Adrenal Imaging with ^{131}I-Adosterol (NCL-6-^{131}I) by Diverging and Pinhole Methods

III. Comparative Studies of Baseline and Dexamethasone Suppression Imaging in Aldosteronism

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ダイバージング及びピンホール法による ^{131}I-Adosterol (NCL-6-^{131}I) 副腎シンチグラフィ

Ⅲ．アルドステロン症における標準及びデキサメサゾン抑制シンチグラフィの比較研究

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アルドステロン症における ^{131}I-Adosterol による標準及びデキサメサゾン抑制シンチグラフィが比較検討された．対象は確定診断の得られた原発性アルドステロン症10例と特発性アルドステロン症1例及び対照群として副腎正常6例の計17例である．デキサメサゾンは tracer 静注3日前より 4mg/日で連日経口投与し，スキャン終了日まで続けた．

腺腫の患側正診率は，ダイバージング法による両側副腎の activity の比較では，標準像で70%（7/10），抑制像で80%（8/10）であり，ピンホール法による一側副腎内の activity の比較では，標準像で89%（8/9），抑制像で100%（7/7）であった．

しかしながら，抑制前後の両側副腎の net counts の比較では，特発性アルドステロン症と対照群では両側副腎の tracer の摂取は同程度に抑制されたが，原発性アルドステロン症では腫瘍側の抑制の程度が小さいもの5例，両側副腎が同程度に抑制されたもの3例，腫瘍側の抑制の程度が逆に大きいものが2例認められた．またピンホール法で抑制前後のシンチグラフィを施行した原発性アルドステロン症7例のうち，腺腫対近傍副腎組織の activity の差は抑制後5例で増大し，2例で

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減少した．このことは，原発性アルドステロン症のデキサメサゾン投与に対する反応は一定ではなく，^{131}I-iodocholesterol の摂取において，ACTH-dependent adenoma と nondependent adenoma の存在を示唆するものである．

アルドステロン症では，ピンホール法で副腎シンチグラフィを行なう場合，副腎の形態が明瞭に描出されるため標準シンチグラフィでも高い腺腫局在正診率が得られること，また ACTH-dependent adenoma の存在が示唆されることより，まず標準シンチグラフィを行ない，それでも腺腫の局在及び腺腫と過形成との鑑別が困難な場合に，抑制シンチグラフィを試みるべきであると考えられた．

Introduction

There are two methods of adrenal imaging with ^{131}I-iodocholesterol in the diagnostic evaluation of the patients with aldosteronism, i.e., baseline imaging (BI) and dexamethasone suppression imaging (DSI). The latter was first reported by Conn et al.[1]. and it has been a useful method for the detection of aldosteronomas and the distinction of aldosteronomas from bilateral hyperplasia[2][3]. In a recent report[4], DSI seems to be used as a first choice of the imaging procedure for aldosteronism and its result of locating aldosteronomas is excellent (90%). The "Pinhole method" enabled us to obtain a high-resolution adrenal image[5] which resulted in very accurate localization of aldosteronomas (94%) by BI alone[6].

In this paper, comparative studies between BI and DSI are made to estimate their diagnostic significance in evaluating the patients with aldosteronism and to clarify the dexamethasone suppression effect upon the adrenal glands of patients with aldosteronism and control patients.

Materials and Methods

Adrenal imaging was performed in seventeen patients with primary aldosteronism (aldosteronomas) and one with idiopathic aldosteronism (bilateral hyperplasia) in our Department from 1975 to 1980. Of these patients, eight with aldosteronomas, two with aldosteronomas whose adjacent cortex showed hyperplasia and one with bilateral hyperplasia were selected for this study because they underwent both BI and DSI. The remaining seven patients underwent BI only. The final diagnosis was made pathologically and with the postoperative clinical data (normalization of venous aldosterone, renin levels, serum potassium and blood pressure etc.) in ten patients with aldosteronomas. One was confirmed to have bilateral hyperplasia by adrenal venography, adrenal venous aldosterone measurements and CT.

For the control group, six patients with no evidence of adrenal diseases (5; essential hypertension, 1; renal hypertension) were selected because they also had undergone both BI and DSI in the course of their final diagnoses.

Each patient was administered about 16 μCi (59.2×10^4 Bq)/kg of body weight of ^{131}I-Adosterol (NCL-6-^{131}I) intravenously which was provided by Daiich Radioisotopes Lab. LTD., Japan. Thyroidal uptake of ^{131}I was blocked by the use of KI powder which was administered orally at 0.3 g a day, beginning one day before and continuing 6 days after injection of the tracer dose. The details of the gammacamera imaging procedure have already been reported[5][7]. Essentially the posterior image of each adrenal gland is separately obtained at 5-9 days (Pinhole method), and the posterior and anterior diverging images, 12-14 days (Diverging method) after administration of the tracer dose. A gamma camera (RC-1C-1205, HITACHI, Japan) coupled to a minicomputer (HITAC 10) was used.

In DSI, 1 mg of dexamethasone was administered orally 4 times a day, beginning 3 days before the tracer injection, continuing throughout the imaging sequence. The interval between the tracer injection for BI and

DSI was at least 4 weeks to avoid the influence of BI upon DSI. In each patient, DSI and BI were identical for imaging technique, the dose of the tracer and the sequence of imaging.

The method of calculating of the adrenal net counts has already been reported[7]. Briefly, the adrenal net counts (ANC) were defined as the sum of posterior and anterior net counts on the computer processed diverging displays obtained 12-14 days postinjection. Various ratios based on the adrenal net counts were obtained to make semiquantitative comparisons between BI and DSI. They were as follows:

1. Af./Co. ratio=Affected (Tumor-bearing)−ANC/Contralateral−ANC
2. R(L)/L(R) ratio=R(L)−ANC/L(R)−ANC
3. S./B. ratio

1) S./B. ratio of each gland=Suppression R(L)−ANC/Baseline R(L)−ANC

2) S./B. ratio of Af./Co. or R(L)/L(R) ratio=Suppression Af./Co. or R(L)/L(R) ratio/Baseline Af./Co. or R(L)/L(R) ratio

The bilateral adrenal radioactivity and the radioactive distribution of each gland were also represented on the 3-dimentional diverging display and the 90°-rotated 3-dimentional pinhole display respectively.

In the "Diverging method", the evaluation of the affected or tumor-bearing gland depended upon the presence of "lateralization" by which is meant the radioactivity of one gland was definitely higher than the contralateral gland on the original posterior image. A hot nodule with radioactivity in the adjacent adrenal tissue was used as an indicator of an adenoma on the original posterior pinhole image in the "Pinhole method[6]".

Results

Table 1 shows the diagnostic comparison of BI and DSI in aldosteronism. In the patients with aldosteronomas, the diagnostic accuracy for locating the tumor-bearing glands were as follows: 70% (7/10) with the diverging images and 89% (8/9) with the pinhole images wich BI, 80% (8/10) with the diverging images and 100% (7/7) with the pinhole images with DSI. In one patient with hyperplasia, the baseline diverging image showed the left slightly higher asymmetry which changed to symmetrical uptake on suppression imaging. Neither imaging techniques could distinguish hyperplasia from an adenoma in thr patient.

Table 1. Diagnostic comparison of BI and DSI in aldosteronism

Case	Sex	Age	BI		DSI		Final diagnosis	
			Diverging image	Pinhole image	Diverging image	Pinhole image	Side	Size of adenoma (cm³)
1. M.Y.	♂	30	?	L	L	—	L	1.3×1.3×0.9
2. K.H.	♂	40	L	L	L	L	L°	2.0×2.0×1.2
3. T.H.	♀	42	L	—	L	—	L	1.6×1.5×1.5
4. K.S.	♀	35	L	L	L	L	L	1.4×1.4×0.6
5. E.A.	♀	43	R	R	R	R	R	1.5×1.6×1.0
6. T.Y.	♀	33	L	L	L	L	L	1.8×1.6×1.2
7. E.I.	♀	46	R(?)	R	R(?)	—	R°	1.5×1.3×1.0
8. H.K.	♀	42	R(?)	B*(?)	R(?)	R	R	1.3×1.4×0.9
9. T.M.	♀	41	R	R	R	R	R	2.0×1.7×1.2
10. K.N.	♀	40	L	L	L	L	L	2.0×2.2×1.7
11. N.I.	♂	53	L(?)	B Adenoma(−)	?	B Adenoma(−)	B	Hyperplasia

°Adenoma with hyperplasia, *Bilateral glands

Table 2. Various comparative ratios of the adrenal net counts between BI and DSI in aldosteronism

Case No.	Affected gland(s)	Af./Co. ratio		S./B. ratio		
		BI	DSI	R	L	Af./Co. ratio
1	L	1.62	3.05	0.40	0.75	1.88
2	L	2.07	3.29	0.53	0.84	1.59
3	L	1.81	2.64	0.60	0.88	1.46
4	L	1.32	1.83	0.71	0.99	1.39
5	R	2.19	2.96	0.77	0.57	1.35
6	L	2.64	2.60	0.87	0.86	0.98
7	R	1.06	1.03	0.54	0.55	0.97
8	R	1.41	1.32	0.59	0.63	0.94
9	R	2.47	2.11	0.50	0.58	0.85
10	L	1.70	1.02	0.79	0.47	0.60
11	B*	1.20**	1.12**	0.51	0.47	0.93**

*Bilateral hyperplasia, **L/R ratio

Table 2 shows various comparative ratios of the adrenal net counts during BI and DSI in aldosteronism. Ten patients with primary aldosteronism were divided into three groups according to the changes of the Af./Co. ratios under dexamethasone administration or by their S./B. ratios. The first group showed an increase of the Af./Co. ratio under suppression which meant the dexamethasone suppressive effect was greater on the contralateral gland than in the tumor-bearing gland (Cases, 1-5). In the second group, no significant changes of the Af./Co. ratios were observed between BI and DSI, which meant the suppressive effect acted equally upon both glands (Cases, 6-8). The third group showed the decrease of the Af./Co. ratio under suppression which meant the tumor-bearing gland responded to the suppressive effect more than the contralateral gland (Cases, 9 and 10). In one case of idiopathic aldosteronism, no significant change of the Af./Co. ratios between BI and DSI was observed (Case 11). The mean value of the S./B. ratios of the contralateral glands was 0.62 ± 0.13 in primary aldosteronism.

Both baseline and suppression pinhole images of each gland were obtained in seven cases of primary aldosteronism and in one case of idiopathic aldosteronism. In the five adenoma-bearing glands of Cases, 2, 4 and 5 in the first group and Cases 6 and 8 in the second group, the difference in radioactivity between the adenoma and its adjacent tissue was increased in the suppression image compared to the baseline image. However, the radioactive difference was decreased in the other two adenoma-bearing glands of Cases 9 and 10 in the third group. In all seven contralateral glands of primary aldosteronism and bilateral glands of idiopathic aldosteronism, the adrenal radioactivity on the suppression image decreased as a whole when compared to that of the baseline image.

In the control group, the S./B. ratio of each gland ranged from 0.46 to 0.73 (mean: 0.56 ± 0.12) in the right side and from 0.49 to 0.73 (mean: 0.57 ± 0.09) in the left side. The S./B. ratio of the R/L ratio ranged from 0.89 to 1.14 (mean: 0.98 ± 0.08) (Table 3). These results indicate that the degree of suppressive effect was almost equal in the bilateral normal glands. The radioactivity of each normal gland on the suppression pinhole image showed the same decrement as that of the contralateral glands in primary aldosteronism and both glands of idiopathic aldosteronism.

The adrenal images of the illustrated cases is presented below. Fig. 1 shows the adrenal images of the patient with a left aldosteronoma (Case 4) whose S./B. ratio of the Af./Co. ratio is 1.39 (the increasing type). The baseline posterior original diverging image and its 3-dimentional display (upper mid) show the

Table 3. Comparative ratios of the adrenal net counts between BI and DSI in the control group

Case	Disease	Sex	Age	R/L ratio		S./B. ratio		
				BI	DSI	R	L	R/L ratio
12. H.Y.	E.H.*	♂	30	1.47	1.43	0.71	0.73	0.97
13. Y.I.	E.H.	♂	19	1.07	0.95	0.49	0.55	0.89
14. Y.M.	E.H.	♂	28	1.26	1.19	0.46	0.49	0.94
15. S.N.	E.H.	♀	38	1.01	1.02	0.50	0.49	1.01
16. S.F.	R.H.**	♂	48	1.13	1.19	0.73	0.64	1.14
17. M.N.	E.H.	♀	46	1.29	1.16	0.46	0.51	0.90

*Essential hypertension, **Renal hypertension

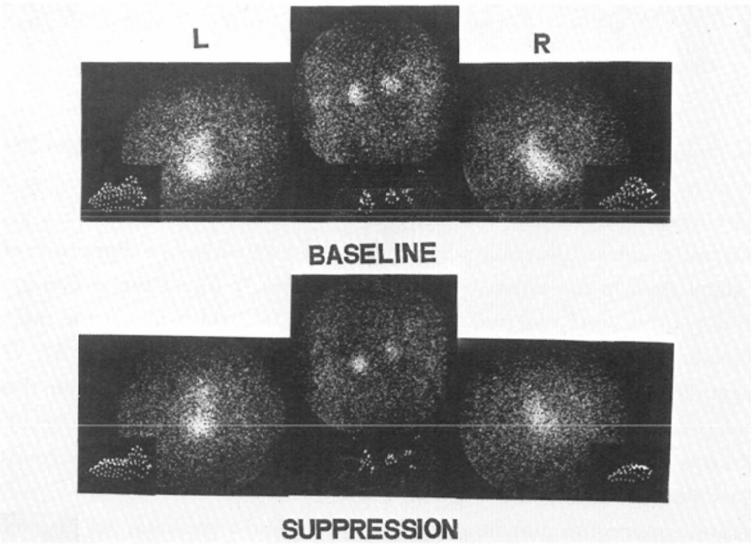

Fig. 1 Primary aldosteronism (the increasing type, Case 4). See text.

"lateralization" of radioactivity in the left gland which becomes clearer on the suppression image and its computer display (lower mid). The baseline pinhole image of the left gland shows a hot nodule at the inferior portion of the gland which is consistent with an adenoma and the peak-formation on its 90°-rotated 3-dimentional display (upper left). The hot nodule is more clearly demonstrated on the suppression image and display because of the decrease radioactivity in the adjacent tissue (lower left). The baseline pinhole image of the right gland shows a normal triangular type whose radioactivity is highest in its midportion (upper right) and which is suppressed on the DSI image and display (lower right).

Fig. 2 shows the adrenal images of the patient with a right aldosteronoma (Case 8) whose S./B. ratio of the Af./Co. ratio is 0.94 (the unchanging type). This is the only case where the adenoma could not be localized by the baseline pinhole images. The baseline diverging image and its 90°-rotated 3-dimentional display show the right higher asymmetry which cannot be differentiated from normal asymmetry (upper mid). The relationship of radioactivity between both glands does not change significantly on the suppression image and display (lower mid). The baseline pinhole image of the left gland and its computer display (upper left) reveal a high-

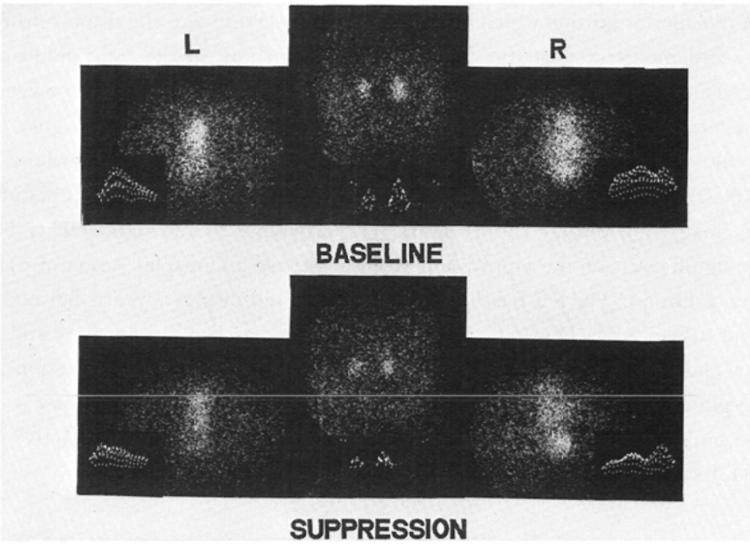

Fig. 2 Primary aldosteronism (the unchanging type, Case 8). See text.

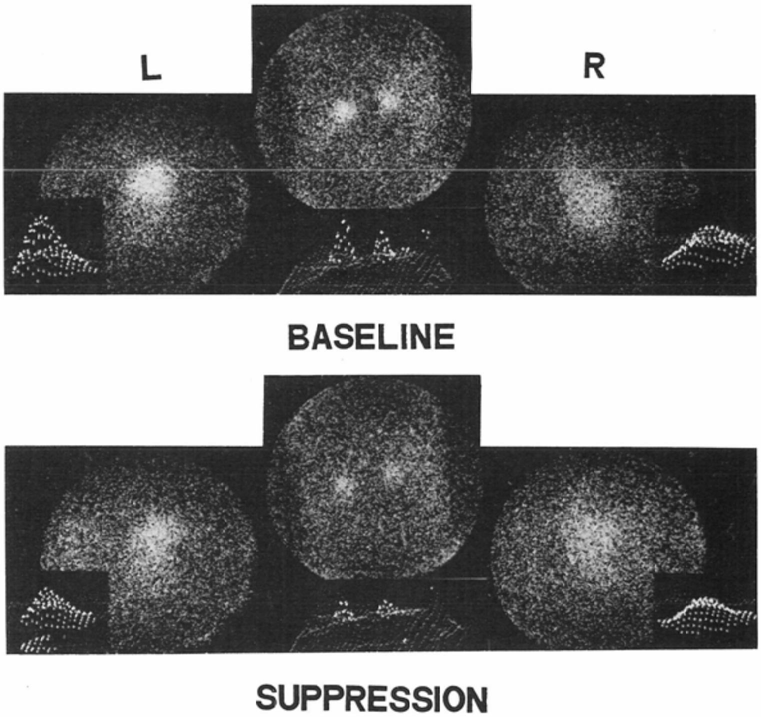

Fig. 3 Primary aldosteronism (the decreasing type, Case 10). See text.

radioactive area at its superior portion which is suppressed on the DSI image and display (lower left). Two high-radioactive areas are demonstrated at the mid and inferior portions of the right gland under the baseline condition (upper right). The high-radioactive area at the midportion is suppressed, however the inferior area is not suppressed and becomes a hot nodule which is consistent with an adenoma (lower right).

Fig. 3 shows the adrenal images of the patient with a left adenoma (Case 10) whose S./B. ratio of the Af./Co. ratio is 0.60 (the decreasing type). "Lateralization" of radioactivity in the left gland is observed on the baseline diverging image and display (upper mid). The difference in the radioactivity between the glands however, decreases significantly on the suppression diverging image and display (lower mid) when compared to that of the baseline condition. The left baseline pinhole image and display reveal a hot nodule at the superior portion of the gland (upper left). This hot nodule, however, decreases in radioactivity and the difference between the adenoma and its adjacent tissue also appears to be smaller on the suppression image and display (lower left). These pinhole images also prove that the uptake of tracer in this adenoma is ACTH-dependent. The right baseline pinhole image and display reveal the normal outline and radioactive distribution of the gland (upper right). Its radioactivity is decreased in DSI (lower right).

Discussion

In the scintigraphic diagnosis of the aldosteronoma-bearing gland, comparison of bilateral adrenal radioactivity was important and lateralization of radioactivity in one gland has been used as a dignostic criterion[2)3)]. However, there were diagnostic problems including lack of lateralization of some patients with aldosteronomas and asymmetrical uptakes of some patients with bilateral hyperplasia in BI[2)3)6)].

DSI was introduced to overcome these diagnostic limitations and has been used as an efficient method for the preoperative detection of aldosteronomas and the distinction of aldosteronomas from bilateral hyperplasia.

The differences in the imaging patterns seen with ^{131}I-NP-59 and ^{131}I-19-iodocholesterol in DSI have been reported[4)]: The contralateral gland was visualized with the former and not visualized with the latter. The differential diagnosis depending upon the time of visualization with ^{131}I-19-iodocholesterol cannot be used any longer in DSI with NP-59.

With ^{131}I-Adosterol in this study, the normal glands, the hyperplasia-bearing glands and the contralateral glands as well as the tumor-bearing glands were all visualized in DSI. Therefore, the diagnosis of aldosteronism with ^{131}I-Adosterol or ^{131}I-NP-59 in DSI depends upon the radioactive lateralization or symmetry of tracer uptake.

Conn et al. reported the tumor-locating accuracy of ^{131}I-19-iodocholesterol was 71% (10/14) in BI and 88% (15/17) in DSI[2)]. In this series with ^{131}I-Adosterol, it was 70% (7/10) in BI and 80% (8/10) in DSI by the "Diverging method" because one of the three symmetrical or slightly asymmetrical cases in BI produced "lateralization" in DSI (Table 1). However, the comparison of the Af./Co. ratios between BI and DSI brought about a very intersting result which revealed the heterogeneity in the uptake of the tracer under dexamethasone suppression in the patients with primary aldosteronism: In primary aldosteronism, the Af./Co. ratio in DSI was increased in five cases (the increasing type), not changed in three cases (the unchanging type) and decreased in two cases (the decreasing type) when compared to that in BI. With the "Pinhole method", the radioactive difference between the adenoma and its adjacent tissue in DSI was increased in three of the increasing type and two of the unchanging type, and decreased in two of the decreasing type when compared to that in BI.

A recent biochemical study by Wenting et al.[8)] revealed two groups of patients with primary aldosteronism: In group I, normalized plasma levels of aldosterone and cortisol during the day were significantly correlated and one day of dexamethasone treatment suppressed aldosterone to subnormal levels. Group II did not show such correlation and had little such suppression effect. The adenomas can be said to be ACTH-dependent in group I and ACTH-independent in group II.

It is not clear whether the increasing or unchanging type of adenoma belongs to group II and the decreasing type of adenoma, group I, because the measurement of plasma aldosterone under dexamethasone suppression was not performed. However, the heterogeneity of response to dexamethasone administration in aldosteronism in this scintigraphic study is consistent with that in the above mentioned biochemical study.

Fortunately, the two decreasing type of adenomas, ACTH-dependent or dexamethasone suppressible in the uptake of ^{131}I-iodocholesterol were quite large, about 2 cm in diameter, and could also be detected by DSI. If the deceasing type of adenoma were smaller, it may not be detected by DSI.

Hoefnagels et al.[9] reported a very interesting case of primary aldosteronism where DSI with ^{131}I-19-iodocholesterol not only failed to reveal a tumor of 1.5 cm in the left adrenal gland, but also showed paradoxical accumulation of radioactivity in the histologically normal right adrenal gland. (This paradoxical scintigraphic phenomenon might be explained by a combination of an ACTH-dependency of the tumor and the normal, right higher, asymmetry[7].)

Although the degree of suppression was not different between glands in the control group and in the one case of hyperplasia, the variety of the response to dexamethasone administration in primary aldosteronism suggests that DSI not only cannot always distinguish an adenoma from hyperplasia, but also may be inferior to BI in detecting the ACTH-dependent adenoma.

As far as the scintigraphic diagnosis depends upon the "Pinhole method", DSI is not recommended as a first choice of the imaging method in primary aldosteronism because independently of asymmetrical or symmetrical uptakes, BI has a high accuracy of locating aldosteronomas (94%, 16/17)[6], may discriminate micronodular hyperplasia from an adenoma due to the high-resolution pinhole image. Even DSI is considered unable to differentiate a macronodule of hyperplasia from an ACTH-dependent adenoma. Therefore, the indication of DSI may be limited to those patients whose pinhole images show the area(s) of increased tracer uptake whose origin(s) cannot be decided by the pinhole imaging patterns[6][7]. The possibility of detecting an adenoma less than 1 cm in diameter also exists, if DSI is performed by the "Pinhole method" and the adenoma is ACTH-independent.

Conclusion

Comparative studies of baseline and dexamethasone suppression adrenal imagings with ^{131}I-Adosterol were conducted in ten patients with primary aldosteronism, one with idiopathic aldosteronism and six with no evidence of adrenal diseases.

In aldosteronoma localization, in baseline conditions the correct diagnosis was made in 70% (7/10) by the "Diverging method" and 89% (8/9) by the "Pinhole method" and 80% (8/10) and 100% (7/7) respectively during dexamethasone suppression.

The semiquantative comparison of the adrenal net counts between baseline and suppression imaging revealed that the heterogeneity in the uptake of the tracer under dexamethasone administration in primary aldosteronism: The degree of suppression was less in the tumor-bearing gland than the contralateral gland in five cases, almost equal in both glands in three cases and greater in the tumor-bearing gland in two cases. In six control cases and one of hyperplasia, both glands were suppressed to the same degree.

The existence of ACTH-dependent adenomas in the uptake of the tracer indicates that the dexamethasone suppression adrenal imaging cannot always differentiate an adenoma from hyperplasia in aldosteronism.

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