (18%). The authors did not describe finer morphological features, which probably were obscured by technical limitations. Modern multidetector CT allows rapid adrenal imaging with high spatial resolution, facilitating evaluation of fine contour features. In our study, bilateral adrenal visualisation was achieved in almost all cases, and electronic callipers in PACS facilitated more accurate measurements.

Several types of morphological changes have been identified in adrenal glands of patients with malignancy at histopathological and imaging examinations in the absence of a gross mass. Vincent et al [7] reported that the mean adrenal size at CT in a group of patients with various types of cancer was larger than in control subjects without a known tumour or primary adrenal dysfunction. However, there was no significant difference in the degree of adrenal gland enlargement in patients with different stages of malignancy. Noting prior studies that confirmed biochemical evidence of abnormal adrenal function in patients with malignant disease [8, 9], the authors postulated that the observed adrenal gland enlargement reflected gland hyperplasia, possibly caused by circulating tumoural factors, rather than metastatic involvement; histopathological correlation, however, was not performed.

Table 1. Patient demographics by tumour type

Tumour type	Male	Female	All
Number of patients			
Lung cancer	98	139	237
Breast cancer	0	228	228
Melanoma	133	91	224
Mean age years (range)			
Lung cancer	62.6 (35–87)	64.4 (37–84)	63.6 (35–87)
Breast cancer	N/A	53.9 (24–90)	53.9 (24–90)
Melanoma	58.2 (25–83)	57.3 (18–80)	57.8 (18–83)

Figure 2. Axial contrast-enhanced CT images showing minor nodular changes at baseline CT, and subsequent development of metastasis at follow-up imaging in a 64-year-old male with lung cancer. (a) Nodular right adrenal gland (arrow) at baseline CT. (b) Right adrenal metastasis (arrow) at follow-up CT obtained 37 months later; metastasis was first evident at 24 months.

Small adrenal masses discovered at CT often pose a diagnostic challenge, unless demonstrating macroscopic fat. Calculation of relative percentage washout at delayed enhanced CT has been reported to accurately differentiate adrenal adenoma and non-adenomatous adrenal masses [10–14], with mean mass sizes >10 mm; the technique may be less reliable for smaller adrenal masses, due to partial volume averaging with surrounding fat.

Despite the importance of accurate assessment of the presence of tumour in an adrenal gland before and during therapy for cancer, relatively little has been reported about the clinical significance of minor morphological irregularities in the appearance of an adrenal gland at CT. Benitah et al [2] studied this issue in patients with lung cancer; in our study, we also included patients

with either breast cancer or melanoma, because those primary tumours are among the most common to metastasise to the adrenal gland [3, 4]. Our data from these three cancer types demonstrated no significant association between the presence of minor morphological abnormalities of the adrenal glands at baseline CT and the presence of subsequent adrenal metastasis; data were too sparse to allow meaningful subgroup analysis based on cancer type. This is concordant with the findings of Benitah et al [2] regarding minor adrenal morphological irregularities in lung cancer.

Vincent et al [7] reported that the mean adrenal size at CT was statistically significantly larger in patients with lymphoma and other various solid malignancies than in control subjects, but excluded patients with focal or multifocal adrenal masses at CT. Also, those patients

Figure 3. Axial contrast-enhanced CT images showing smooth enlargement of adrenal at baseline CT, and subsequent development of metastasis at follow-up imaging in a 45-year-old female with melanoma. (a) Smoothly enlarged left adrenal gland (arrow) at baseline CT. (b) Left adrenal metastasis (arrow) and multiple liver metastases evident at follow-up CT obtained 3 months later.

Table 2. Adrenal categorisation at initial and follow-up CT by reader

Initial assessment	Reader	Number of adrenals	Metastasis at follow-up
Normal	1	1242	72 (5.80%)
	2	1230	51 (4.15%)
Nodular	1	29	2 (6.9%)
	2	25	3 (12%)
Smoothly enlarged	1	40	1 (2.5%)
	2	57	3 (5.3%)
Mass ≤ 10 mm	1	6	0 (0%)
	2	5	0 (0%)

were evaluated with 10mm-thick CT sections, which probably reduced sensitivity for minor contour irregularities and small masses.

Adrenal hyperplasia is one common cause of adrenal morphological irregularities. Affected glands may exhibit diffuse or nodular enlargement, and bilaterality is considered indicative of hyperplasia. With primary functional adrenal tumours, the ipsilateral remaining adrenal tissue and the contralateral gland appear normal or atrophic. Minor morphological irregularities of the adrenal gland also may be present in patients with non-malignant medical conditions, including acromegaly, hyperthyroidism and hypertension with arteriosclerosis [15].

Both readers in our study interpreted a smaller proportion of adrenal glands as abnormal than did the readers in the study of Benitah et al [2]. This difference may be due to various readers' thresholds for classifying an adrenal gland in each category, the use of a training set in our study or differences in the prevalence of minor morphological abnormalities in the different patient populations.

The discrepancy in numbers of adrenal metastases that manifested at follow-up CT as determined by the two readers is because some of those adrenal glands were classified at baseline CT as normal by one reader and not normal by the other. This point has implications in classification of the one adrenal metastasis from lung cancer that was first evident at follow-up CT obtained 24 months after baseline; it is unlikely that the minor abnormality seen by only one of the readers at baseline represented the early manifestations of metastasis, as a metastasis of lung cancer typically grows rapidly. As a result, the implications of minor adrenal morphological changes at baseline CT are probably even less than our results suggest.

Given that minor morphological changes in adrenal glands at baseline CT did not represent early metastasis in the vast majority of patients, we suggest that it is not helpful to clinicians for radiologists to routinely state that

Table 3. Inter-reader agreement for classifying adrenal gland morphology at initial and follow-up CT

Time of CT	Adrenal gland laterality	κ statistic
Initial	Combined right and left	0.52
	Right	0.49
	Left	0.51
Follow-up	Combined right and Left	0.70
	Right	0.77
	Left	0.65

such changes may represent metastasis, or that 'metastasis cannot be excluded'. Instead, we support the suggestion of Benitah et al [2] that such findings should only be mentioned in the Findings section of a report, and to not draw unwarranted attention to them in the Impression section. In our practice, we discourage our radiologists from mentioning these minor morphological changes in the Impression section of their reports.

Our study was limited by its retrospective nature. However, we did perform independent two-reader review of the actual CT images, rather than relying on adrenal assessments in the official written reports. Use of the training set of images probably contributed to the moderate to substantial levels of inter-reader agreement. Some studies were obtained with relatively thick CT sections, but thicker sections would not be expected to obscure an adrenal mass >10 mm, which was the clinically relevant end point in this study. A tiny fraction of adrenal glands was not identified at baseline CT or at follow-up CT, but this would not substantially influence our results because the clinically important end point—the presence of a new adrenal mass—would not be affected by lack of visualisation of the adrenal gland. No mass was evident in the adrenal bed in these cases.

There were insufficient cases in each category of adrenal morphological abnormality to allow meaningful subgroup analyses. Moreover, the relatively small number of Not Normal adrenal glands limited the power of the study to show an association between non-normal adrenal glands and adrenal metastasis. These limitations were partly overcome by performing an analysis in which all types of abnormal adrenal gland interpretations (*i.e.* smoothly enlarged, nodular and mass ≤ 10 mm) were combined into a Not Normal category. Other potential prognostic indicators of adrenal metastasis (*e.g.* tumour stage, histological grade, cancer treatments received) were not analysed because so few metastases developed that multivariate analysis would not be feasible. Death can occur before an adrenal metastasis is imaged, which could weaken any apparent association with the presence of minor adrenal morphological abnormalities; death was not included as a variable in this study. Similarly, some patients might have been lost to follow-up after initial CT, and would thus not be included in this study.

Histopathological verification of metastasis was available in only 1 of 94 adrenal glands classified as containing a (new) mass >10 mm at follow-up. However, in a patient with a primary malignancy that has a high propensity to metastasise to the adrenal gland (such as the three primary tumours included in our study), an adrenal mass that increases in size is inferred to represent a metastasis; we attribute the paucity of confirmatory tissue diagnoses in new adrenal masses to this standard clinical practice.

Ancillary extra-adrenal findings of tumour progression, which may independently influence patient management, also may have been evident at follow-up CT; for the purposes of this study, we limited our evaluation solely to the adrenal glands. Readers were not blinded to the presence of extra-adrenal findings, however, which may have introduced bias. In addition, the readers knew that the second scan was a follow-up scan, which might have biased their interpretation; however, we believe it

unlikely that such knowledge resulted in failure to identify a new adrenal metastasis. We did not record whether patients received chemotherapy, but we believe that few, if any, adrenal metastases ≤ 10 mm would have remained unchanged for a substantial follow-up period due to such therapy. We did not exclude patients with conditions known to produce enlargement of the adrenal glands, such as endocrinological disorders, generalised medical conditions, chronic inflammatory disorders or chronic steroid therapy; nevertheless, this would not be expected to affect the ability to detect the interval development of an adrenal mass.

In conclusion, we are unable to conclude that minor morphological irregularities of the adrenal glands represent early adrenal metastasis in patients with lung cancer, breast cancer or melanoma. The radiology report of such minor adrenal findings could either explicitly state a lack of proven association with adrenal metastasis, or downplay the adrenal findings altogether. If our findings are confirmed in future, larger studies, clinicians and patients may be spared from the routine (and potentially frightening) statement that 'adrenal metastasis cannot be excluded', which may serve no useful purpose in this circumstance.

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