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Do additional imaging studies change operative management in patients undergoing adrenalectomy?

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Abstract

BACKGROUND—The purpose of this study is to determine the incidence of a secondary imaging modality (SIM) in the workup of adrenal masses and the usefulness of this additional imaging in changing surgical management.

METHODS—A retrospective analysis of our adrenalectomy database was performed on adult patients who underwent at least one imaging study prior to surgery. A multivariate logistic regression model was then constructed to identify patient factors that predisposed SIM.

RESULTS—From February 2001–August 2014, 264 cases met inclusion criteria, of which 98 (37%) were identified to have SIM. Patients with cancer ($p=0.001$), incidentaloma ($p=0.002$), and pheochromocytoma ($p<0.0001$) were more likely to undergo additional imaging. Magnetic resonance imaging (MRI) was the most commonly obtained SIM. In addition, 90/98 cases (92%) met indications for adrenalectomy with primary imaging study and biochemical screening alone. Of the remaining 8 cases, in only 4 instances (4%) did SIM modify surgical decision making.

CONCLUSION—The high incidence of unnecessary additional imaging performed in patients undergoing adrenalectomy is counter-productive to efforts towards cost-conscious, high quality healthcare. Patients with adrenal tumors would benefit from early surgical referral to allow the surgeon to help guide clinical decision-making and to avoid the use of excessive imaging.

Introduction

Adrenalectomy is increasingly being performed for benign and malignant indications.¹ Nationwide, annual volumes have increased from 3,241 in 1998 to 5,323 in 2006.² This is in part due to the widespread use of thoracic and abdominal imaging in addition to an aging population, as the incidence of adrenal adenomas increases with age. According to the American Association of Clinical Endocrinologists (AACE) and the American Association

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of Endocrine Surgeons (AAES) Medical Guidelines for the Management of Adrenal Incidentalomas, the incidence of adrenal incidentaloma, a lesion greater than 1cm in diameter found during a radiologic study for another purpose, has a prevalence of 8.7% in autopsy series.³ Recent prospective evaluation on the prevalence of an adrenal lesion found on computerized tomography (CT) is estimated to be 4.4%.⁴ Critical aspects in the workup of an adrenal mass include determining the functionality of the tumor, any radiologic characteristics of malignancy, and any history of previous malignancy. Adrenal resection, whether laparoscopic or open, is indicated for any mass that is found to be biochemically active. Other indications for adrenalectomy include Cushing's disease patients refractory to neurosurgery and medical treatments, suspicion for malignancy, isolated adrenal metastasis, and a mass ≥4cm as the risk of cancer increases with increasing tumor size. Additionally, growth of an adrenal mass of more than 0.5cm in 6 months is also an indication for resection.⁵

There is not one perfect diagnostic approach for all patients found to have an adrenal mass. However, a high degree of diagnostic confidence can be achieved with a combination of biochemical and radiographic studies. Hormonal screening is essential in the workup of adrenal masses. Biochemical evaluation not only identifies patients that have hormonal overproduction, but also identifies those patients that will need careful preoperative blockade or evaluation for glucocorticoid therapy postoperatively. Due to the wide range of available imaging techniques, many patients during the workup of their adrenal mass undergo a secondary imaging modality (SIM).

The aims of this study were to determine the incidence of a SIM in the workup of adrenal masses and if any patient factors could predict additional imaging workup being obtained. We also examined who was ordering these studies and the utility of this additional imaging in changing surgical management.

Methods

This was a retrospective analysis of a prospectively collected adrenal surgery database at the University of Wisconsin. We examined adult patients, age ≥18 years, who underwent at least one imaging study prior to adrenalectomy from February 2001 to August 2014. All available pre-operative radiology reports and clinic notes were reviewed for comments regarding the recommendation and/or the completion of additional imaging studies. The first imaging procedure obtained that identified the adrenal mass was considered the primary imaging test. Any additional imaging obtained after the first test for further evaluation of the adrenal mass was considered SIM. SIM included computerized tomography (CT), magnetic resonance imaging (MRI), fluorine 18 fluorodeoxyglucose (FDG) positron emission scan (PET) as well as PET/CT, nuclear medicine (NM) imaging such as metaiodobenzylguanidine (MIBG) or NP-59 scanning, and abdominal ultrasound (US). Invasive diagnostic procedures, such as adrenal venous sampling and tissue biopsy, were not included as a SIM in this study.

Statistical analysis

Patient's baseline demographics, and clinical characteristics were compared between SIM and no SIM groups using Pearson's Chi-squared test or Fisher's exact test for categorical variables, and Student's *t*-test was used for continuous variables. Based on the statistically significant result found on univariate analysis by indication for adrenalectomy, a subgroup analysis was performed. From significant univariate factors, a multivariate logistic regression model was constructed using the significant results from the univariate analysis. All statistical calculations were performed using SPSS (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.)

Results

Demographics and clinical characteristics

Of the 292 cases in our database, we excluded 26 patients who had incomplete records, and 2 pediatric patients (age < 18). This left a total of 264 patients in our analysis. There was a slight female predominance and the majority of the operations were performed laparoscopically, with a conversion rate of 1.7%. Over half of our patients had biochemically active tumors. For non-functional masses, aside from size and enlargement, the most common indication for adrenalectomy was isolated adrenal metastasis. In addition, suspicious features on imaging such as lipid poor lesions with high enhancement on CT or worrisome T2 weighted signaling on MRI prompted a recommendation of surgery. Table I includes a complete list of clinical characteristics and demographic information for our patient cohort grouped by use of SIM.

Primary imaging

The first imaging test to identify the adrenal pathology was considered primary imaging. Of the 98 patients in our series who underwent secondary imaging, CT comprised 87.7% (86/98) of primary imaging, followed by MRI in 11% (11/98), and FDG-PET in 1% (1/98). Dates of imaging studies were only available in 35% (34/98) of cases, with the majority of SIM identified through clinic notes. As such, details such as type of CT scan performed and exact time-interval between primary and secondary imaging studies were not available on all patients. Of the patients with this information available, 85.3% (29/34) underwent a contrast CT scan, 5.9% (2/34) had a non-contrast CT colonography, and 8.8% (3/34) had a contrast MRI as primary imaging. The mean time in days between primary and secondary imaging was 25.0 ± 4.2 days; in those with suspicion or previous history of malignancy, the mean was reduced to 15.6 ± 4.5 days.

Incidence of SIM

98 (37.1%) cases were identified to have SIM. (See Figure 1). Analysis of these 98 patients revealed that MRI was the most commonly obtained SIM, used in 52 (53%) cases. This was followed by PET in 28 (29%), NM in 9 (9%), CT in 2 (2%), and US in 1 (1%) case. The remaining 6 cases (6%) underwent a combination of two of these additional imaging tests. 4 (4%) cases underwent MRI + PET, and 2 (2%) with NM + PET. PET included both FDG-

PET (13 cases) and PET/CT (21 cases). Interestingly, half of all available PET/CT reports specifically comment on the non-diagnostic quality of the CT portion of the protocol.

A total of 29 patients underwent SIM with suspicion of cancer, defined as either primary adrenal malignancy, or isolated adrenal metastasis from another primary. Lung cancer (48.3%) was the most common suspected etiology of isolated adrenal metastasis, followed by melanoma and colon cancer at 10.3% each. Final pathology revealed metastatic disease in 20 (69%) patients, 5 (17.2%) adenomas, and 4 (13.8%) pheochromocytomas. All patients, except one with a suspected unilateral adrenal cortical carcinoma, underwent PET imaging to ensure lack of widespread disease prior to adrenalectomy. As PET is commonly used to stage cancer patients, we conducted a subgroup analysis of SIM distribution on the 69 patients without malignant lesions. Again, MRI was the most frequently obtained SIM used in 50 (72.5%) cases. This was followed by NM in 9 (13.0%), PET in 7 (10.1%), CT in 2 (2.9%) and US in 1 (1.5%). Among the 69 patients in this subgroup, radiology reports were available for review in 43 (62%) cases. Of these, 24/43 (56%) of the reports either directly recommended, or suggested that additional imaging could be obtained to better characterize the adrenal findings.

Factors contributing to SIM

Univariate analysis was conducted to determine significant differences between SIM and no SIM groups. As CT was the predominant primary imaging modality, we did not include this variable in our predictive model. There was a statistically significant difference among the indications for adrenalectomy with pheochromocytoma, aldosteronoma, and cancer being the most different and clinically meaningful, thus warranting further analysis (Table II). From the significant factors found on univariate analysis, a multiple variable logistic regression was constructed to determine patient factors associated with the use of SIM. The presence of symptoms adjusted in our multiple regression model did not reveal an increased risk of undergoing SIM ($p=0.726$, OR 0.872, [0.41–7.87]). Patients with incidentally discovered adrenal findings ($p=0.002$, OR 3.373 [1.57–7.26]) were more likely to undergo a secondary imaging study. Additionally, those with cancer ($p=0.001$, OR 4.104 [1.81–9.28]), and pheochromocytoma ($p<0.001$, OR 5.190 [2.18–12.35]) were also more likely to have another imaging study performed. Aldosteronoma was found to increase the risk of undergoing SIM (OR 1.585 [0.63–4.0]), however this was not significant ($p=0.329$). Table III illustrates our final multiple regression model.

Ordering of SIM

Of the 98 cases where SIM were performed, 94 cases (96%) were ordered by non-surgeons. As SIM is often obtained prior to surgical referral, incompleteness of original reports in the electronic medical record made it difficult to discern whether SIM was based on clinical concern or radiology recommendation. However, in the four cases where imaging was requested by the surgeon, all were based on clinical suspicion for localization or concern of possible malignancy. The first case involved ordering a dedicated adrenal CT with IV contrast for a large incidentaloma found on non-contrast CT colonography due to concern for malignant features. The second case involved an MIBG scan to rule out metastatic pheochromocytoma. The third involved a patient with a biochemical profile suggestive of

hyperaldosteronism and bilateral adrenal findings who was unable to obtain nuclear medicine scanning, and instead underwent an MRI. And finally, the last case of surgeon initiated secondary imaging involved the use of an MIBG to localize a pheochromocytoma not visualized on CT scan ordered by the patient's internist. The referral source for these patients was not always clear, as patients commonly see several physicians prior to surgical consultation. We therefore did not specifically examine referring physician specialty as a factor.

Impact of SIM on operative management

Invasive diagnostic procedures were not considered SIM in this study. Of the 264 included cases in our analysis, 23 (8.7%) underwent adrenal venous sampling and 10 cases (3.8%) were recommended to undergo FNA analysis. Of the 98 patients who underwent SIM, 90 cases (92%) met indications for adrenalectomy with their initial imaging study and biochemical screening alone. Of the remaining 8 cases, 4 (4%) did not extract any additional benefit from more imaging. Three of these four cases were performed for subclinical Cushing's disease, and the fourth case involved bilateral adrenal nodularity which necessitated invasive venous sampling. This leaves only 4(4%) instances in which SIM modified surgical decision-making. Three cases involved patients with bilateral adrenal masses in which an MIBG was able to lateralize the tumor. The final case also employed MIBG to find a small pheochromocytoma not seen on CT (Figure 2). While MRI was the most commonly ordered SIM amongst adrenalectomy patients, in no cases did the addition of MRI change the management plan.

Discussion

It is important to accurately characterize adrenal masses on imaging studies. Due to the heterogeneous appearance of these lesions, several imaging modalities including CT, MRI, and PET/CT all have reported benefits. A recent review from the American Journal of Radiology discusses the particular advantages of each of these different imaging studies.⁶ Different phases of CT and washout are useful in discriminating between benign and malignant lesions, while PET has the advantage of determining metastatic spread. A meta-analysis has also shown FDG PET and PET/CT to be both highly sensitive and specific in distinguishing between benign and malignant adrenal lesions.⁷ MRI, the most popular secondary imaging study, better identifies tissue characteristics of water and fat. Newer imaging methods such as adrenal spectroscopy are also being developed and studied in order to better characterize adrenal lesions.⁶ However, the fact that so many imaging modalities each with different benefits and pitfalls speak to the heterogeneity of adrenal lesions.

Algorithms to characterize adrenal lesions on imaging are complex and involve knowledge of patient history, which is not always known or included when the scan is being reviewed.⁸ In addition, there are multiple points in the algorithm where the lesion is indeterminate, and further testing is the next diagnostic step. While additional imaging studies are often recommended, fine needle aspiration (FNA) or biopsy are also sometimes recommended in radiology reports during the workup of adrenal masses. Recent studies however have demonstrated that the use of FNA in incidentally found adrenal lesions has limited utility, is

potentially harmful, and should be avoided.⁹ The most recent guidelines put forth by the AACE/AAES on the workup of adrenal incidentaloma do not include biopsy in the diagnostic algorithm.³ Because there is currently no single imaging modality that has been identified to be accurate for all adrenal masses, a workup algorithm which may include additional imaging modalities and studies is currently employed. This however does not preclude the use of clinical context. Therefore, we would caution against reflexive ordering of additional imaging and procedures. With the appropriate patient history and biochemical screening, one primary imaging modality is usually sufficient to guide clinical decision making.

Determining functionality of adrenal masses is another cornerstone of diagnosis and workup. Approximately half of the patients in our cohort were found to have a biochemically active lesion, which by itself is an indication for surgery. Thorough evaluation of all adrenal masses should be performed, even in the setting of a positive history of previous malignancy^{10–11}. We have previously demonstrated that almost 25% of isolated adrenal lesions thought to be adrenal metastasis in origin are actually pheochromocytomas on biochemical screen, and an additional 15% are adenomas on final pathology.¹²

Though not categorized as a secondary imaging study in this analysis, invasive techniques are also utilized in the diagnosis of adrenal lesions. The role and utility of selective adrenal venous sampling (AVS) cannot be ignored in the diagnostic algorithm, especially for primary hyperaldosteronism. It is therefore not surprising that the diagnosis of an aldosteronoma did not portend a significantly increased risk of undergoing SIM since AVS was excluded. In our cohort of 264 cases, 65 (25%) of patients underwent adrenalectomy for hyperaldosteronism. Among these patients, 23 (35%) underwent adrenal venous sampling. Among the patients who underwent AVS, only one patient underwent SIM. The patient had bilateral adrenal thickening on both CT and MRI and with the aid of AVS was able to lateralized to tumor and undergo a unilateral laparoscopic adrenalectomy.

With the improvement in diagnostic capabilities in modern imaging modalities, adrenal masses are increasingly being found. Currently, much of the workup is being performed prior to surgical referral, usually by primary care or endocrinology. A major decision point is to determine if the mass warrants resection. The majority of the patients in our cohort were found to meet criteria for surgical intervention with functional screening and initial imaging study alone, which argues that earlier involvement of the surgeon in the work-up would be beneficial. The benefits of a multi-disciplinary approach also include a smoother transition to surgery if and when resection is deemed appropriate.

While radiologic imaging is an important tool in the diagnosis and treatment of adrenal lesions, we have demonstrated that additional imaging is often ultimately not useful in the final clinical decision-making. SIM acquisition also has negative implications for patients. Varying imaging modalities, MRI in particular, can be time consuming and uncomfortable for patients inducing symptoms of anxiety, and claustrophobia. While difficult to quantify, these variables are certainly significant to patients and their quality of life. Other radiologic studies such as FDG PET/CT, CT and NM scans expose patients to additional doses of

radiation.¹³ Even at low doses, excessive radiation confers a small but increased risk of developing cancer.¹⁴ As with all clinical decisions, the probability of benefit must be weighed against the risks and imposition on the patient prior to recommendation.

The rising cost of healthcare is an important factor in today's practice of medicine. Efforts towards quality care while maintaining cost-conscious spending has been the goal of many studies and investigations across all areas of medicine and surgery. According to the University of Wisconsin (UW) Health billing department, the total facility and physician fees for different imaging modalities are listed in Table IV. While these numbers are not adjusted for individual patient factors, and likely do not reflect the actual amount paid for each of these imaging studies, they do highlight the fiscal ramifications of ordering these studies in the workup of adrenal masses. Certainly, this is further contributing to the rising cost of healthcare.

Our study is limited by the retrospective nature of chart-review. Only those clinic notes and radiology reports available in our electronic medical record were able to be reviewed. Thus, the incidence of secondary imaging could actually be much higher than reported. In addition, by only examining adrenalectomy patients, we are overlooking those with adrenal findings who undergo additional imaging and ultimately do not undergo surgery. For example, patients with clearly benign findings on imaging, or those found to have widely metastatic disease on PET scan. This not only underrepresents the incidence of SIM, but also underestimates its impact on cost. As with many tertiary referral centers with a large geographic referral base, patients are referred from many different healthcare systems and providers, each with their own medical record system. Implementation of our findings must start by changing current referral practices as the majority of patients with newly diagnosed adrenal lesions are first seen by a non-surgeon physician. Despite these limitations however, we have quantified the incidence of over-use of secondary imaging studies in the workup of adrenal lesions.

In conclusion, we have demonstrated a high incidence of excessive imaging used during the diagnosis and workup of adrenal masses prior to surgical referral. With improvements in current diagnostic imaging technology, adrenal lesions will continue to be increasingly found. In the current environment of cost-effective health care, this trend cannot be ignored. Early multi-disciplinary care will allow increased surgeon involvement in the diagnostic algorithm and minimize the use of unnecessary imaging studies.

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Figure 1.

The distribution of secondary imaging modalities used during the workup of adrenal masses, number of patients who underwent each radiographic test is indicated above each bar. (A) Secondary imaging modality distribution among patients for all indications. (B) Secondary imaging modality distribution among patients with non-malignant diagnosis. MRI = Magnetic Resonance Imaging, PET = Positron Emission Tomography, NM = Nuclear Medicine testing, CT= Computed Tomography, US = ultrasound

Figure 2.

Impact of secondary imaging of adrenal lesions on operative planning for adrenalectomy

Results presented *n* (%)

SIM= secondary imaging study, OR = operating room

Table I

Adrenalectomy patient demographics and clinical characteristics

	SIM (n=98)	No SIM (n=166)	p-value
Gender:			
Male/Female	36(37%)/62(63%)	64(39%)/102 (61%)	.794
Age, y	56 [27–64]	54 [43–63]	.629
BMI, kg/m ²	30.3 (28.4–32.3)	32.7 (31.2–34.1)	.056
Laparoscopic/Open	84(86%)/14(14%)	151(91%)/15(9%)	0.223
Incidental:			
Yes	65 (66%)	75 (45%)	.001
No	33(34%)	91 (55%)	
Functional:			
Yes	50 (51%)	92 (55%)	.524
No	48 (49%)	74 (45%)	
Symptoms:			
Yes:			.015
HTN	44 (45%)	87 (52%)	
Pain	6 (6%)	21 (13%)	
Other *	7 (7%)	13 (8%)	
No (asymptomatic)	41 (42%)	45 (27%)	
Mass >4cm			
Yes	39 (40%)	74 (44.5%)	.520
No	59 (60%)	92 (55.5%)	
Indications for surgery:			
Pheochromocytoma	30 (31%)	31 (19%)	<0.001
Aldosteronoma	14 (14%)	51 (31%)	
Cushing's	4 (4%)	12 (7%)	
Size >4cm or enlarging [†]	22(22%)	53 (32%)	
Cancer [‡]	25 (26%)	15 (9%)	
Other [§]	3 (3%)	4 (2%)	

Univariate comparisons for categorical variables using Pearson's Chi-square test or Fisher's exact test, comparisons for continuous variables made with Student's t-test, as appropriate.

Results presented as median [25th; 75th percentile], mean (95% CI), or *n* (%). SIM = Secondary imaging modality; SE = Standard error; BMI = Body mass index

* Other includes hirsutism, weight gain, headaches, palpitations or sweating, fatigue, adrenal crisis, and bleeding

[†] Enlarging refers to any adrenal mass with growth of greater than 0.5cm within a 6 month interval on serial imaging

[‡]Cancer refers to all patients with suspicion or primary adrenal malignancy or known prior medical history of non-adrenal malignancy

[§]Other includes symptoms of pain, and bleeding

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Table II

Subgroup univariate analysis of adrenalectomy patients by indication

Variable	SIM (n=98)	No SIM (n=166)	p-value
Pheochromocytoma	30 (31%)	31 (18.5%)	.034
Aldosteronoma	14 (14%)	51 (31%)	.003
Cancer	25 (25.5%)	15 (9%)	.001
Reference *	29 (29.5%)	69 (41.5%)	.065

Results presented n (%)

* Reference refers to remaining indications for adrenalectomy: Cushing's, size ≥4cm, enlarging, and symptoms of pain and bleeding

Table III

Factors associated with undergoing a secondary imaging modality during workup of adrenal mass in a reduced multivariate model.

	OR	95% CI	p
Symptoms	0.872	0.41–7.87	.726
Incidental	3.373	1.57–7.26	.002
Cancer	4.104	1.81–9.28	.001
Pheochromocytoma	5.190	2.18–12.35	<0.001
Aldosteronoma	1.585	0.63–4.0	.329

Table IV

Combined facility and physician fee associated with varying imaging modalities at University of Wisconsin Hospital, values for fiscal year July 1, 2014 to June 30, 2015¹⁵

Imaging Modality	Cost in US dollars
MRI abdomen with and without contrast	4,209
FDG-PET	6,355
PET/CT	6,904
CT abdomen with and without contrast	6,646
MIBG scan	2,503
Abdominal US	1,267

MRI = Magnetic Resonance Imaging, FDG = Fluorodeoxyglucose, PET = Positron Emission Tomography, CT= Computed tomography, MIBG = metaiodobenzylguanidine, US = ultrasound