Preictal SPECT in Temporal Lobe Epilepsy: Regional Cerebral Blood Flow Is Increased Prior to Electroencephalography-Seizure Onset

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Peri-ictal SPECT provides unique information on the dynamic changes in regional cerebral blood flow (rCBF) that occur during seizure evolution and, thus, could be useful in clarifying the poorly understood interplay of the interictal and ictal states in human focal epilepsy. The regional hyperperfusion observed on ictal SPECT is generally believed to be a consequence of electrical seizure activity. However, recent studies using invasive long-term cortical CBF monitoring have demonstrated that rCBF changes occur up to 20 min prior to ictal electroencephalography (EEG) onset. Because of apparent technical difficulties, no preictal SPECT studies have been reported so far. Therefore, we present our results on two patients with temporal lobe epilepsy in whom preictal SPECT scans were performed fortuitously under continuous video-EEG monitoring control. **Methods:** Technetium-99m-hexamethyl propyleneamine oxime was injected 11 min (Patient 1) and 12 min (Patient 2) before clinical and EEG seizure onset, as documented from simultaneous video-EEG monitoring in two patients with temporal lobe epilepsy. We obtained accurate anatomical reference of CBF changes visible on SPECT by a special coregistration technique of MRI and SPECT. **Results:** Whereas interictal SPECT showed a hypoperfusion of the temporal lobe ipsilateral to the seizure focus, on preictal SPECT, a significant increase in rCBF in the epileptic temporal lobe could be observed. These rCBF changes were not accompanied by any significant changes of the ongoing EEG. **Conclusion:** Our study provides evidence that rCBF is increased in the epileptic temporal lobe several minutes before EEG seizure onset. Thus, rCBF changes observed on peri-ictal SPECT scan cannot be considered a mere consequence of EEG seizure activity but may rather reflect a change in neuronal activity precipitating the transition from the interictal to the ictal state.

Key Words: temporal lobe epilepsy; SPECT; epilepsy surgery

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Human focal epilepsy can be viewed as a dynamic process in space and time with several more or less distinct phenomena, including the interictal and the ictal states (*1,2*). Whereas the cellular mechanisms underlying the transition from the interictal to the ictal state have been investigated thoroughly (*3–5*), much less is known about the processes mediating this transition in human epilepsy (*2*). Clarification of these mechanisms is not only of scientific interest but is also of clinical relevance: the design of therapeutically applicable seizure-preventing strategies, including warning devices, would facilitate a time- and location-specific therapy (*2*).

Peri-ictal SPECT can provide unique information on the dynamic changes of regional cerebral blood flow (rCBF) that occur during seizure evolution and, thus, could be useful in clarifying the interplay of the interictal and ictal states. Ictal SPECT has become an established method for the localization of the epileptogenic zone in patients with medically intractable epilepsy (*6–16*). Characteristic sequences of peri-ictal and postictal rCBF changes (*8,17,18*), as well as rCBF patterns that are specific for various subtypes of temporal lobe epilepsy, have been identified (*19*). Correct and unambiguous interpretation of peri-ictal SPECT studies requires simultaneous video-electroencephalography (EEG) monitoring because rCBF changes have to be correlated with clinical seizure semiology and the ongoing EEG (*7,20*).

The regional hyperperfusion observed on ictal SPECT is generally believed to be a consequence rather than a cause of seizure activity (*21,22*). Thus, one would expect CBF changes to occur simultaneously or after the onset of ictal electrographic activity. However, recent studies using invasive long-term cortical CBF monitoring have demonstrated that rCBF changes occur up to 20 min prior to ictal EEG onset on subdural strip electrodes (*23–26*).

Here, we present two patients with temporal lobe epilepsy in whom preictal SPECT scans were performed fortuitously under continuous video-EEG monitoring control.

MATERIALS AND METHODS

Patients

We studied two patients with medically refractory temporal lobe epilepsy who were evaluated with prolonged video-EEG monitoring for a definitive localization of the seizure focus.

Patient 1 was a 25-yr-old right-handed woman who developed epilepsy after viral meningitis at age 4 yr. The patient experienced no aura. Seizures consisted on an initial alteration of consciousness associated with a motionless stare followed by dystonic posturing of the left upper extremity and automatisms of the right upper extremity, suggesting a right temporal lobe onset. Neurological examination and MRI scan of the brain were normal.

Patient 2 was a 41-yr-old right-handed woman with a history of meningitis as an infant and seizure onset at age 17 yr. Seizures started with an epigastric aura, which was followed by an alteration of consciousness and a motionless stare. Some seizures evolved into secondarily generalized tonic-clonic seizures with a prior version to the left, indicating a right temporal lobe onset. Neurological examination was normal. MRI scan showed a right-sided hippocampal sclerosis.

Video-EEG Monitoring and Preictal and Interictal SPECT

Both patients underwent intensive video-EEG monitoring with a commercially available monitoring system (EMS Company, Korneuburg, Austria) for 1 wk (*27*). Electroencephalography was recorded from gold disk electrodes, placed according to an ex-

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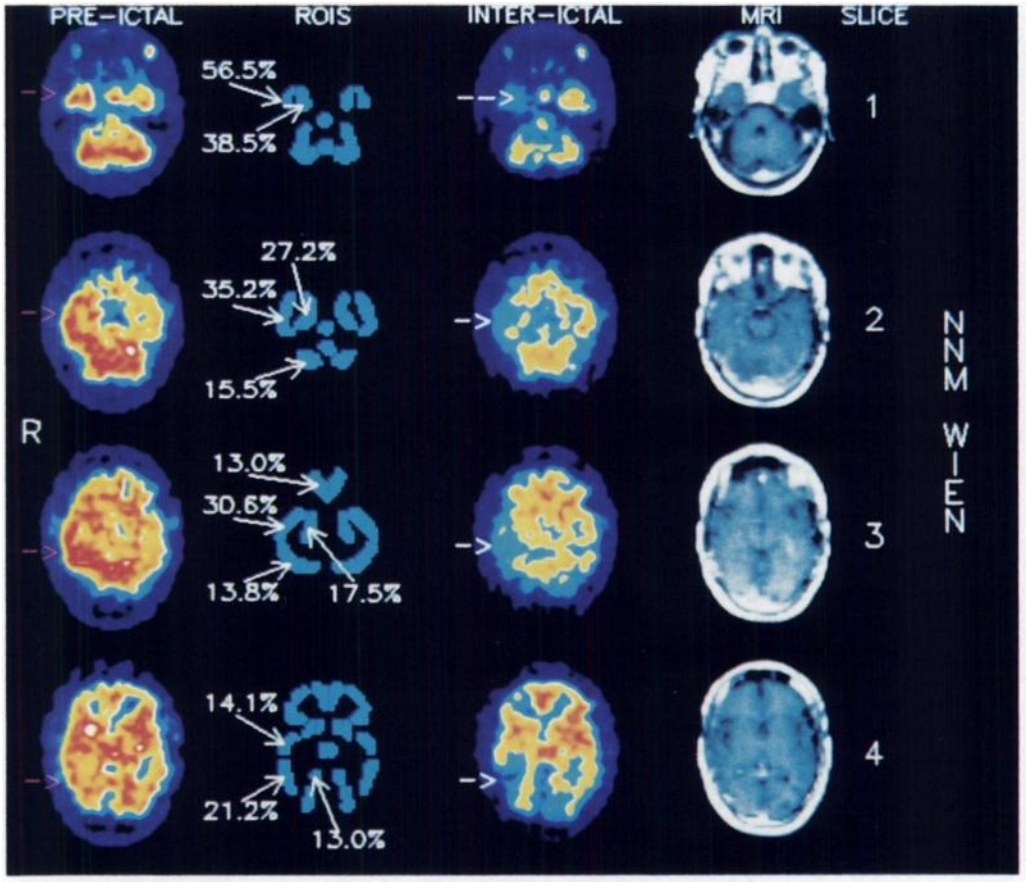

FIGURE 1. Preictal and interictal SPECT in Patient 1. Four adjacent, coregistered 10.35-mm-thick slices (rows) of preictal SPECT (first column from left), interictal SPECT (third column) and MRI (fourth column). The second column displays corresponding regions of interest with percentage increases of normalized regional cerebral blood flow (rCBF) values between the interictal and preictal condition (only increases above 12%, which were considered significant, are shown). Red and white arrows in the first and third columns from left indicate increased and decreased rCBF values, respectively. In the preictal scan, a significant increase of rCBF in the right temporal lobe (both mesial and lateral), right cerebellum, right orbito-frontal cortex and right anterior-occipital lobe can be seen.

tended International 10-20 System, and from bilaterally placed sphenoidal electrodes (*28*). To obtain ictal SPECT scans, all patients were recorded at the department of nuclear medicine for 1 day during the week of monitoring. A physician continuously observed the patient as well as the ongoing EEG and injected the isotope immediately when a clinical or EEG seizure started.

If no seizure occurred during the entire day designated for ictal SPECT, the isotope was injected in the evening to obtain an interictal scan. However, these particular two patients developed seizures exactly 11 min (Patient 1) and 12 min (Patient 2) after the application of the isotope while still attached to the video-EEG monitoring system. Thus, we fortuitously were able to record preictal SPECT studies in both patients. Interictal SPECT scans were acquired subsequently on a separate occasion after a seizure-free period of at least 24 hr.

SPECT was performed with a three-headed rotating scintillation camera equipped with ultrahigh-resolution collimators. The spatial resolution of the system was 6.5–7 mm FWHM in the reconstructional plane. Ten to twenty minutes after intravenous administration of 740 MBq (20 mCi) ^{99m}Tc-HMPAO, data acquisition was started in step-and-shoot mode. A total of 180 projections were recorded during 30 min (2° steps, 30 sec/angle) in 128 × 128 matrices using a diameter of rotation of 255 mm. After acquisition, projections were filtered before reconstruction to improve the signal-to-noise ratio. After reconstruction (filtered backprojection, Butterworth filter, cutoff frequency 0.9), cross-sections were corrected for tissue absorption (Chang's method).

To ensure comparison of identical anatomical structures, both SPECT studies (preictal and interictal) and MRI scans were realigned using an interactive technique for three-dimensional image reconstruction (*29*). Thereafter, three 3.45-mm-thick (voxel size) transversal cross-sections were summed consecutively to obtain a set of nine overlapping 10.35-mm-thick cross-sections. A total of 107 regions of interest (ROIs) were drawn on the interictal SPECT images and then transferred to the corresponding cross-sections of the preictal studies. For analysis, only four cross-sections with a total of 56 ROIs covering both temporal lobes were considered. Normalized rCBF values [regional indices (RIs)] were calculated as the ratios between the mean counts per voxel of a specific ROI and the mean counts per voxel of all ROIs [RI = mean of specific ROI (counts/voxel)/mean of all ROIs (counts/voxel)]. The relative changes of rCBF for a specific ROI between the interictal and preictal states were calculated as the ratios of the RIs as follows: $\{[(RI_{preictal}/RI_{interictal}) \times 100] - 100\}$. Thus, a positive value of this ratio is equivalent to an activation of a specific ROI, whereas a negative value corresponds to a deactivation. According to a previous study on the reproducibility of rCBF in normal volunteers, a RI change of at least 12% between the two conditions was considered significant (*30*).

RESULTS

Patient 1

Interictal EEG showed an intermittent rhythmic slow activity over the right temporal region and 100% right temporal interictal spikes, with a maximum at the right sphenoidal electrode. A total of five habitual seizures were recorded. Ictal EEG was characterized by an initial regional right temporal rhythmic theta activity, with a maximum at the right sphenoidal electrode, and started at an average of 2 sec (range 1–5 sec) after clinical seizure onset.

On interictal SPECT, right mesial and lateral temporal structures were hypoperfused (Fig. 1). For preictal SPECT, the isotope was injected 11 min prior to clinical and EEG seizure onset. Preictal SPECT showed a significant increase of rCBF in the entire right temporal lobe (both mesial and lateral), right cerebellum, right orbito-frontal cortex and right anterior-occip-

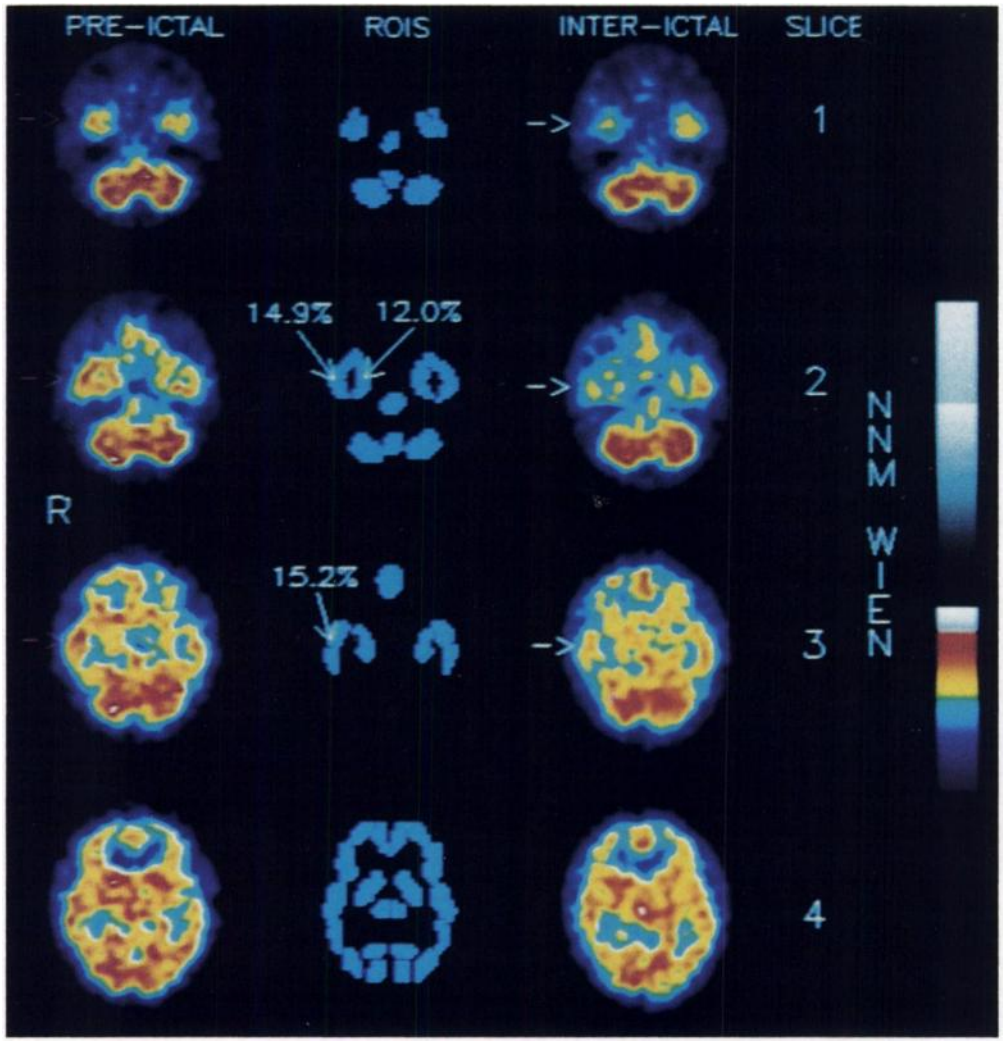

FIGURE 2. Preictal and interictal SPECT in Patient 2. Four adjacent, coregistered 10.35-mm-thick slices (rows) of preictal SPECT (first column from left) and interictal SPECT (third column). The second column displays corresponding regions of interest with percentage increases of normalized regional cerebral blood flow (rCBF) values between the interictal and preictal condition (only increases above 12%, which were considered significant, are shown). Red and white arrows in the first and third columns from left indicate increased and decreased rCBF values, respectively. Preictal SPECT was notable for a significant increase of rCBF in the right mesial and lateral temporal structures.

ital lobe (Fig. 1). The last seizure before the preictal SPECT study occurred 5 hr 15 min earlier.

Patient 2

On interictal EEG, an intermittent rhythmic slow activity could be observed over the right temporal region. Ninety-nine percent of interictal spikes occurred over the right temporal lobe, with a maximum at electrodes F8 and Sp2. Five habitual seizures were recorded, which showed a right temporal EEG onset consisting of a rhythmic theta activity occurring at an average of 7 sec (range 6–8 sec) after clinical seizure onset.

Interictal SPECT showed a hypoperfusion of the right temporal lobe (both mesial and lateral; Fig. 2). The isotope was injected 12 min prior to seizure onset for the preictal scan. Preictal SPECT was notable for a significant increase of rCBF in right mesial and lateral temporal structures (Fig. 2). The last seizure before the preictal SPECT study was recorded 14 hr 35 min earlier.

DISCUSSION

Our results indicate that a significant increase in CBF occurs in the epileptic temporal lobe already 11–12 min before clinical and EEG seizure onset. Our findings are in agreement with previous studies on long-term surface cortical CBF monitoring using subdural thermal diffusion flowmetry CBF probes (*25,26*) and laser Doppler probes attached to custom-made subdural electrodes (*23,24*). These studies documented a significant increase of CBF from baseline in the epileptic temporal lobe 10–20 min prior to EEG seizure onset, whereas rCBF in the contralateral temporal lobe was either decreased (*24,26*) or only slightly increased (*25*).

Thus, peri-ictal rCBF changes in temporal lobe epilepsy exhibit a characteristic time sequence (*8,17,25*). Initially, at 10–20 min before seizure onset, there is already a gradual increase in rCBF in the epileptic temporal lobe. At the time of seizure onset, there is an abrupt and brief drop in CBF, followed quickly by an increase of rCBF in the whole temporal lobe during the seizure (*25*). Up to 2 min postictally, there is hyperperfusion of the medial temporal lobe, while the lateral temporal structures are hypoperfused. From 2 to 15 min postictally, the whole temporal lobe is hypoperfused (*8,17,18*).

Several possible criticisms of our study have to be considered. First, EEG recordings were conducted with scalp electrodes only. Invasive EEG recordings probably would have picked up the ictal EEG changes earlier. However, it is extremely unlikely that the time difference of ictal onset between invasive and scalp EEG was on the order of 10 min, which would influence the interpretation of our results. Thus, the possibility of ictal EEG changes not recognized at the scalp as an explanation for our findings can be excluded. Second, hyperperfusion on interictal SPECT that either persisted or resolved on repeat scans was observed in few patients in previous studies (*31,32*). These findings could possibly be attributed to patient selection because the side of the epileptogenic focus was not established by other methods in this study, to ipsilateral heterotopic or tumoral lesions (*7,33,34*) and, finally, to overinterpretation or inadvertent injection in proxim-

ity to a seizure (*7*). In our study, all these possibilities can be excluded because high-resolution MRI and continuous video-EEG monitoring were performed. Third, persisting changes in CBF after the last seizure before the injection of the isotope may be held responsible for our results. However, SPECT and ^{15}O PET studies demonstrated a return of rCBF to baseline 5–20 min after a seizure, which is much shorter than the interseizure intervals of more than 5 hr in our study (*17,18,35*). Fourth, ^{99m}Tc-HMPAO SPECT is a relative measure of rCBF only. Thus, the observed changes of rCBF could actually represent a decrease in rCBF in the contralateral temporal lobe. This possibility, however, is extremely unlikely in view of previous reports of peri-ictal SPECT scans, the results of chronic subdural blood flow monitoring and the results of the interictal scans in our study. We, therefore, believe that our results demonstrate a true preictal increase in rCBF.

The hypothesis that the increase in CBF observed on ictal SPECT is a mere consequence of the electrical seizure discharges, therefore, should be reconsidered (*21,22*). Our findings suggest that an increased perfusion of the epileptic temporal lobe actually heralds and does not simply follow the impending seizure activity. The mechanisms underlying this redistribution of CBF remain to be clarified. Furthermore, it is unclear if these rCBF changes eventually are causative for the transition from the interictal to the ictal EEG state.

One possible explanation for the increase in rCBF in the ictal onset zone could be some change in neuronal activity preceding the visually discernible EEG onset. This hypothesis is supported by studies applying the theory of nonlinear dynamics, i.e., chaos theory, to invasive EEG recordings (*36,37*). These authors found a pronounced transition from high- to low-dimensional system states in the ictal onset zone approximately 10 min prior to EEG seizure onset. In the terms of chaos theory, a low-dimensional state or complexity loss reflects synchronized neuronal activity. Thus, one may speculate that some synchronized neuronal activity associated with an increase in rCBF precedes the actual EEG seizure onset for some significant period of time. In our patients, visual inspection of the ongoing EEG as well as quantification of interictal spikes at the time of tracer injection did not show any significant differences compared to the interictal state.

CONCLUSION

The mechanisms underlying the transition from the interictal to the ictal state in human focal epilepsy are poorly understood. Our study provides evidence that rCBF is increased in the epileptic temporal lobe several minutes before the actual EEG or clinical seizure onset. Thus, rCBF changes observed on peri-ictal SPECT scans cannot be considered a mere consequence of the electrical seizure activity but may rather reflect a change in neuronal activity precipitating the initiation of the ictal state. Our results are supported by studies using invasive long-term cortical CBF monitoring and chaos theory applied to invasive EEG recordings. We believe that peri-ictal SPECT can be considered a powerful, noninvasive technique to investigate fundamental questions of human epilepsy. Future studies should concentrate on elucidating the neuronal bases of these preictal changes in rCBF by direct comparisons with invasive EEG recordings and possibly intracellular recordings. We hope that these studies will be helpful in clarifying the mechanisms causing the transition from the interictal to the ictal state and will ultimately contribute to the design of seizure-preventing therapeutic strategies.

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In Vitro and In Vivo Primate Evaluation of Carbon-11-Etomidate and Carbon-11-Metomidate as Potential Tracers for PET Imaging of the Adrenal Cortex and Its Tumors

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Methods: With the purpose of developing a PET imaging agent for tumors of the adrenal cortex, we developed syntheses for ^{11}C-etomidate and its methyl analog, ^{11}C-metomidate. (R)-[O-ethyl-1-^{11}C]Etomidate and (R)-[O-methyl-^{11}C]metomidate were prepared by reaction of the appropriate respective ^{11}C-labeled alkyl iodide and the tetrabutylammonium salt of the carboxylic acid derivative. The specificity of binding to the adrenal cortex was tested through the use of frozen section autoradiography of different tissues of the rat, pig and human. Inhibition of tracer binding was evaluated with etomidate, ketoconazole and metyrapone, well-known inhibitors of enzymes for steroid synthesis. Tracer binding to different human tumor samples was compared to immunohistochemical staining with antibodies for the steroid synthesis enzymes P450 11β (11β-hydroxylase), P450 scc (cholesterol side-chain cleavage enzyme), P450 C21 (21-hydroxylase) and P450 17α (17α-hydroxylase). Three PET investigations, one with ^{11}C-etomidate and two with ^{11}C-metomidate, were performed in rhesus monkey sections, including the adrenals, liver and kidneys. Time-activity curves were generated from measured tracer uptake in these organs. **Results:** In frozen section autoradiography of various tissues, high binding was seen in the adrenal cortex from all species, as well as in the tumors of adrenal cortical origin. The level of liver binding was about 50% of that in the adrenals, whereas that of all other organs was <10% of the adrenal binding. The adrenal binding was blocked by etomidate and ketoconazole at low doses but not by metyrapone. The binding in the adrenal tumor samples correlated with immunostaining for P450 11β. PET studies in the monkey demonstrated high uptake in the adrenals with excellent visualization. The uptake increased with time without indication of washout. Slightly lower uptake was seen in the liver as compared to the adrenals, and in the late images, no organs other than adrenals and liver were seen. **Conclusion:** These investigations indicate that ^{11}C-etomidate and ^{11}C-metomidate have the potential to be useful specific agents for the visualization of the normal adrenal cortex and to provide positive identification of adrenal cortical tumors.

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As a result of the increased use of CT, MRI and ultrasound, incidentally found masses in the location of the adrenal glands have emerged as a clinical problem. Patients undergoing CT for reasons other than suspected adrenal disease manifest adrenal lesions with a frequency of approximately 1% (*1–3*). The potential extent of this problem is illustrated by the fact that adrenal lesions are found at autopsy in 1.9%–8.7% (*4,5*). In most cases (70%–94%), these incidentally found tumors, termed "incidentalomas," consist of benign cortical nonhypersecretory adenomas (*6*). If an adrenal lesion has been radiologically detected in a patient, a biochemical hormonal screening is performed to rule out both adrenal medullary and cortical hypersecretory tumors. If hypersecretion is established biochemically, these patients are normally considered candidates for surgery. For patients without evidence of adrenal hypersecretion, the differentiation of the common adenomas from other benign lesions such as cysts and lipomas or from malignant lesions, i.e., adrenal cortical carcinoma or extra-adrenal metastasis, must be established. In view of the low specificity of CT, MRI and other imaging methods for such differentiation, patients with nonhypersecretory tumors that are >3 cm in diameter are often referred for surgery to rule out a primary adrenal cortical carcinoma.

Iodine-123-iodomethylnorcholesterol (NP-59) imaging (*7–9*) has a high specificity and accuracy in defining adrenal cortical masses. A limitation of the method is the long waiting period (4–7 days) from injection to imaging, making it cumbersome and costly. Both hypersecretory and nonhypersecretory adenomas (and some hypersecretory adrenal cortical carcinomas) accumulate NP-59, whereas nonfunctioning primary and secondary malignant lesions, as well as other space-occupying lesions, demonstrate decreased, distorted or absent uptake.