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ORIGINAL PAPER

ACCURACY OF ADRENAL IMAGING MODALITIES IN PREDICTING HISTOLOGICAL TUMOR DIMENSION FOLLOWING ADRENALECTOMY

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Abstract

Background. Computed tomography (CT) and magnetic resonance imaging (MRI) are the imaging modalities used for the identification of an adrenal neoplasm. Traditionally, the adrenal gland radiological size (RS) is underestimated by any preoperative imaging compared to the actual histological size (HS).
The objective of the study was to investigate whether recent and more sophisticated imaging techniques can more accurately predict adrenal tumors' size.
Material and methods. We retrospectively analyzed 129 patients (86 females, 67%) with mean age 54.2 years (median: 56; range: 6 – 82), who underwent adrenalectomy (1 bilateral adrenalectomy) during the period 11/2016 to 2/2019. The 130 adrenal tumors

Résumé

Précision des modalités d'imagerie de la glande surrénale dans la prédiction de la dimension tumorale histologique suite à la surrénalectomie

Introduction. La tomodensitométrie (TDM) et l'imagerie par résonance magnétique (IRM) sont les outils de diagnostic utilisés pour l'identification d'un néoplasme surrénalien. Traditionnellement, la taille radiologique (RS) de la glande surrénale est considérée comme sous-estimée par toute imagerie préopératoire par rapport à la taille histologique réelle (HS).
L'objectif de l'étude était de déterminer si des techniques d'imagerie récentes et plus sophistiquées

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were divided according to their RS in: A, ≤ 3 cm, B, > 3 cm and ≤ 6 cm, C, > 6 cm. Agreement between RS and HS was evaluated by the intraclass correlation coefficient (ICC).

Results. In the total population, RS underestimated HS by 34% using CT or either imaging with good agreement; 28% using MRI with fair agreement. Only for RS 3 – 6cm CT, MRI or either method underestimated HS by 35% with fair agreement; for RS > 6 cm underestimation was 15% using CT, or 6% using either imaging with fair agreement.

Conclusions. In defiance of the technological progress in imaging modalities, the present study confirmed previous findings that adrenal imaging by CT or MRI, cannot predict accurately the real size of adrenal tumors. In case of an adrenal incidentaloma this disagreement has a major impact not only on achieving an effective decision- making process favoring a conservative treatment or a surgical excision, but also on deciding when surgery is the option of the appropriate approach by open or laparoscopic adrenalectomy.

Keywords: adrenal tumor, computed tomography, magnetic resonance imaging, adrenalectomy.

pouvaient prédire avec plus de précision la taille de la tumeur.

Matériel et méthodes. Nous avons analysé rétrospectivement 129 patients (86 +femmes, 67%) d'âge moyen 54,2 ans (médiane: 56; extrêmes: 6 – 82), qui ont subi une surrénalectomie (1 surrénalectomie bilatérale) du 11/2016 au 2/2019. Les 130 tumeurs surrénales ont été divisées selon leur RS en: A, ≤ 3 cm, B,> 3 cm et ≤ 6 cm, C,> 6 cm. L'accord entre RS et HS a été évalué par le coefficient de corrélation intra-classe (ICC).

Résultats. Dans la population totale, RS a sous-estimé HS de 34% en utilisant la TDM ou l'imagerie avec un bon accord; 28% utilisent l'IRM avec un accord équitable. Uniquement pour RS 3 – 6cm CT, l'IRM ou l'une ou l'autre méthode sous-estimée HS de 35% avec un accord équitable; pour RS> 6 cm, la sous-estimation était de 15% en utilisant la tomodensitométrie, ou de 6% en utilisant l'une ou l'autre des images avec un accord juste.

Conclusions. Malgré les progrès technologiques dans les modalités d'imagerie, la présente étude a confirmé les résultats précédents que l'imagerie surrénale par CT ou IRM, ne peut pas prédire avec exactitude la taille réelle des tumeurs surrénales. Dans le cas d'un incidentalome surrénalien, ce désaccord a un impact majeur non seulement pour la réalisation d'un processus décisionnel efficace favorisant un traitement conservateur ou une excision chirurgicale, mais aussi lorsque la chirurgie est l'option décidant l'approche appropriée par une surrénalectomie ouverte ou laparoscopique.

Mots-clés: tumeur surrénale, tomodensitométrie, imagerie par résonance magnétique, surrénalectomie.

Introduction

Computed tomography (CT) is the initial method for the identification of an adrenal neoplasm according to the Clinical Practice Guideline for the management of adrenal incidentalomas[1]. When CT imaging is not diagnostic, magnetic resonance imaging (MRI) is the next alternative, with similar accuracy in discriminating between benign and malignant tumors [2,3]. However, clinically the adrenal gland size is considered to be underestimated by the preoperative imaging [radiological size (RS)] compared to the actual histological size (HS)[4-9]. Adrenal tumor size is a major criterion not only for the follow-up planning of an adrenal mass but also for performing open or laparoscopic surgical excision[1].

The objective of the study was to investigate whether recent and more sophisticated imaging techniques, can more accurately predict adrenal tumors' size.

Materials and methods

We retrospectively analyzed patients who underwent adrenalectomy in a referral center (Third Department of Surgery, Athens General Hospital „G. Gennimatas", Greece) during the period 11/2016 to 2/2019. The current study was approved by local institutional ethics committee. A complete pathology and imaging report (CT or MRI) were recorded for all patients to be included in the analysis. Cases of biopsy or partial adrenalectomy were excluded from the analysis. Overall, 129 patients (one had bilateral adrenalectomy) were investigated and 130 histological specimens along with their respective preoperative imaging study were analyzed. The major dimension

of the HS (median value) was compared with the major dimension of the RS (median value). All scans were performed within 12 weeks from the surgery. The adrenal tumors were divided according to their RS in three groups, A: ≤ 3 cm, B: > 3 cm and ≤ 6 cm, C: > 6 cm.

Statistical analysis

The continuous variables were expressed as mean±1-standard deviation (SD). Linear correlations between different sizes were assessed by Spearman correlation coefficient. Multiple linear regression analysis was performed for the prediction of HS measurements by imaging estimates adjusted for demographic parameters. Agreement between different tumor size estimates was evaluated by the intraclass correlation coefficient (ICC) with values < 0.40 for poor agreement, 0.40 – 0.59 for fair, 0.60 – 0.74 for good, 0.75 – 1.00 for excellent agreement[10]. Mean differences and SD of differences (SDD) were calculated. The limits of agreement between different size measurements were defined as: Lower limit = mean difference – 1.96 × SDD and upper limit = mean difference + 1.96 × SDD. Bland-Altman analysis was also performed. P-values of 0.05 were considered to represent statistical significance and all tests were two-sided. Statistical analysis was performed by IBM-SPSS Statistics for Windows, Version 23.0(IBM Corp, Armonk, NY, USA).

Results

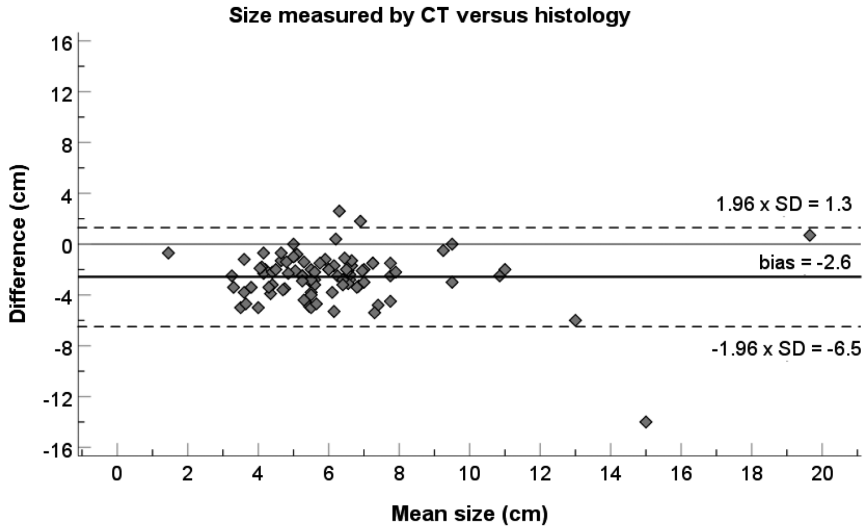
We studied 129 patients (86 females, 67%) with mean age 54.2 years (median: 56; range: 16-82), who were submitted to adrenalectomy. The HS had mean and median values 7.31 and 7 cm (range: 2 – 22), respectively; the RS had mean and median values 4.96 and 4.50 cm (range: 1 – 20), respectively. In the subgroup ≤3 cm, 26 patients (18 females, 69%) had HS mean and median diameter 5.8 and 6 cm (range: 2 – 8) and RS mean and median diameter 2.23 and 2.4 cm (range: 1 – 3); in the subgroup > 3cm and ≤ 6cm, 80 patients (56 females, 70%) had HS mean and

Table 1. Agreement and correlation of radiological size (RS) with histological size, following computed tomography (CT), magnetic resonance imaging (MRI) and CT or/and MRI in the total population and within subgroups with imaging size (a) < 3, (b) 3-6 and (c) > 6 cm.

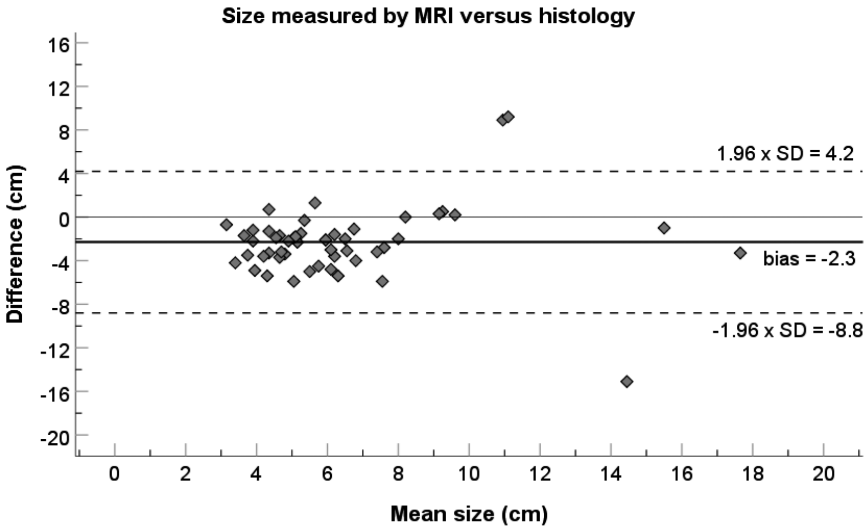
Statistic parameter	CT *vs* Histology	MRI *vs* Histology	CT or/and MRI *vs* Histology
The total population studied			
N	89	52	130
Mean difference (cm; %)	-2.6; -34%	-2.3; -28%	-2.3; -32%
SD of differences (cm)	2.0	3.3	2.4
Limits of agreement (cm)	-6.5 – 1.3	-8.8 – 4.2	-7.0 – 2.4
Spearman r	0.627*	0.533*	0.586*
ICC	0.728*	0.523*	0.621*
Subgroup with imaging size <3 cm			
N	17	13	26
Mean difference (cm; %)	-3.5; 61%	-3.6; 59%	-3.6; 61%
SD of differences (cm)	1.5	1.3	1.4
Limits of agreement (cm)	-6.4 – 0.6	-6.1 – 1.0	-6.3 – 0.9
Spearman r	0.342	0.013	0.122
ICC	0.367	-0.104	0.140
Subgroup with imaging size 3-6 cm			
N	56	28	81
Mean difference (cm; %)	-2.4; 35%	-2.5; 35%	-2.5; 35%
SD of differences (cm)	1.2	1.5	1.3
Limits of agreement (cm)	-4.7 – 0.05	-5.4 – 0.4	-5.0 – 0.05
Spearman r	0.463 *	0.346	0.424 *
ICC	0.567 *	0.494 *	0.527 *
Subgroup with imaging size >6 cm			
N	16	11	23
Mean difference (cm; %)	-2.0; 15%	-0.2; 5%	-0.6; 6%
SD of differences (cm)	3.8	6.4	4.5
Limits of agreement (cm)	-9.4 – 5.4	-12.7 – 12.3	-9.4 – 8.2
Spearman r	0.763 *	0.115	0.462 *
ICC	0.566 *	0.124	0.534 *

* p<0.05

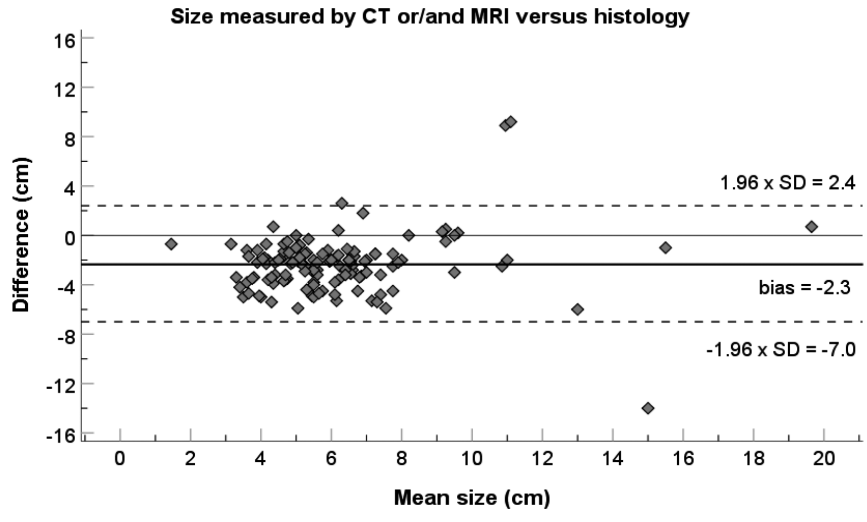
I



II



III



* $p<0.05$

Figure 1. Bland-Altman plot of differences in tumor size measurements by (I) computed tomography (CT), (2) magnetic resonance imaging (MRI) and (3) CT or/and MRI, versus histology, according to mean tumor size. Dashed lines indicate limits of agreement (mean difference ± 1.96 × SD of differences), while the bold horizontal line indicates the bias (mean difference).

Table 2. A summary of the more recent published data regarding the rates of histological size (HS) underestimation of adrenal tumors by radiological size (RS) compared to the (HS), following computed tomography (CT), magnetic resonance imaging (MRI) and CT or/and MRI in the total population and within subgroups with imaging size (a) < 3, (b) 3-6 and (c) > 6 cm.

		RS (cm)	Underestimation HS versus RS (%)	
	Patients (N)		by MRI	by CT
Linos, 1997	28	≤3		36*
	26	3-5		16*
	10	5-7		24*
	12	>7		15*
	76	all sizes		22*
Lau, 1999	65	≤3		13*
	17	3-6		23*
	82	≤6		17
	10	>6		12
	92	all sizes		16*
Kouriefs, 2001	9	≤3	7	
	12	3-6	19*	
	13	>6	19*	
	15	≤3		9≠
	18	3-6		23*
	14	>6		20*
	47	all sizes		18*
	27	all sizes	20.5*	17*
Present study, 2019	17	≤3		61
	56	3-6		35*
	16	>6		15*
	13	≤3	59	
	28	3-6	35*	
	11	>6	5	
	26	≤3	61	
	81	3-6	35*	
	23	>6	6*	
	89	all sizes		34*
	52	all sizes	28*	
	130	all sizes	32*	

≠ overestimation; * $p < 0.05$

median diameter 6.96 and 7 cm (range: 4-11) and RS mean and median diameter 4.5 and 4.5 cm (range: 3 – 7) respectively; in the subgroup >6cm, 23 patients (12 females, 52%) had HS mean and median diameter 10.24 and 9 cm (range: 5-22) and RS mean and median diameter 9.65 and 9 cm (range: 6 – 20) respectively.

For small sizes (≤3 cm) there is almost no agreement between imaging and histology measurements, as indicated by the Spearman (r) and ICC coefficients. Size estimation by CT exhibited the greatest association and agreement (higher r and ICC values) with HS within the second subgroup (imaging sizes between 3 – 6 cm) compared to the large sized group (> 6cm). At the large sized group (> 6 cm) the limits of agreement between imaging and histology were very wide and the SDD was quite increased, indicating a weak precision in size estimation by imaging modalities compared to HS measurements.

In order to improve the performance characteristics of imaging, the following equations were determined by linear regression analysis for the correction of the underestimation of HS by radiological estimations.

Only CT: $HS = 0.808 \times CT_{size} + 3.497$; [$R^2 = 0.535$, $p < 0.001$]

Only MRI: $HS = 0.49 \times MRI_{size} + 4.976$; [$R^2 = 0.274$, $p < 0.001$]

CT or MRI: $HS = 0.569 \times (MRI_{size}$ or $CT_{size}) + 4.487$; [$R^2 = 0.389$, $p < 0.001$]

Size measurement by CT was better correlated with HS. Age and sex were also examined as potential

determinants of HS with the latter exhibiting a significant correlation (p=0.004). When sex entered the multivariate model R^2 was improved:

HS = 0.547 × (MRI_{size} or CT_{size}) – 0.846 × sex [0: male, 1: female] + 5.164; [R^2 = 0.412, p < 0.001]

For example, for a female patient with RS 5.8 cm measured by CT, HS estimated is 7.49 cm whereas the real HS was found to be 7.5 cm.

In the total population, RS underestimated HS by 34% using CT with good agreement (ICC 0.728), 28% using MRI with fair agreement (ICC 0.523), and 32% using either imaging study with good agreement (ICC 0.621) (Table 1, Figure 1). Specifically for RS<3cm, CT underestimated HS by 61%, 59% using MRI and 61% using either imaging but without statistical agreement (ICC 0.367, –0.104, 0.140, respectively); for RS 3-6 cm CT, MRI or either method underestimated HS by 35% with fair agreement (ICC 0.567, 0.494, 0.527, respectively); for RS > 6cm RS underestimated HS by 15% using CT, 5% using MRI, and 6% using either imaging with fair agreement for only CT or either method (ICC 0.566 and 0.534, respectively) and poor for MRI (ICC 0.124) (Table 1). A positive correlation was seen in the whole cohort studied between RS and HS (Table 1, Figure 1).

Discussion

Adrenal size has a central role in the decision to follow-up only or to excise an adrenal neoplasm[11], and in case of surgery to the relevant approach and extent of surgery[12,13]. Traditionally, the surgeons are expecting to find a larger adrenal gland during the operation than the size estimated by the imaging studies[5-9,14]. This view is based on studies performed in early 2000's that documented discordance between imaging with either CT or MRI and the actual size of an adrenal neoplasm[5-9]. This disagreement has been attributed to the oval shape that most adrenal tumors have, being difficult to be measured by a cross-sectional imaging[6,9] or to the fact that they grow in the craniocaudal or oblique direction not easily assessed by CT measuring transverse diameter[7,8].

Herein, we demonstrated that despite the technological advances, both CT and MRI underestimate the actual HS of the adrenal tumors as previously published[5-7,9], with CT exhibiting a better agreement compared to MRI. We have also documented that the inclusion of the gender in the equation to correct RS improved further this agreement.

A summary of the results from the previous studies is exposed in Table 2. In our series, we have found higher rates of underestimation in tumors <6cm but lower in tumors > 6cm. Moreover, RS measurements by CT were superior to MRI regarding their agreement with HS. We have also confirmed the linear relationship of RS and HS implying the need of an equation to correct preoperatively the RS with a diameter closer to the real adrenal size as previously documented[6]. However, only CT showed a significant correlation between HS and RS in all subgroups assessed (Table 1). The use of the equation to estimate HS had the maximum R-square, and consequently more precision, when only CT was used. Moreover, we found that the use of the gender in the equation improved the agreement of RS and HS.

In the era of personalized medicine, where the size of a tumor of neuroendocrine origin has been several times used as a criterion to proceed with an additional oncological surgery[15-18], it is important to know the accordance or the discordance of the techniques used to identify the real size of a tumor. On the other hand, qualitive data may have an equally important role on decision making since may differentiate malignant from benign lesions[19,20].

The major limitation of the study is the small number of cases, despite that it represents the larger number published because of the rarity of the specific operation. However, we have used only the recent data collected in a short period of time in order to include only more recent imaging technologies. The use of multinational registries may help to shed more light on the 'adrenal size' as a criterion for surgery or follow-up of an adrenal tumor.

In conclusion, the present study confirmed previous findings that adrenal imaging by CT or MRI cannot predict accurately the real size of adrenal tumors. However, the proposed correction of size estimated by CT along with the inclusion of the gender may provide the most accurate prediction of the actual size of the tumor. In essence, when physicians are facing an adrenal incidentaloma and in order to achieve an effective decision-making process to proceed with a surgical excision or to decide adrenalectomy by an open or laparoscopic approach, clinicians have to take into consideration that the size of an adrenal tumor is underestimated by current imaging techniques.

Authors' contributions

Conceptualization, K.I.A, G.N.Z.; methodology, K.I.A, G.N.Z..; software, T.G.P; validation, T.G.P; formal analysis, K.I.A, T.G.P; investigation, I.A, S.K., G.N., K.P.; resources, K.I.A.; data curation, K.I.A, E.K., T.G.P.; writing–original draft preparation, K.I.A, T.G.P.; writing–review and editing, G.C.S., D.K., C.A., G.A.K, G.N.Z.; visualization, T.G.P.; supervision, G.C.S., G.A.K, G.N.Z.;.; project administration, G.N.Z.. All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article"

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law."

„All the patients signed an informed consent. The study was approved by the Ethics Committee of the Athens General Hospital „G. Gennimatas", Greece"

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