Diagnostic Evaluation of the Adrenal Incidentaloma: Decision and Cost-Effectiveness Analyses

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The goal of this study was to examine the clinical and economic outcomes of alternative diagnostic strategies for differentiating benign from malignant adrenal masses. **Methods:** We used cost-effectiveness assessment derived from decision analysis and the economic perspective of the payer of health care services. One-time evaluation with fine-needle aspiration (FNA) and combinations of chemical-shift MRI, noncontrast CT, ^{131}I-6β-iodomethylnorcholesterol (NP-59) scintigraphy, with or without FNA, in a hypothetical cohort of 1000 patients with incidentally discovered unilateral, nonhypersecretory adrenal masses. We calculated and compared the diagnostic effectiveness, costs and cost-effectiveness of the alternative strategies based on estimates from published literature and institutional charge data. **Results:** At an assumed baseline malignancy rate of 0.25, diagnostic utility varied from 0.31 (CT_0) to 0.965 (NP-59) and diagnostic accuracy from 0.655 [noncontrast CT using a cut-off attenuation value of $\geq$0 (CT_0)] to 0.983 (NP-59). The average cost per patient per strategy ranged from $746 (NP-59) to $1745 (MRI $\pm$ FNA). The best and worst potential cost-to-diagnostic utility ratios were 773 (NP-59) and 2839 (CT_0) and 759 (NP-59) and 1982 (MRI $\pm$ FNA) for cost and diagnostic accuracy, respectively. The NP-59 strategy was the optimal choice regardless of the expected outcome examined: cost, diagnostic utility, diagnostic accuracy or cost-effectiveness. Varying the prevalence of malignancy did not alter the cost-effectiveness advantage of NP-59 over the other diagnostic modalities. **Conclusion:** Based on available estimates of reimbursement costs and diagnostic test performance and using reasonable clinical assumptions, our results indicate that the NP-59 strategy is the most cost-effective diagnostic tool for evaluating adrenal incidentalomas over a wide range of malignancy rates and that additional clinical studies are warranted to confirm this cost-effectiveness advantage.

Key Words: adrenal mass; incidentaloma; adrenocortical scintigraphy; cost-effectiveness analysis

J Nucl Med 1998; 39:707–712

Adrenal masses that are incidentally discovered when a CT scan is performed for reasons other than known or suspected adrenal disease have been termed incidentalomas (*1,2*). These lesions have become a common clinical problem with the more frequent and widespread use of high-resolution imaging procedures. In the vast majority of patients, adrenal incidentalomas are benign, nonhypersecretory adenomas (*1,2*). Nevertheless, it is important to distinguish benign lesions from others, such as primary adrenal cancer or metastases to the the adrenals, in which intervention, or the lack thereof, may alter morbidity and mortality. Presently, there is little or no consensus regarding the diagnostic approach to biochemically nonhypersecretory incidentalomas. Management strategies based on adrenal mass size are neither sensitive nor specific (*2*). Although 76%–100% of adrenal masses greater than 5 cm in diameter are benign, as many as 50% of those smaller than 2.5 cm are malignant (*3–8*).

Other diagnostic strategies, used alone or in combination, have included serial, conventional CT with size determinations to assess stability (adenomas) or growth (tumor), morphologic characterization with MRI or CT, with measurements of x-ray attenuation or functional adrenal imaging with ^{131}I-6β-iodomethyl-norcholesterol (NP-59) and biopsy using percutaneous fine-needle aspiration (FNA). Biopsy is an invasive procedure with a small, but significant, morbidity of 3%–12% (*9–17*). Thus, some researchers have suggested using noninvasive imaging to optimize the selection of patients for adrenal biopsy and/or choice of definitive therapy.

The reality of increasingly limited resources for health care creates new pressures for providers to achieve the best possible outcomes for patients at the lowest cost. To accomplish this, increased attention is being directed to the determinants of cost-effectiveness of the spectrum of diagnostic options available in the work-up of a patient with a particular disease state. To date, however, available biopsy or imaging techniques for the work-up of adrenal incidentalomas have not been formally subjected to a rigorous comparative investigation. The clinical and economic consequences of various management approaches incorporating one or more of these procedures is unknown.

Using decision analysis (*18–20*), published literature and institutional charge data, we examined the costs, diagnostic utility, diagnostic accuracy and the cost-effectiveness (*21,22*) of several diagnostic strategies for differentiating between benign and malignant adrenal incidentalomas incorporating one or more combinations of chemical-shift MRI, CT using nonenhanced attenuation values, NP-59 and/or FNA. Sensitivity analysis was used to evaluate the impact of changes in clinical input and resource use parameters on the results.

MATERIALS AND METHODS

Decision Analytic Model

Using the software program Decision Analysis by TreeAge (DATA 3.0, Williamstown, MA), we constructed a computer simulation of the diagnostic evaluation of incidentally discovered unilateral nonhypersecretory adrenal masses. The analysis involved a hypothetical cohort of patients without known malignancy in whom adrenal incidentalomas were identified during thoracoabdominal imaging for unrelated medical problems. The patients had undergone clinical and biochemical evaluation to exclude adrenal hyperfunction before entering the model. The decision analytic model begins with a decision node representing an active choice of one of nine strategies incorporating chemical-shift MRI, noncontrast CT with measurement of x-ray attenuation in Houndsfield

Received Jan. 27, 1997; revision accepted Jul. 4, 1997.

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units (HU), NP-59 scintigraphy and/or FNA categorized as follows.

Imaging

1. CT_0 (≥0 HU cutoff);
2. CT_{10} (≥10 HU cutoff);
3. MRI;
4. NP-59;

Biopsy

5. FNA;

Imaging-Biopsy

6. CT_0 and, if positive FNA, CT_0 ± FNA;
7. CT_{10} and, if positive FNA, CT_{10} ± FNA;
8. MRI and, if positive FNA, MRI ± FNA;
9. NP-59 and, if positive FNA, NP-59 ± FNA.

The points of uncertainty (malignancy or nonadenoma rates, complication rates and diagnostic test performance characteristics) are represented by a chance node and each is associated with a probability. Each branch of the tree ends with a terminal node or final outcome incorporating the four test outcomes [true-positive (TP), true-negative (TN), false-positive (FP) and false-negative (FN)] and representing the average costs and diagnostic effectiveness of each respective decision path. The estimated value of a strategy was determined by weighting the value of the outcome by the path probability. Each test or test sequence result is interpreted as positive or negative for a nonadenoma. For evaluating two-test strategies, we assumed conditional independence and calculated performance characteristics according to established methodology using a conjunctive positivity criterion, i.e., result of testing is considered positive only if both tests are positive (*23,24*) (Appendix 1). Thus, the next test in sequence is performed only if these preceding test result was positive suggesting malignancy. Any negative test excludes patients from additional testing and presumes that the lesion is benign. (Decision tree is available upon request from BAD.)

Assumptions

We developed the following assumptions:

1. FNA is used alone (strategy 5) or only as the final modality in a test sequence (strategies 6–9) in clinical practice.
2. There are no tangible complications associated with noncontrast CT, chemical-shift MRI or NP-59 scintigraphy.
3. There are no indeterminate test results.
4. The costs of initial clinical and laboratory evaluation before entering the model are the same regardless of strategy.
5. Patients are indifferent to the choice of strategy.

Data Sources

Input variables used in the model were obtained from published literature (MEDLINE database for English-language articles and review of bibliographies of selected articles, current issues of peer-reviewed general medicine, diagnostic imaging, surgical and endocrinology journals) on the prevalence of nonhypersecretory adenomas, adrenocortical carcinoma, adrenal metastases in adrenal incidentalomas, diagnostic performance of biopsy and imaging procedures and morbidity of invasive modalities and from costs of diagnostic procedures (from hospital charges and professional fee data).

Summary of Available Data for Baseline Estimates and Range of Values

Prevalence of Adrenal Incidentaloma. In nononcologic and general patient populations, 70%–94% of adrenal incidentalomas are nonhypersecretory adenomas (*2*) (Table 1). In the setting of a known or suspected extra-adrenal primary malignancy, the incidence of metastases increases, ranging from 32% to 73% (*2*).

TABLE 1
Baseline Probabilities, Estimates and Range of Values

Variable	Base case values	Range of values
Probability of nonadenoma (*2*)	0.25	0.05–0.50
Sensitivity of FNA (*13,14,16,17*)	0.83	0.50–1.00
Specificity of FNA (*13,14,16,17*)	0.99	0.50–1.00
Sensitivity of CT_0 (*25–28,44*)	1.00	0.50–1.00
Sensitivity of CT_{10} (*25–28*)	0.96	0.50–1.00
Specificity of CT_0 (*25–28*)	0.54	0.50–1.00
Specificity of CT_{10}(*25–28*)	0.73	0.50–1.00
Sensitivity of NP-59 (*8,36–40*)*	0.93	0.50–1.00
Specificity of NP-59 (*8,36–40*)	1.00	0.50–1.00
Sensitivity of MRI (*29–32*)	0.99	0.50–1.00
Specificity of MRI (*29–32*)	0.89	0.50–1.00
Morbidity of FNA	0.00	0–0.15
Cost of FNA-morbidity ($)	1000	0–2500
Cost of FNA ($)	1138	250–2500
Cost of CT ($)	880	250–2500
Cost of NP-59 ($)	746	250–2500
Cost of MRI ($)	1369	250–2500

*For adrenal masses of ≥2 cm in diameter.

Diagnostic Tests

Table 2 is a summary of diagnostic test characteristics from the published literature, and Appendix 2 summarizes diagnostic test criteria used in the evaluation of hormonally inactive adrenal incidentalomas. Overall test characteristics for each modality were obtained by pooling available data for which there was sufficient information to permit construction of contingency tables and calculation of weighted averages. Definition of test outcomes are shown in Appendix 3.

Noncontrast CT. Several recent publications have suggested that nonenhanced CT attenuation values may be used to distinguish benign from metastatic lesions better than size (*25–27*). A nonenhanced CT attenuation coefficient of 0 HU or less has been reported as 100% specific for a benign adenoma versus a metastatic lesion (*25–27*). However, given the high percentage of benign adrenal adenomas with attenuation values greater than 0 HU, low sensitivities of only 33% to 58% (*25–27*) have been reported. Similarly, thresholds of 10–18 HU have yielded variable results (*25–27*). Korobkin et al. (*28*) have summarized the results of four large published series totalling 195 patients. The sensitivity-to-specificity ratios for adenomas were 54:100% and 73:96% for thresholds of ≤0 HU and ≤10 HU, respectively.

MRI. Several MRI techniques may provide tissue characterization of adrenal masses. Chemical-shift imaging, first reported by Mitchell et al. (*29*) has the greatest promise of MRI accuracy. This technique relies on differences in resonance frequencies between the protons in water and lipid molecules to distinguish lesions with relatively high lipid content (e.g., adenomas) from those with low

TABLE 2
Diagnostic Test Performance Characteristics

Test	No. of masses	Sensitivity	Specificity
FNA (*13,14,16,17*)	391	0.83	0.99
MRI (*29–32*)	252	0.99	0.89
NP-59 (*8,40*)	229	0.93	1.00
CT_0 (*25–28*)	195	1.00	0.54
CT_{10} (*25–28*)	195	0.96	0.73

lipid content (e.g., metastases). Signal intensity changes may be analyzed visually in reference to another tissue (e.g., liver or spleen) or quantitatively (*30–32*).

FNA Biopsy of the Adrenal Gland. Histologic distinction between adenomas and well-differentiated primary malignancy of the adrenal gland is often difficult. Percutaneous aspiration biopsy is best able to distinguish adrenal from nonadrenal tissues and thus may be most useful in patients with known extra-adrenal malignancies who are at risk for adrenal metastases. This raises the question of whether a person without a known cancer should undergo FNA of an adrenal mass given the risk of needle tract seeding of malignant cells and that diagnosis may be uncertain. Multiple biopsies of a single mass may be necessary for adequate sampling (*9–17*).

NP-59 Scintigraphy. Adrenocortical scintigraphy provides both anatomic localization and in vivo functional characterization of the adrenal glands due to the uptake and accumulation of the radiotracer [e.g., [^{131}I]−6β-iodomethyl-norcholesterol (NP-59)] by functioning adrenal cortical tissues (normal hyperplastic glands and adenomas) (*8,33–40*). Nonfunctioning primary and secondary malignancies of the adrenal gland demonstrate an imaging pattern of decreased, distorted or absent radiocholesterol uptake by the affected adrenal gland which is described as "discordant" (*8,33–40*). Nonhypersecretory adrenal adenomas demonstrate NP-59 accumulation and thus scintigraphic visualization on the side of the known adrenal mass (concordant pattern) (*8,33–35,40*). The efficacy of NP-59 for adrenal masses that are ≥ 2 cm is 0.93 and 1.0 sensitivity and specificity, respectively (*40*).

Procedure-Related Complications. Strategies that use FNA biopsy of adrenal masses may subject patients with nonhypersecretory adrenal cortical adenomas to an invasive procedure that carries a low incidence of well-documented serious risks (*9–17*). The most common complication is pneumothorax. Silverman et al. (*17*) reported a 3% pleural complication rate with two-thirds of these patients requiring chest tube placement. Complication rates range from 0% to 12% with reported overall rates of 5.3% (*9*).

Outcome Measures

Clinical Outcomes. We determined, for each strategy, diagnostic utility and diagnostic accuracy. The diagnostic utility is the probability-weighted sum of the utilities of the four test outcomes: TP, TN, FP and FN. The details of this concept have been well described elsewhere (*41*) (Appendix 4). The diagnostic accuracy is the fraction of correctly identified masses.

Economic Outcomes. The average cost per per patient by strategy was computed using charges for diagnostic procedures, which consisted of hospital and professional (physician, pathology and/or technical) fees.

Cost-Effectiveness. Strategies were compared by determining cost per diagnostic utility and cost per diagnostic accuracy from the perspective of the third-party payer.

We also determined the incremental cost-effectiveness of a confirmatory FNA after a positive imaging test. In estimating the incremental cost-effectiveness ratio, the numerator and denominator both represent differences between the alternative strategies (*22,42*): Incremental cost-effectiveness = difference in cost/difference in effectiveness, where difference in cost = cost of strategy − cost of alternative, and difference in effectiveness = effectiveness of strategy − effectiveness of alternative.

Sensitivity Analyses

To evaluate the impact of changes in clinical input and resource use parameters on the results of the baseline analysis, the probability of nonadenomatous adrenal masses and the other variables were subjected to sensitivity analysis over the range of values shown in Table 1.

TABLE 3
Average Costs, Number of Correct Diagnoses, Diagnostic Utility and Diagnostic Accuracy by Strategy Under Baseline Conditions

Strategy	Average cost	Correct diagnoses	Diagnostic utility	Diagnostic accuracy
CT_0	880	655	0.310	0.655
CT_{10}	880	788	0.575	0.788
MRI	1369	915	0.830	0.915
NP-59	746	983	0.965	0.983
FNA	1138	950	0.900	0.950
CT_0-FNA	1557	954	0.908	0.954
CT_{10}-FNA	1384	947	0.894	0.947
MRI-FNA	1745	880	0.761	0.880
NP-59-FNA	1011	943	0.886	0.943

RESULTS

Baseline Analyses

The results of the primary analysis of the different testing strategies are presented in Table 3. Diagnostic utility varied from 0.310 (CT_0) to 0.965 (NP-59), whereas diagnostic accuracy varied from 0.655 (CT_0) to 0.985 (NP-59 only). The average cost per patient strategy ranged from $746 (NP-59) to $1745 (MRI ± FNA). The optimal cost/diagnostic utility and the cost/diagnostic accuracy are $773 and $759 (NP-59). NP-59 is the optimal choice regardless of whether the expected payoff is cost, diagnostic utility, diagnostic accuracy or cost-effectiveness (Fig. 1). The CT_0 only strategy was less cost-effective than CT_{10}. Accounting for the complications of FNA did not alter the dominance of the NP-59 strategy but resulted in an increase in the total costs of each of the FNA-based strategies.

Incremental Cost-Effectiveness

Incremental cost-effectiveness ratios under baseline conditions are shown in Table 4.

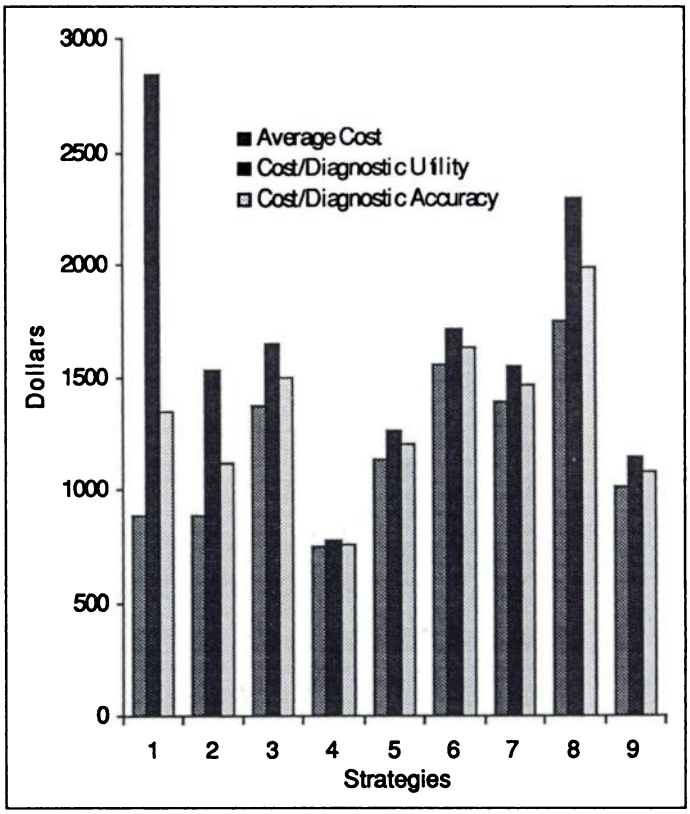

FIGURE 1. Costs and cost-effectiveness ratios of the different strategies under baseline conditions (1 = CT_0; 2 = CT_{10}; 3 = MRI; 4 = NP-59; 5 = FNA; 6 = CT_0 ± FNA; 7 = CT_{10} ± FNA; 8 = MRI ± FNA and 9 = NP-59 ± FNA).

TABLE 4
Incremental Cost-Effectiveness Ratios*

Strategies compared	Cost/Diagnostic utility	Cost/Diagnostic accuracy
CT_0 ± FNA vs. CT_0	1132	2264
CT_{10} ± FNA vs. CT_{10}	1580	3170
MRI ± FNA vs. MRI	MRI dominates	MRI dominates
NP-59 ± FNA vs. NP-59	NP-59 dominates	NP-59 dominates†

*Incremental cost-effectiveness indicates the additional cost per additional unit of diagnostic effectiveness.

†NP-59 (or MRI) dominates: more expensive strategy (i.e., NP-59 ± FNA or MRI ± FNA) not more effective (than NP-59 or MRI).

These ratios indicate the additional cost incurred for each additional unit of effectiveness obtained using a more costly strategy (in this case by performing FNA after a positive imaging test).

Sensitivity Analyses

The cost-effectiveness advantage of the NP-59 only strategy was not altered by clinically plausible changes in the malignancy rate and sensitivity of any of the diagnostic tests when either of the measures of cost-effectiveness were used but was sensitive to variations in the cost of the diagnostic tests. The advantage of NP-59 was impacted by changes in the specificity of NP-59, CT_0 and CT_{10} when cost/diagnostic utility was the C/E measure of interest. Using cost/diagnostic accuracy as the outcome measure, the results of the analysis were insensitive to variations in diagnostic test characteristics except the specificity of NP-59. The thresholds of cost and specificity required for NP-59 to remain cost-effective were ≤$1180 and ≥0.68 for cost/diagnostic utility and ≤$1155 and ≥0.63 for the cost/diagnostic accuracy measure. Varying the rate and cost of complications from FNA affected only the biopsy (strategy 5) and the imaging-biopsy (strategies 6–9) options.

DISCUSSION

Most adrenal incidentalomas are nonhypersecretory adenomas (*2*). It is important, however, to distinguish these benign lesions from primary adrenal cancer or metastases to the adrenal glands to provide timely and appropriate treatment. Despite the multiplicity of testing modalities, there is no consensus regarding the most appropriate diagnostic strategy. With the current health care climate, there is a need for more and better awareness of the costs and benefits of diagnostic tests. As a result, physicians are requested to behave in a more cost-effective manner when choosing among numerous alternatives. We have used decision analytic modeling to estimate the cost-effectiveness of several available diagnostic strategies for differentiating between benign and malignant adrenal incidentalomas.

Our results showed that an NP-59 strategy was associated with the lowest total costs, highest diagnostic utility, highest diagnostic accuracy and was the most cost-effective. Although the efficacy of NP-59 is derived from our experience, recent results from other smaller series independently confirm the clinical utility of scintigraphy in the evaluation of the incidentally discovered adrenal mass (*36–40*). This cost-effective advantage was maintained when the malignancy (nonadenoma) rate was subjected to sensitivity analyses. Accounting for the complications of FNA did not alter the dominance of the NP-59 strategy but resulted in an increase in the total costs of each of the FNA-based strategies. The thresholds of cost and specificity required for NP-59 to remain cost-effective were ≤ $1180 and (*3*) 0.68 for cost/diagnostic utility and ≤ $1155 and (*3*) 0.63 for the cost/diagnostic accuracy measure. The cost thresholds are higher and the specificity thresholds are lower than are currently available in clinical practice, suggesting that NP-59 is currently the most preferred test in evaluating adrenal incidentalomas.

Because the endpoints of interest were diagnostic effectiveness and the costs associated with a one time evaluation of adrenal incidentalomas, quality-adjusted life years (QALYS) were not used. It is conceivable that the long-term clinical and economic outcomes of using the alternative strategies, incorporating therapeutic choices and survival outcomes may be different from that obtained by this model.

Our model reveals that confirmatory testing with FNA is seldom, if ever, preferred to a single test for all disease probabilities, given that the single-test strategies were generally more cost-effective than the two-test diagnostic approaches. Although imaging appears cost-effective and would spare patients the risk and discomfort of FNA and other invasive testing, it is not clear whether physicians or patients are willing to base management decisions regarding adrenal incidentalomas on the results of a noninvasive test alone.

There was no advantage in evaluating patients with FNA instead of NP-59 or MRI or subjecting patients with positive imaging tests to confirmatory FNA. Additionally, strategies that use FNA may subject patients with benign adrenal incidentalomas to invasive procedures, which carry a low incidence of well-documented serious risks (*9–17*). The awareness that cytologic distinction between adenomas and well-differentiated primary malignancy of the adrenal gland is often difficult raises the question of whether a person without a known cancer should undergo FNA of an adrenal mass given the risk of needle tract seeding of malignant cells and an often inconclusive result.

MRI ± FNA and CT_0 strategies appeared to be the least cost-effective. For the former, this may be a reflection of the fact that chemical-shift MRI is not only the newest imaging technique for characterization of adrenal masses but is currently the most expensive, with diagnostic accuracy and utility no better than NP-59 or FNA. For the latter, this is because, despite excellent sensitivity, it has the lowest specificity. This study indicates that in situations where CT may be the only modality available for noninvasive evaluation of adrenal incidentalomas, a threshold of > 10 HU may be more useful: it was associated with higher diagnostic utility and diagnostic accuracy and more cost-effective than the > 0 HU criterion. Although, CT_0 ± FNA was associated with slightly higher diagnostic utility and diagnostic accuracy than CT_{10} ± FNA, the latter was more cost-effective using either cost/diagnostic utility or cost/diagnostic accuracy.

Although we assumed that patients are indifferent to the type of strategy chosen, it is well known that some patients may be risk-averse and prefer noninvasive imaging to FNA or other invasive procedures. Although, there may be no tangible complications from the imaging procedures, it is possible that patients' attitudes toward the claustrophobia associated with MRI suites, potential radiation risks from CT or NP-59 and the relative costs of the different tests, among other factors, may be relevant to choice of strategy.

Many physicians, especially in the community hospital setting, may be using serial, conventional CT with size determinations to assess stability (adenomas) or growth (tumor) of

adrenal incidentalomas. However, the optimal number of subsequent studies and intervals between them are not well established (*2*). There is no documented growth rate predictive of malignancy and operating characteristics for these approaches have not been defined. Typically, additional (two to five) CT scans may be performed over 18–24 mo before malignancy is excluded.

We did not assess this strategy as part of the baseline analysis because of insufficient data from the published literature. However, assuming perfect diagnostic performance and an average of three CT scans per patient, the average cost per patient (as well as cost per diagnostic accuracy and cost per diagnostic utility) will be $2640, making serial CT testing the least cost-effective approach. Additionally, patients may be subjected to significant cumulative radiation, may be lost to follow-up and/or those with malignancies diagnosed by demonstrable tumor growth may suffer a delay in potentially curative therapy.

Within the limitations of our assumptions and based on available estimates of reimbursement costs and diagnostic test performance, we conclude that:

1. The NP-59 strategy is the most cost-effective diagnostic tool for evaluating adrenal incidentalomas over a wide range of malignancy rates; and
2. Comparative clinical studies to confirm this cost-effectiveness advantage are warranted.

ACKNOWLEDGMENTS

This work was presented in part at the 43rd Annual Meeting of the Society of Nuclear Medicine, June 3–5, 1996, Denver, CO.

APPENDIX 1: DIAGNOSTIC PERFORMANCE AND COST OF TWO-TEST STRATEGIES

Using conditional independence and a conjunctive positivity criterion, the sensitivity (Se) of a testing strategy involving two tests A and B is $Se_A \times SeB$, whereas the specificity (Sp) is $Sp_A + Sp_B - Sp_A \times Sp_B$. This means a high specificity (and a low sensitivity), which, according to Bayesian statistics, is appropriate and important when probability of disease is low as is the case for nonadenomas. The cost of a two-test strategy is equal to the cost of the first test and the fraction P(T+) of the cost of the second test where P(T+) is the probability of a positive test result.

APPENDIX 2: DIAGNOSTIC TESTS: INTERPRETATION CRITERIA

Modality	Abnormal or positive test result (nonadenoma)	Normal or negative test result (adenoma)
CT_0	Attenuation value >0 HU	Attenuation value ≤0 HU
CT_{10}	Attenuation value >10 HU	Attenuation value ≤10 HU
MRI	No visible or quantitative changes in signal intensity on opposed-phase or fat suppression images (compared to liver/spleen)	Visible or quantitative signal intensity loss on opposed-phase or fat-suppression images (compared to liver/spleen
NP-59	Discordant	Concordant

APPENDIX 3: DEFINITION OF TEST RESULTS

Characteristic	Definition
TP	Patients with nonadenomas who test positive
FP	Patients with adenoma whose test results are positive
TN	Patients with adenoma who test negative
FN	Patients with nonadenomas who test negative
Sensitivity [TP/(TP + FN)]	The ability of a test to correctly identify nonadenomas
Specificity [TN/(TN + FP)]	The ability of a test to correctly classify masses as adenomas
Diagnostic accuracy [(TP + TN)/(TP + TN + FP + FN)]	The ability to correctly determine the true nature of an incidental adrenal mass.

APPENDIX 4: DIAGNOSTIC UTILITY

The concept of diagnostic utility (DU) (*41*) helps to select the most appropriate diagnostic test for a clinical problem from several tests with different sensitivity and specificity. The DU is the sum of the probability-weighted utilities of the four outcomes: TP, TN, FP and FN. The assigned utility values (U) range between −1 (worst possible outcome) to +1 (best possible outcome) with intermediate values as appropriate.

Using the simplest case where U(TP) = U(TN) = +1 and U(FP) = U(FN) = −1, DU = P(TP) +P(TN) − P(FP) − P(FN). If Pd is the probability of disease, Se is the sensitivity of test and Sp is specificity of test, then P(TP)=Pd Se; P(TN) = (1 − Pd)Sp; P(FP) = (1 − Pd)(1 − Sp); P(FN) = Pd(1 − Se) and DU = 2Pd(Se − Sp) + 2Sp − 1.

APPENDIX 5: GLOSSARY OF TERMS*

Cost-Effectiveness Analysis (CEA). An analytic tool in which the costs and effects of a program and at least one alternative are calculated and presented in a ratio of incremental effect. Effects are health outcomes such as cases of a disease diagnosed, years of life gained, etc., rather than monetary measures.

Decision Analysis. An explicit quantitative, systematic approach to decision making under conditions of uncertainty in which probabilities of each possible event, along with the consequences of those events, are stated explicitly.

Effectiveness. The extent to which medical interventions achieve the desired health outcomes in the real world.

Incremental Cost. The cost of one alternative less the cost of another.

Perspective. The viewpoint from which a cost-effectiveness analysis is performed such as that of a patient, the third-party payer, hospital or society.

Sensitivity. The probability of a positive test result in patients who have the disease of interest.

Sensitivity Analysis. Mathematical calculations that isolate factors involved in a decision analysis or economic analysis to indicate the degree of influence each factor has on the outcome of the entire analysis. These analyses measure the uncertainty of the probability estimates.

Threshold Analysis. A type of analysis in which the analyst varies the parameter over a range to determine the values of the parameter that would lead to major changes in conclusions.

*Source: Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-effectiveness in health and medicine*. New York: Oxford University Press; 1996.

Utility. A concept in decision analysis referring to the preference for or desirability of a particular outcome. For example, in our analysis, TP and TN test results are assigned a utility of +1 and FP and FN a utility of −1.

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Radioiodine Treatment Outcomes in Thyroid Glands Previously Irradiated for Graves' Hyperthyroidism

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Persistent or recurrent Graves' hyperthyroidism after an initial treatment dose of radioactive iodine (RAI) is not uncommon and usually necessitates additional administrations. The radiation sensitivity of the previously irradiated thyroid gland is unknown but is of importance in selecting the retreatment dose. **Methods:** A retrospective analysis of patients receiving RAI for Graves' hyperthyroidism was undertaken. A first treatment dose was given to 1076 patients, and 168 of these patients subsequently required a second dose for persistent or recurrent hyperthyroidism (interval between RAI treatments, 8.5 ± 17.1 mo). **Results:** Paired comparisons for retreated patients showed similar RAI doses (291 ± 95 MBq and 283 ± 129 MBq; p = ns) and treatment intensities (3.26 ± 1.87 MBq g^{-1} and 3.48 ± 1.88 MBq g^{-1}; p = ns) for first and second treatments. Hypothyroidism occurred significantly earlier and more frequently after the first RAI dose (p = 0.002), but there was no difference for persistent or recurrent hyperthyroid events (p = 0.14). Multivariate regression established that the RAI treatment number (first or second) was a significant independent determinant of hypothyroid (p = 0.008) and combined (p = 0.001) events, whereas RAI dose and dose intensity were not. **Conclusion:** We conclude that previous RAI treatment failure does not lessen the chance of successfully eradicating Graves' hyperthyroidism with additional RAI treatment. Furthermore, the previously irradiated thyroid gland may be less susceptible to early hypothyroidism than the RAI-naive thyroid gland.

Key Words: hyperthyroidism; Graves' disease; iodine-131

J Nucl Med 1998; 39:712–716

Received Jan. 27, 1997; revision accepted Jun. 12, 1997.

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