of 36 patients studied at VAMC and BNL (*23*). We anticipate the total therapeutic dose to be between 10–20 mCi (370–740 MBq) for a 70-kg patient. Favorable biokinetic, nuclear physical and chemical characteristics combined with our preliminary pain palliation results suggest that $^{117m}$Sn(4+)DTPA meets most of the requirements for an ideal bone pain palliation agent (Table 3). Double-blind studies comparing the results with a placebo or the FDA-approved $^{89}$Sr-chloride are required before final judgments are made on this new agent. An application to the FDA to begin Phase III clinical trials is under preparation.


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# Scintigraphic Assessment of Therapeutic Success in Aldosteronomas Treated by Transcatheter Arterial Embolization Using Absolute Ethanol


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Adrenocortical scintigraphy was examined as an indicator of therapeutic success in aldosteronomas treated by transcatheter arterial embolization (TAE) with absolute ethanol (AE). **Methods:** Adrenocortical scintigraphy was performed 7 days after intravenous injection of 37 MBq $^{131}$I-6-β-iodomethyl-19-norcholesterol before and after TAE. Complete or incomplete therapeutic success was determined by periodic measurements of the levels of plasma aldosterone and correlated with the scintigraphic results. **Results:** The aldosteronoma was visualized as a hot nodule in nine patients and a warm nodule in one patient before TAE. Scintigraphy showed a hot, residual hot or warm nodule on seven occasions (six occasions after the first TAE and one occasion after the second TAE) when the techniques were incompletely successful and disappearance on seven occasions when success was achieved (three occasions after the first TAE and one occasion after the second TAE). Of the seven occasions when TAE was unsuccessful, four patients received the second or third TAE to result in complete destruction of the aldosteronoma; three patients underwent unilateral adrenalectomy. **Conclusion:** Adrenocortical scintigraphy can correctly predict the effect of TAE on aldosteronomas and is a valuable indicator for decisions on the necessity of repeated TAE or adrenalectomy.



**Key Words:** adrenal gland; primary aldosteronism; transcatheter arterial embolization; absolute ethanol

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Primary aldosteronism is one of the causes of secondary hypertension. Its incidence is assumed to be <2% of hyperten-

**TABLE 1**
Patient Characteristics before TAE

| Patient no. | Age (yr) | Sex | Blood pressure (mmHg) | Serum K (mEq/l) | Plasma levels | | Lesion | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Aldosterone* (ng/dl) | Renin activity† (ng/ml · hr) | Side | Size on XCT (mm) |
| 1 | 44 | F | 190/120 | 2.8 | 34 | <0.1 | R | 9 |
| 2 | 37 | F | 180/100 | 2.9 | 195 | 0.1 | L | 19 |
| 3 | 55 | F | 210/108 | 2.8 | 64 | <0.1 | R | 10 |
| 4 | 65 | F | 180/110 | 1.7 | 66 | <0.1 | R | 10 |
| 5 | 43 | M | 170/110 | 3.1 | 56 | <0.1 | R | 14 |
| 6 | 43 | F | 160/107 | 3.6 | 34 | 0.2 | L | 14 |
| 7 | 38 | F | 150/100 | 2.7 | 66 | 0.1 | R | 10 |
| 8 | 37 | F | 170/100 | 2.8 | 64 | 0.4 | L | 10 |
| 9 | 48 | F | 150/90 | 2.9 | 44 | <0.15 | R | 10 |
| 10 | 28 | F | 180/120 | 3.0 | 61 | <0.1 | L | 18 |

*Normal range = 2–24 ng/dl.
†Normal range = 0.3–5.4 ng/ml · hr.

sive patients (*1*). A unilateral aldosterone-hypersecreting adenoma (aldosteronoma) is the main cause in many patients with primary aldosteronism. Once the diagnosis of a unilateral aldosteronoma is established, the therapy of choice is unilateral adrenalectomy. After this type of therapy, blood pressure returns to normal in approximately 50% of patients, with significant reduction of hypertension in another 25% (*1*). However, we encountered several patients with unilateral aldosteronoma who refused or were reluctant to undergo surgery. Therefore, we sought an alternative therapy and developed a method to destroy aldosteronomas called transcatheter arterial embolization (TAE) of the aldosteronoma using absolute ethanol (AE), that is, infusion of AE into the arterial branches feeding the aldosteronoma (*2,3*). AE is an effective and safe occlusive embolic agent (*4,5*). Previously, it has been used for arterial embolization of carcinoma of the kidney (*6*) and primary and metastatic malignant adrenal tumors (*7*).

Iodine-131-6-β-iodomethyl-19-norcholesterol($^{131}$I-NCL-6) (*8*) or NP-59 (*9*) is a radiopharmaceutical which concentrates in the adrenal cortex and has been used as an adrenal imaging agent for the location and differential diagnosis of Cushing's syndrome as well as primary aldosteronism and for the evaluation of clinically silent adrenal masses (*10–15*). In this article, we evaluated the efficacy of adrenocortical scintigraphy with $^{131}$I-NCL-6 to the success of the TAE with AE for treatment of aldosteronomas.

## MATERIALS AND METHODS

This study included 10 patients (one man, nine women; age range 28–65 yr; mean age 44 ± 10 yr) with unilateral aldosteronoma who were treated between August 5, 1992 and March 30, 1994 (Table 1). The diagnosis of unilateral aldosteronoma was made by radiograph CT (XCT), adrenocortical scintigraphy, adrenal arteriography and/or venous sampling after the diagnosis of primary aldosteronism was established by the following criteria: hypertension, high concentration of aldosterone in plasma and urine and suppression of plasma renin activity after furosemide and exercise stimulation (*1*). The aldosteronomas ranged from 9 to 19 mm (mean 12 ± 4 mm) in diameter on XCT.

TAE of the aldosteronoma was performed as follows (*2,3*): The diagnostic angiography was performed to identify the adrenal arterial branches feeding the aldosteronoma; and an aortogram and selective angiograms of the renal, middle adrenal and inferior phrenic arteries were obtained to analyze the target arteries that fed the aldosteronoma. One week later, TAE was performed after obtaining informed consent. When tumor staining was observed by angiography of these arteries using an outer catheter, a 5-Fr catheter in the shape of Shepherd's crook or cobra type, their small branches were catheterized by the coaxial technique using a microcatheter to infuse AE into the branches feeding the aldosteronoma. The volume of AE administered was approximately the same volume as that of the water-soluble iodinated contrast medium used to fill the adenoma to produce tumor staining. AE was infused slowly as a single injection by hand, at a rate of approximately 1 ml/min after intra-arterial infusion of 1 ml of 1% xylocaine via the microcatheter and intravenous injection of 15–30 mg of pentazocine for pain relief. Angiography was then repeated to confirm the status of the occlusion of the target branches at the same microcatheter position. When the target branches had completely occluded, angiograms of the other adrenal arteries were obtained with the outer catheter after withdrawing the microcatheter to locate any other branches feeding the aldosteronoma. The volume of AE eventually infused on a single TAE occasion ranged from 0.2 to 3.0 ml. Vital signs such as blood pressure, pulse, changes of electrocardiograms, body temperature and the patient's subjective complaints were closely monitored during and immediately after the therapy. We also had available drugs against hypertensive crisis. The procedure was performed once in four patients, twice in five patients and three times in one patient.

The levels of plasma aldosterone, renin activity and serum potassium were periodically measured after therapy. Measurements of the levels of plasma aldosterone and renin activity were made by radioimmunoassay at SMI Bristol (Sagamihara, Japan) until October 1993 and at SRL (Tokyo, Japan) thereafter. It took approximately 5 days to obtain the results of measured hormonal values.

Adrenocortical scintigraphy was performed 7 days after the intravenous injection of 37 MBq $^{131}$I-NCL-6. The thyroidal uptake of free $^{131}$I was blocked by daily oral administration of 300 mg of potassium iodide from 1 day before to 6 days after intravenous injection of the tracer, respectively. The posterior adrenal image with 22,000 counts was obtained using a gamma camera with a pinhole collimator. The energy peak was centered at 364 keV with a 20% window. Adrenocortical scintigrams were repeatedly obtained 15–52 days after the therapy (Table 2).

Scan interpretation was based on typical scintigraphic $^{131}$I-NCL-6 appearance of aldosteronoma: a hot or warm nodule before therapy. We termed the nodule detected by XCT a hot nodule when the nodule showed a round focus of intense uptake surrounded by less intense activity which corresponded to the extranodular adre-

**TABLE 2**
Plasma Aldosterone Levels and Adrenocortical Scintigraphic Findings before and after TAE and Blood Pressure after TAE in Ten Patients with Unilateral Aldosteronoma

| Patient no. | Number of TAE | Plasma aldosterone levels (ng/dl) | | | | | | Scintigraphic findings | | Blood pressure | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Before | After TAE | | | | | | | | |
| | | (days) | 1 day | 7 days | 14–21 days | S (days) | F (mo) | Before | After TAE | S | F |
| 1 | 1 | 34 | – | 1 | 6 | 11 (29) | 11 (31) | H (C) | D (D) | 130/90 | 124/84 |
| 2 | 1 | 195 | 8 | 3 | 10 | 10 (24) | 11 (17) | H (C) | D (D) | 148/110 | 124/72 |
| 3 | 1 | 64 | 3 | 1 | 4 | 4 (17) | 10 (2) | H (C) | D (D) | 150/90 | 150/90 |
| 4 | 1 | 66 | 20 | 53 | 60 | 60 (22) | | H (C) | R (C) | 180/110 | |
| | 2 | 60 (0) | 3 | 1 | 4 | 5 (52) | 3 (30) | | D (D) | 160/100 | 140/80 |
| 5 | 1 | 60 | 13 | 37 | 40 | 51 (22) | | H (C) | R (C) | 160/110 | |
| | 2 | 51 (0) | 4 | – | 6 | 9 (37) | 13 (21) | | D (D) | 170/120 | 136/106 |
| 6 | 1 | 43 | 13 | 30 | 56 | – | | H (C) | – | | |
| | 2 | 56 (0) | 4 | 3 | 6 | 5 (29) | 11 (15) | | D (D) | 154/90 | 130/85 |
| 7 | 1 | 66 | 6 | 39 | 43 | 43 (15) | | H (C) | H (C) | 160/110 | |
| | 2 | 60 (8) | 10 | 60 | 68 | – | – | | – | | |
| | 3 | 68 (0) | 4 | 2 | 5 | 3 (18) | 4 (18) | | D (S) | 120/80 | 120/80 |
| 8 | 1 | 64 | 15 | 32 | – | – (24) | | W (S) | W (S) | 180/100 | (Adrenalectomy) |
| 9 | 1 | 44 | 6 | 13 | 27 | 27 (21) | | H (C) | R (S) | 150/90 | |
| | 2 | 34 (4) | 8 | 11 | 23 | – | | | – | 170/90 | (Adrenalectomy) |
| 10 | 1 | 61 | – | 18 | 23 | 23 (22) | | H (C) | R (C) | 180/120 | |
| | 2 | 35 (22) | – | 27 | 17 | 62 (43) | | | H (S) | 180/130 | (Adrenalectomy) |

days = days after the last measurement after the previous TAE, S (days) = days of $^{131}$I NCL-6 imaging after TAE, F (mo) = months of the final follow-up after the last TAE, S = around the day of $^{131}$I NCL-6 imaging, F = on the day of final follow-up, H = hot nodule; W = warm nodule; D = disappearance of hot nodule; R = residual hot nodule; (C) = concordant uptake; (D) = disconcordant uptake; (S) = symmetrical uptake.

nal tissue and a warm nodule when it showed the same intense activity as the extranodular activity (*15*). The scintigraphic appearance of the nodule after therapy was compared with that before therapy. The hot nodule with less avid activity than the one before therapy was termed a residual hot nodule. The relative activity between both adrenal glands was classified as a concordant uptake (the uptake is higher in the adenoma-bearing gland than the opposite gland), disconcordant uptake (the uptake is lower in the adenoma-bearing gland than the opposite gland) and symmetrical uptake (*14*). Follow-up studies including measurements of blood pressure, levels of plasma aldosterone, renin activity and serum electrolytes were periodically made over 15 mo in six patients and for 2 mo in one patient who was lost to follow-up thereafter. The remaining three patients underwent adrenalectomy to achieve normalization of the levels of plasma aldosterone.

## RESULTS

Table 2 shows the plasma aldosterone levels and adrenocortical scintigraphic findings before and after TAE, and blood pressure after TAE in the 10 patients with unilateral aldosteronoma. Successful and complete destruction of the aldosteronoma was achieved in three patients after the first TAE, three patients after the second TAE and one patient after the third TAE: No hypersecretion of aldosterone was observed during the period from 15 to 31 mo post-TAE in six patients and in one patient for 2 mo who was then lost to follow-up. The remaining three patients who failed to respond to TAE underwent unilateral adrenalectomy.

On the day after TAE, plasma aldosterone levels were all within normal limits in the six completely and eight incompletely successful procedures. On the seventh day after TAE, the levels were within normal limits in the six completely and three incompletely successful procedures and high in seven incompletely successful occasions, and on the 14–21st day were within normal limits in seven completely and three incompletely successful procedures and high in six incompletely successful procedures. The levels of plasma aldosterone around the day of $^{131}$I-NCL-6 imaging were within normal limits for the seven occasions of complete success and one occasion of incomplete success and high in five occasions with incompletely successful procedures. Thus, the levels of plasma aldosterone obtained after the TAE could not predict incomplete therapeutic success for aldosteronomas on all of eight occasions on the day after TAE, in three of ten occasions by the seventh day, and three of nine occasions by the 14–21st day.

For the seven completely successful TAEs, the levels of plasma renin activity remained suppressed in all of the six patients (not measured in one) on the day after TAE, returned to the normal range in three patients by the seventh day and in the other three by the fourteenth day, and remained suppressed in another patient until the last follow-up day. Hypokalemia was also noted in the same six patients on the day after TAE. Then the serum potassium levels improved to the normal range in two patients by the seventh day, in the other four by the fourteenth day and in another patient by the sixteenth day. Finally, the levels of plasma aldosterone, renin activity and serum potassium showed to be all within normal limits on the last follow-up day, except for a low level of plasma renin activity in Patient 6, in the seven completely successful TAE patients. In the case of 10 incompletely successful TAEs, the levels of plasma renin activity remained suppressed in five patients, increased slightly in two patients and definitely in one patient (not measured in two) on the day after TAE, remained suppressed in four, increased slightly in three and definitely in three on the seventh day. However, they returned to the suppressed state in nine (not measured in one) on the fourteenth day. Hypokalemia was noted in all of the eight patients (not measured in two) on the day after TAE. The levels of serum potassium remained in the hypokalemic range in seven patients and were within normal limits in two (not measured in one) on the seventh day. On the fourteenth day, the serum potassium levels were in the hy-

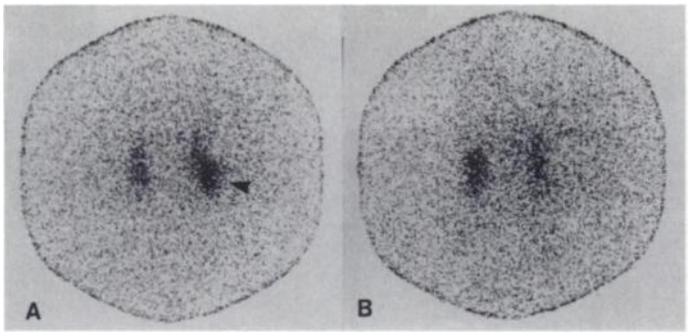


**FIGURE 1.** Adrenocortical images of Patient 1 with right aldosteronoma before and after the first successful TAE. The hot nodule (arrowhead) at the inferior portion of the right adrenal before the TAE (A) disappeared after the TAE (B).

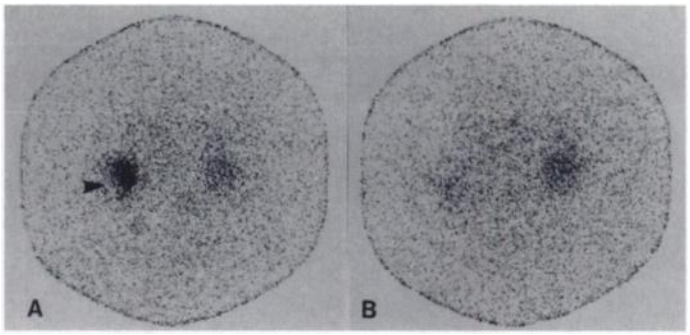


**FIGURE 2.** Adrenocortical images of Patient 2 with left aldosteronoma before and after the first successful TAE. The hot nodule (arrowhead) of the left adrenal before the TAE (A) disappeared after the TAE (B).

pokalemic range in six and within normal limits in three (not measured in one).

The scintigraphic results were as follows: The aldosteronoma was visualized as a hot nodule in nine patients who also showed concordant uptake, and a warm nodule in one patient with symmetrical uptake before the first TAE. A hot, warm or residual hot nodule was observed on seven occasions when success of TAE of aldosteronomas was incomplete. Concordant uptake was preserved on four occasions while symmetrical uptake was observed on the remaining three occasions. A hot nodule disappeared on seven occasions when TAE of the aldosteronoma was completely successful and the pretherapeutic pattern of concordant uptake changed into one of disconcordant uptake in six patients and symmetrical uptake in one patient. Figures 1 and 2 show the scintigraphic changes in two patients whose aldosteronomas were completely cured by the first TAE. Figure 3 shows the scintigraphic changes in a patient whose aldosteronoma was incompletely responsive to the first therapy and completely cured by the second therapy. Figure 4 shows the scintigraphic changes in a patient whose aldosteronoma was not completely responsive to therapy even with the second TAE.

The scintigraphic findings after TAE agreed with the levels of plasma aldosterone measured around the day of $^{131}$I-NCL-6 imaging on 12 occasions. However, the plasma aldosterone level was within normal limits when a residual hot nodule was demonstrated on one occasion.

Blood pressure remained in hypertensive range around the day of $^{131}$I-NCL-6 imaging or just before adrenalectomy on 13 occasions and was in the normotensive range on two occasions. On the final day of follow-up, blood pressure was normal in five patients with completely successful TAE of aldosteronomas and reduction in severity of hypertension was observed in the remaining two patients.

## DISCUSSION

The TAE of aldosteronoma is less invasive than adrenalectomy and can provide a long-term cure, which has been demonstrated in this study. However, completely successful therapeutic responses of aldosteronomas were achieved by the first TAE in only 3 of 10 patients. A second or third TAE was required to abolish the function of aldosteronoma in four other patients, while the remaining three patients required adrenalectomy.

We used AE as an embolic agent. The embolic effects of AE are related to its protein denaturant and hygroscopic properties which would be expected to result in tissue damage and necrosis. Its major effects on blood vessels may be due to damage to the vascular endothelium with activation of the coagulation systems and a direct irritant effect, causing vascular spasm, which in turn slows blood flow and contributes to thrombosis (*3,4*). When AE was infused into the renal artery in dogs, it produced renal infarction with thrombi in the renal arterial branches and complete coagulation necrosis of the renal cortex (*3*). Therefore, if AE is adequately infused into the aldosteronoma, it should become to be necrotic and secondarily inactive. However, it is difficult to judge whether AE perfuses the entire adenoma during therapeutic infusion of AE because it is radiolucent. The most sensitive method to assess the embolic effect on aldosteronomas may be the measurement of the levels of plasma aldosterone. Nevertheless, in our series, the levels on the day after TAE were invariably within normal range in all patients regardless of whether the TAE was incompletely or completely successful.

Therefore, the next day values could not predict complete or incomplete therapeutic success. The reasons why the falsely normal levels of plasma aldosterone were obtained on the day after TAE in case of incompletely successful TAE are unknown. However, the transient blockade of blood supply for the adenoma by the interventional prosedures such as insertion of the outer and microcatheters into the adrenal artery and its branches feeding the adenoma, injection of the contrast medium into these branches, and the true but partial necrotic effect of AE on the adenoma might all reduce the aldosterone-producing cell function of the adenoma to result in the falsely normal values. Although the levels of plasma aldosterone remained within normal range after all completely successful TAEs, the values in the normal range were shown in 3 of 10 eventually unsuccessful TAE procedures on the seventh day and in three of nine unsuccessful TAE procedures on Days 14–21. Therefore about 30% of unsuccessful TAEs could not be predicted by measurements of the levels of plasma aldosterone performed even a 7–21st day after TAE. Such delay to show the increase in the levels of plasma aldosterone in some incompletely responsive cases is a problem for patient management. If incomplete therapeutic responses can be predicted as soon as possible, the management plan can also be modified earlier.

Iodine-131-NCL-6 is an analog of cholesterol which is the precursor for steroid hormone biosynthesis and is accumulated by and esterified in adrenocortical cells of the normal or hyperplastic adrenal cortex, aldosteronomas, cortisol-producing adenomas, sex hormone-producing adenomas and nonhyperfunctioning (silent) adenomas (*10–15*). Therefore, the adrenal cells must be viable to take up this tracer. Adrenocortical scintigraphy with this agent correctly visualized the state of aldosteronomas after TAE: a hot or warm nodule in case of unsuccessful TAE, a residual hot nodule in case of partially

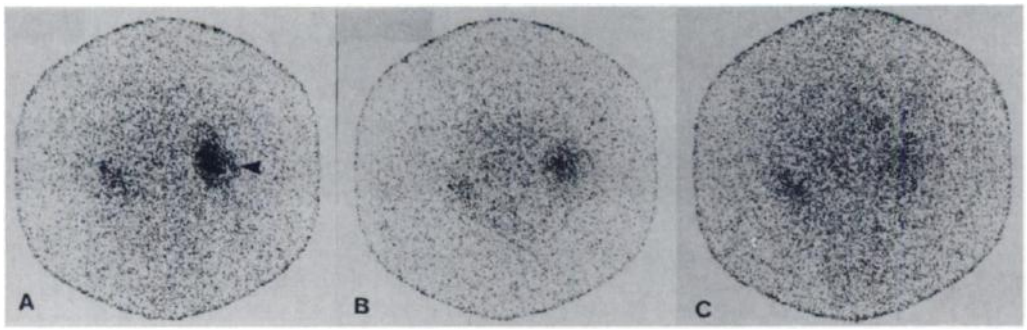


**FIGURE 3.** Adrenocortical images of Patient 4 with right aldosteronoma before and after the first unsuccessful and second successful TAEs. The hot nodule (arrowhead) of the right adrenal before the TAE (A) decreased in activity but still demonstrated residual activity after the first TAE (B). Disappearance after the second successful TAE (C).

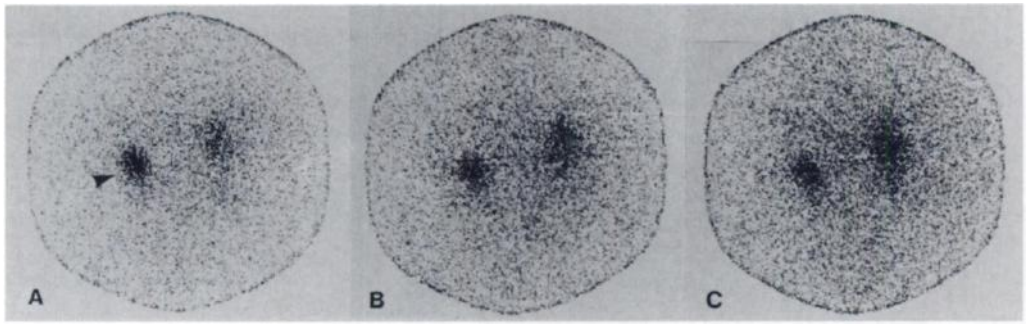


**FIGURE 4.** Adrenocortical images of Patient 10 with left aldosteronoma before and after the first and second unsuccessful TAEs. The hot nodule (arrowhead) of the left adrenal before the TAE (A) decreased in activity after the first TAE (B). The nodule persisted and increased in tracer uptake after the second TAE (C), suggesting unsuccessful therapeutic intervention.

successful TAE and disappearance of a hot nodule in case of completely successful TAE. This suggests that adrenocortical scintigraphy is a sensitive indicator to assess the effects of TAE with AE on aldosteronomas. The use of this scintigraphic method by injection of $^{131}$I-NCL-6 within one week after TAE, in combination with measurements of plasma aldosterone levels may allow for more precise assessment of the complete or incomplete success of the TAE of aldosteronomas within 2 wk and provide earlier information on the decision for a next steps management such as no further therapy, repeated TAE or surgical operation than only the measurement of the levels of plasma aldosterone.

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EDITORIAL

# The Incremental Value of Diagnostic Tests

In a recent editorial in *JNM*, Peter Valk of the Northern California PET Imaging Center (*1*) described problems in determining the specificity of [$^{18}$F]fluorodeoxyglucose (FDG) studies in the care of patients with cancer. As an example, Valk considered the validation of FDG imaging for detection of hepatic metastases. Even if all patients undergo subsequent surgery, lesions can only be detected if they are superficial or large enough to be palpated in the accessible portions of the liver. Small or deeper lesions will remain unconfirmed, and sensitivity of the FDG imaging will possibly be over estimated.

While measurement of sensitivity and specificity of diagnostic procedures, such as [$^{18}$F]FDG studies, whether performed by dedicated PET instruments or by recently developed dual-detector coincidence detections (SPECT) systems, are helpful, such parameters are not sufficient and often not knowable. Of increasing importance is the establishment of the value of the tests in meeting patients' needs reliably and consistently and in a cost-effective manner.

Assessment of the incremental value of diagnostic tests is an idea whose time has come. In modern medicine we try to be as scientific as possible. We try to make our tests as precise and as accurate as possible. Precision is a measure of the

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