**ORIGINAL PAPER**

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

Krystallenia I. ALEXANDRAKI1, Ioanna ANTONOPOULOU1, Theodoros G. PAPAIOANNOU2, Styllanos KYKALOS3, Georgios C. SOTIROPOULOS3, Denise KOLOMODI1, George NTOKOS4, Konstantinos PATEAS4, Chrysanthi AGGELI4, Gregory A. KALTSAS5, Georgios N. ZOGRAFOS4

1 Endocrine Unit, First Department of Propedeutic Medicine, Laiko University Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece
2 First Department of Cardiology, Medical School, National and Kapodistrian University of Athens, Athens, Greece
3 Second Department of Propaedeutic Surgery, National and Kapodistrian University of Athens, Medical School, Athens, Greece
4 Third Department of Surgery, Athens General Hospital „G. Gennimatas”, Athens, Greece

Received 29 Mar 2020, Accepted 16 May 2020
https://doi.org/10.31688/ABMU.2020.55.3.01

**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 surréna!e 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
were divided according to their RS in: A, ≤ 3 cm, B, > 3 cm and 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.

**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 incidentalomas⁴. When CT imaging is not diagnostic, magnetic resonance imaging (MRI) is the next alternative, with similar accuracy in discriminating between benign and malignant tumors ¹. 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)⁵. 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 excision⁶.

**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: \( \leq 3 \text{ cm} \), B: \( > 3 \text{ cm} \) and \( \leq 6 \text{ cm} \), C: \( > 6 \text{ cm} \).

**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. 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 \( \leq 3 \text{ cm} \), 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 \( > 3 \) cm and \( \leq 6 \text{ cm} \), 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*        | 0.532*         | 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           | 1.4             | 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           | 1.3             | 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             | 6.4                       |
| Limits of agreement (cm) | -9.4 – 5.4  | -12.7 – 12.3   | -14.6 – 8.2              |
| Spearman r          | 0.763 *       | 0.115           | 0.462 *                   |
| ICC                 | 0.566 *       | 0.124           | 0.534 *                   |

* p<0.05
* p<0.05

Figure 1. Bland-Altman plot of differences in tumor size measurements by (1) 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).
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 (> 6 cm). 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 × CT size + 3.497; [R² = 0.535, p < 0.001]
Only MRI: HS = 0.49 × MRI size + 4.976; [R² = 0.274, p < 0.001]
CT or MRI: HS = 0.569 × (MRI size or CT size ) + 4.487; [R² = 0.389, p < 0.001]

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

|           | Patients (N) | RS (cm) | Underestimation HS versus RS (%) |
|-----------|--------------|---------|----------------------------------|
|           |              | 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*                            |
| 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

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.
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 \times (MRI_{\text{size}} \text{ or } CT_{\text{size}}) - 0.846 \times \text{sex}$ [0: male, 1: female] + 5.164; \left[ R^2 = 0.412, p < 0.001 \right]

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\cite{11}, and in case of surgery to the relevant approach and extent of surgery\cite{12,13}. Traditionally, the surgeons are expecting to find a larger adrenal gland during the operation than the size estimated by the imaging studies\cite{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\cite{5-7,9}. This disagreement has been attributed to the oval shape that most adrenal tumors have, being difficult to be measured by a cross-sectional imaging\cite{8} or to the fact that they grow in the craniocaudal or oblique direction not easily assessed by CT measuring transverse diameter\cite{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\cite{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\cite{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\cite{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, qualitative data may have an equally important role on decision making since may differentiate malignant from benign lesions\cite{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”

“No funding for this study”

Acknowledgments:

None

REFERENCES

1. Fassnacht M, Arlt W, Bancos I, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. European Journal of Endocrinology 2016;175(2): G1-G34.
2. Datta J, Rose RE. Surgical management of adrenocortical carcinoma: an evidence-based approach. Surgical Oncology Clinics of North America 2016;25(1): 153-170.
3. Wale DJ, Wong KK, Viglanti BL, Rubello D, Gross MD. Contemporary imaging of incidentally discovered adrenal masses. Biomedicine & Pharmacotherapy 2017;87:256–262.
4. Belldegrun A, Hussain S, Selzter SE, Loughlin KR, Gittes RF, Richie JP. Incidentally discovered mass of the adrenal gland. Surgery, Gynecology and Obstetrics 1986;163(3): 203-208.
5. Cerfolio RJ, Jr Vaughan ED, Jr Brennan TG, Hirvella ER. Accuracy of computed tomography in predicting adrenal tumor size. Surgery, Gynecology and Obstetrics 1993;176(4): 307-309.
6. Linos DA, Stylopoulos N. How accurate is computed tomography in predicting the real size of adrenal tumors? A retrospective study. Archives of Surgery 1997;132(7): 740-743.
7. Lau H, Lo CY, Lam KY. Surgical implications of underestimation of adrenal tumor size by computed tomography. British Journal of Surgery 1999;86(3): 385-387.
8. Kouriefs C, Molbok K, Lericus A, Williams NJ, Carpenter R. Surgical implications of underestimation of adrenal tumor size by computed tomography. British Journal of Surgery 1999;86(12): 1589.
9. Kouriefs C, Molbok K, Choy C. Is MRI more accurate than CT in estimating the real size of adrenal tumours? European Journal of Surgical Oncology 2001;27(5): 487-490.
10. Cicchetti DV. Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. Psychological Assessment 1994;6:284-290.
11. Kaltsas G, Chrisoulioudou A, Piaditis G, Kassi E, Chrousos G. Current status and controversies in adrenal incidentalomas. Trends in Endocrinology and Metabolism 2012;23(12):602–609.
12. Menegaux F, Chèreau N, Peix JL, et al. Management of adrenal incidentaloma. Journal of Visceral Surgery 2014;151(5):355–364.
13. Brunaud L, Cormier L, Ayav A, et al. Does the size of pheochromocytoma influence the results of its laparoscopic excision? Annales de Chirurgie 2002;127(5):362–369.
14. Zografos GN, Pasyrinakis I, Kyrodimou E, Kassi E, Kaltsas G. Surgical treatment of potentially primary malignant adrenal tumors: an unresolved issue. Hormones (Athens) 2015;14:47–58.
15. Alexandraki KI, Grossman AB. Adrenal incidentalomas: ‘the rule of four’. Clinical Medicine (London, England) 2008;8:201-204.
16. Canellas R, Lo G, Bhowmik S, Ferrone C, Sahani D. Pancreatic neuroendocrine tumor: Correlations between MRI features, tumor biology, and clinical outcome after surgery. Journal of Magnetic Resonance Imaging 2018;47:425-432.
17. Grozinsky-Glasberg S, Alexandraki KI, Barak D, et al. Current size criteria for the management of neuroendocrine tumors of the appendix: are they valid? Clinical experience and review of the literature. Neumendocrinology. 2013;98:31–37.
18. Ye YL, Yuan XX, Chen MK, Dai YP, Qin ZK, Zheng FF. Management of adrenal incidentaloma: the role of adrenal-ectomy may be underestimated. BMC Surgery 2016;16(1):41.
19. Chatzellis E, Kaltsas G. Adrenal incidentalomas. In: Feingold KR, Anawalt B, Boyce A, et al., eds. Endotext. South Dartmouth (MA): MDText.com, Inc.; 2000.
20. Azoury SC, Nagarajan N, Young A, et al. Computed Tomography in the management of adrenal tumors: does size still matter? Journal of Computed Assisted Tomography 2017;41(4):628–632.