

# Diagnosis and Growth dynamics of Adrenal incidentalomas: a 6-month retrospective analysis

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## Introduction

Adrenal incidentalomas are adrenal masses discovered incidentally on imaging studies originally not performed for suspected adrenal disease.

## Aim

To characterise a cohort of adrenal incidentalomas found on CT imaging the adrenal region.

## Methods

This was a retrospective analysis, taking into account all the adrenal incidentalomas discovered on CT between July and December 2014 at Mater Dei Hospital. Only lesion greater than 1cm were included in the study. These were then classified according to their radiological features. Previous CT scans and any CT scans done after the study period were also reviewed to establish any change in size of the lesions.

## Results

A total of 9100 CT scans were reviewed and adrenal incidentalomas were identified in 296 patients. 216 incidentalomas could be adequately classified and included in the study; 80.1% were confirmed adenomas, 12.9% metastasis, 5.6% myelolipomas and 1.3% ganglioneuromas. 49.1% of patients with an adenoma were males as opposed to 71.4% in the metastasis group. Bilateral lesions were commoner in the metastasis group (9% in adenoma vs 18% in metastasis group). Longest median radiological diameter was 18mm (IQR 14.0-24.0) in the adenoma group and 26.0mm (IQR 16.0-36.0) in the metastasis group ( $P<0.001$ ). Median follow up in the adenoma group was longer in the adenoma group 20.9 months (IQR 4.5-39.0) vs 11.2 months (IQR 0-29.3) in the metastasis group ( $P<0.001$ ). Median change in size was also statistically significant: 0.0mm (IQR -1-0.8) in the adenoma as compared to 22.5mm (IQR 12.5-30) in the metastasis group ( $P<0.001$ ).

## Conclusion

This study continues to confirm that adrenal adenomas are the commonest adrenal lesion encountered in clinical practice and the majority, by far remain stable in size over time.

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## INTRODUCTION

Adrenal incidentalomas are adrenal masses detected on imaging studies, carried out for reasons other than suspected adrenal pathology. The widespread use of abdominal imaging in recent years has led to a steep increase in the discovery of such lesions. Although most of these lesions are benign and hormonally non-functional, there is a small proportion which are malignant or associated with hormonal excess.

In keeping with trends internationally, the Endocrine Department at Mater Dei Hospital, is coming across an increasing number of referrals for patients with adrenal incidentalomas, with the aim of excluding malignancy and hormonal excess. The aim of this study was to perform an analysis on a cohort of adrenal incidentalomas discovered locally.

## SUBJECTS AND METHODS

This was a retrospective study taking into account all the adrenal incidentalomas discovered during a six-month period. All CT scans, imaging the adrenal region, performed at Mater Dei Hospital between July and December 2014 were reviewed. These included all CT scans of the abdomen, pelvis, and thoracic region, CT scan of the kidney/ureter/bladder (CT KUB), CT intravenous urogram (IVU), CT pulmonary angiography and CT colonoscopy. Those reported to have any adrenal pathology were singled out. The actual scans of those singled out were closely re-reviewed, after been reported by radiologist in routine clinical practice.

In line with other studies,<sup>1-2</sup> all adrenal lesions greater than 1cm were included in the study, irrespective of reason of referral. Patients under the age of 18 years were excluded. Data collected included; indication for the CT scan, size (mm) and side of lesion (left/right), homogeneity, unenhanced density (HU), early enhanced density (HU) and 15min delayed density (HU), where indicated. This allowed us to calculate the relative or absolute washout where appropriate.

Imaging characteristics typical of adrenal adenoma included unenhanced density of less than 10HU, relative or absolute washout of 40% or 60% respectively<sup>3</sup> and in the absence of appropriate imaging study, CT imaging following a 12 month period showing unchanged mass characteristics were also considered as a surrogate criterion and included as an adenoma. Previous CT scans, when available, and consecutive scans were also reviewed. The size and radiological features of the lesions present on such scans were also documented in detail as outlined above. In this way, any change in size or characteristics of adrenal lesions were identified.

The adrenal lesions were then classified according to these radiological features into benign adenoma,

myelolipoma, adrenal cyst, ganglioneuroma, malignant carcinoma, and indeterminate.

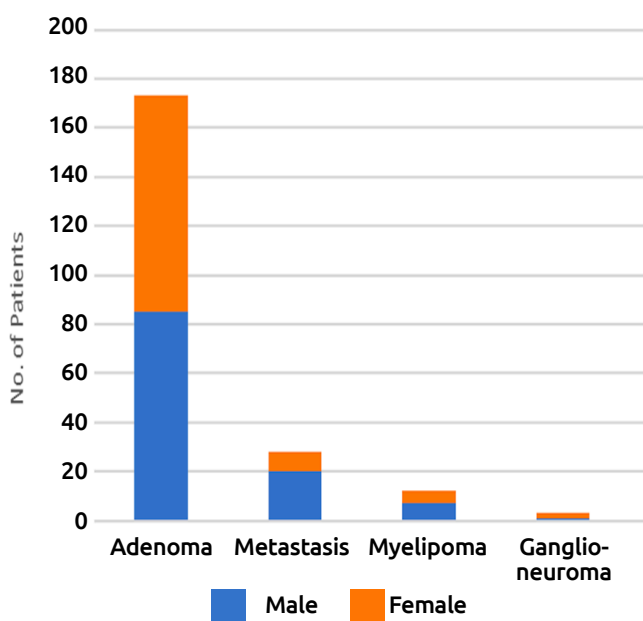
## STATISTICAL ANALYSIS

The Kolmogorov Smirnov test was used to assess whether the data collected is normally distributed or not. As predicted, in this study, most of the data was not normally distributed and therefore non-parametric statistics were required to explore the relationship between the variables. The non-parametric statistics included Chi-squared, Mann-Whitney test and Kruskal-Wallis test. Results were expressed as a P value, and a value of less than 0.05 was considered as statistically significant.

## RESULTS

A total of 9100 CT scans were reviewed. Adrenal incidentalomas larger than 1cm were identified in 296 patients, a frequency of 3.3%. 80 (27.0%) adrenal lesions could not be classified, this was because they either had only 1 scan (with no unenhanced imaging available) or washout calculations were unavailable. Of the remaining 216 incidentalomas, 173 (80.1%) were confirmed adenomas (Hounsfield units <10, relative or absolute washout values of >40% or 60% respectively or no increase in size over 12 months), 28 (12.9%) were metastatic lesions, 12 (5.6%) myelolipomas and 3 (1.3%) ganglioneuromas (Figure 1).

The mean age of all patients was 65.8 years ( $\pm 12.2$ SD). 52.3% of all patients were males. The median longest radiological diameter of all incidentalomas at 1st scan documented was 19.0mm (IQR 15.0-25.0). 81.5% of patients had more than one scan carried out, therefore change in size of the



**Figure 1** Characterisation of incidentalomas

**Table 1** Basic characteristics of all adrenal incidentalomas (Kruskal-Wallis test used)

	All characterised incidentalomas	Adrenal adenomas	Adrenal metastasis	Myelolipoma	Ganglioneuroma	p-value
Number (%)	216	173 (80.1)	28 (12.9)	12 (5.6)	3 (1.3)	
Age mean (±SD)	65.8 (12.2)	65.2 (12.4)	69.3(11.1)	64.8 (11.1)	70.3 (11.8)	NS
Males number (%)	113 (52.3)	85 (49.1)	20 (71.4)	7 (58.3)	1 (33.3)	NS
Longest radiological tumour diameter at 1st scan (mm) median (IQR)	19.0 (15.0-25.0)	18.0 (14.0-24.0)	26.0 (16.0-36.0)	24.0 (17.5-42.5)	25.0 (25.0-41.0)	<0.001
Change in tumour size (mm) median (IQR)	0.0 (-1.0 – 1.0)	0.0 (-1.0 – 0.8)	22.5 (12.5 – 30.0)	0 (0-0)	-5.0 (-6.0 – -2.5)	<0.001
Follow up period (months) median (IQR)	18.0 (2.9-38.6)	20.9 (4.5-39.0)	11.2 (0-29.3)	21.3 (3.9-38.3)	7.1 (3.8-11.2)	<0.001

lesions could be assessed. The median change in tumour size for all incidentalomas was 0mm (IQR -1.0 – 1.0) with a median follow up time of 18.0 months (IQR 2.9-38.6) (Table 1).

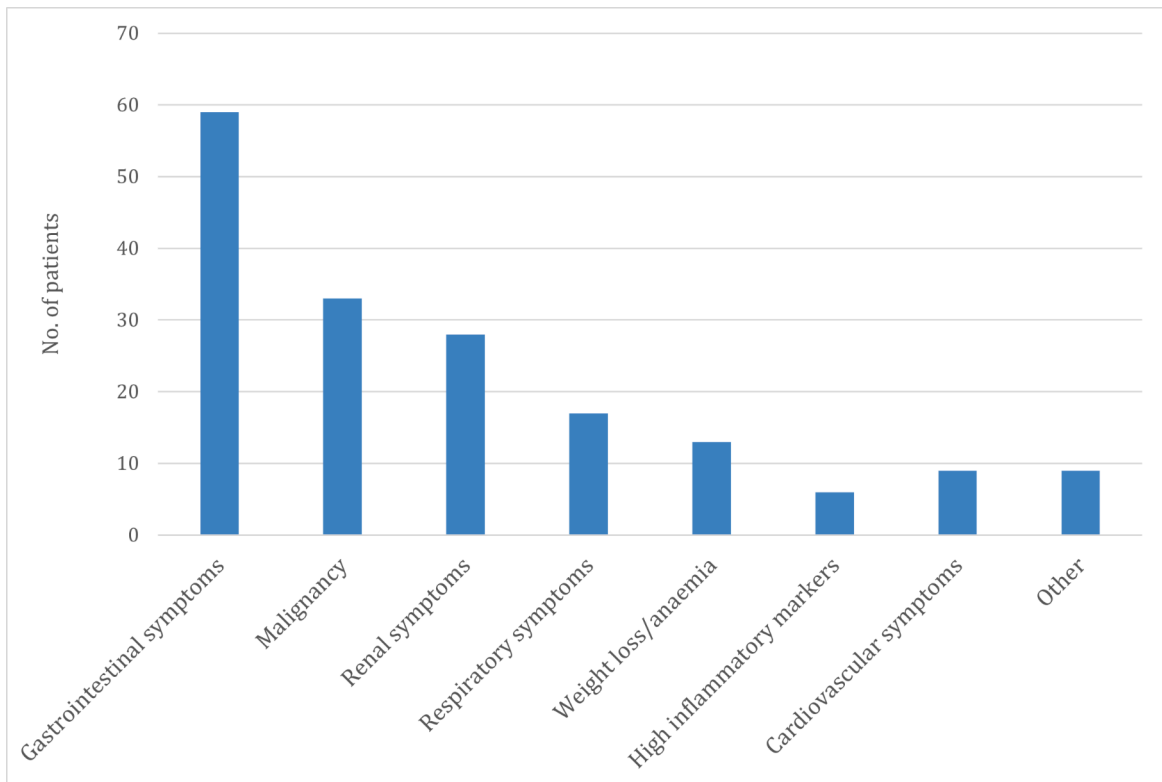
Reasons why the CT scan was carried out in the first place varied, with gastrointestinal symptoms being the commonest reason (34.1%) (Figure 2). Interestingly, out of all patients who had a CT scan because of an underlying malignancy and found to

have an adrenal incidentaloma (63 patients), 33 patients (52.4%) were found to have an adrenal adenoma, 26 patients (41.3%) had metastasis and 4 (6.3%) patients had a myelolipoma.

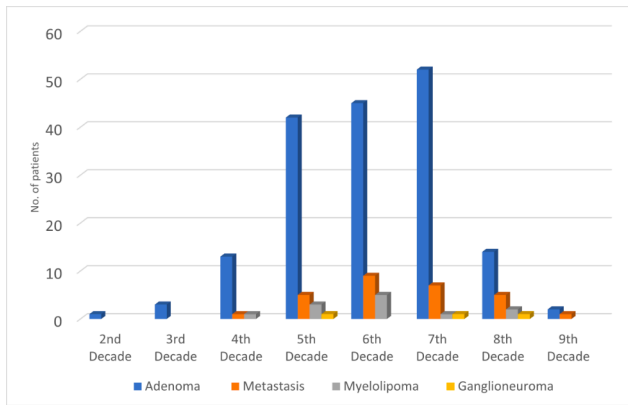
### SUBTYPE CLASSIFICATION

#### ADRENAL ADENOMA

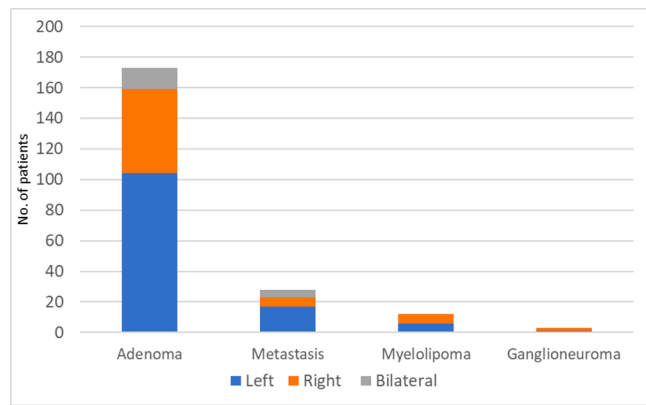
Of the 173 patients with an adrenal adenoma, 49.1% were males with a mean age of 65.2 years (±12.4). The



**Figure 2** Reason for CT in patients with adrenal adenoma



**Figure 3** Adrenal incidentalomas according to decade of presentation



**Figure 4** Laterality of adrenal lesions

7th decade was the commonest decade for presentation (30.0%), followed by the 6th (26.6%) (Figure 3). 59.5% had a left-sided lesion (Figure 4).

### Laterality of adrenal lesions

The longest median radiological diameter was 18.0mm (IQR 14.0-24.0) in the adenoma group (Table 1). In the whole adenoma group, during a median follow up of 20.9 months (ICR 4.5–39.0) the median change in size was 0.0mm (IQR -1.0 – 0.8) (Table 1).

### Adrenal Metastasis

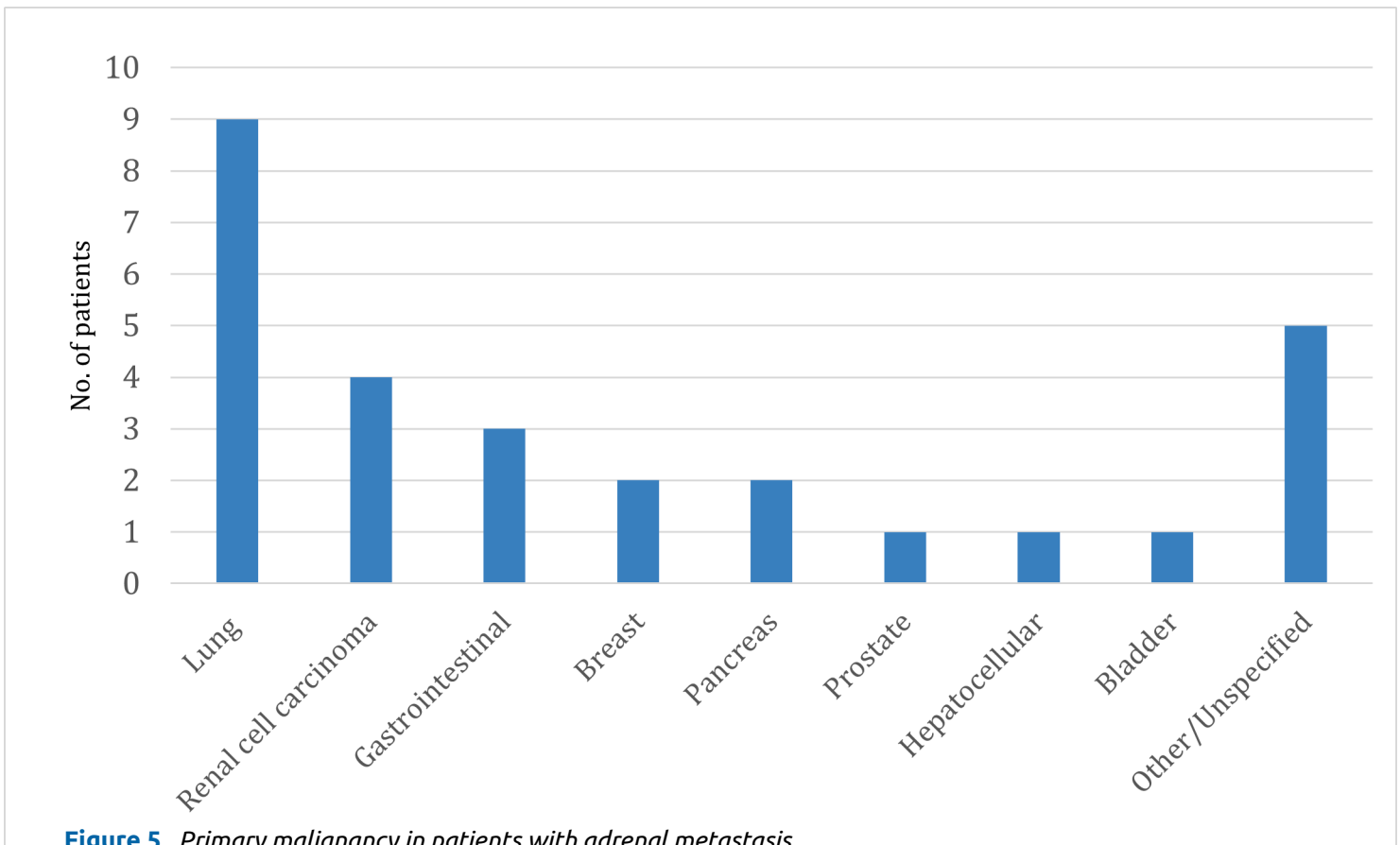
In the metastasis group (28 patients), 71.4% were males (Table 1). The mean age was 69.3 years ( $\pm 11.1$ SD). In this cohort, most patients presented in the 6th decade (32.1%), (Figure 3). 60.7% had left

sided lesions (Figure 4). The longest median radiological diameter was 26.0mm (IQR 16.0 – 36.0) in the metastasis group. Median follow up for this group was 11.2 months (ICR 0-29.3) whereas the median change in size was 22.5mm (IQR 12.5 - 30.0) (Table1).

The commonest primary malignancy was lung cancer (9 patients) (Figure 5). None of the patients required biopsy for the confirmation of the diagnosis of metastasis.

### Comparing Different Subtypes

When comparing the different groups described above, there was an appreciable statistically significant difference in change in size ( $p < 0.001$ ), with median change in size in the adenoma group being



**Figure 5** Primary malignancy in patients with adrenal metastasis

**Table 2** Comparing frequency of adrenal incidentalomas from this study with that published in the literature

Authors	Type	Date	n	Age (years) *mean (±SD) **range	Tumour size (mm) mean (±SD)	Subtype classification (%)							
						Adrenal Adenoma Non functional	Cortisol excess	Mineralo-corticoid excess	Phaeochromocytoma	ACC	Adrenal metastasis	Myelolipoma	Other
Kloos et al	Meta-analysis	1995	86,842				36-94		0-11	0-25	0-21	7-15	
Mantero et al	Retrospective study	2000	1,004	*56 (12.9)	36 (25)	85.1	9.2	1.6	4.2	4.7	0.7	8	15
Barzon et al	Meta-analysis	2003	3,868	*56.9	30-35 (range 5-250)	71.2	7.9	1.2	5.6	4.4	2.1		
Mansmann et al	Meta-analysis	2004	3,648	*57	34		5-47	1.6-3.8	5.0	4.7			
Cawood et al	Meta-analysis	2009		*58	32		6.4	0.6	3.1	1.9	0.7		
Young Cho et al	Retrospective analysis	2013	282	*57.15 (10.49)	23 (14)	78.0	9.9	1.8	2.1	0.7	0.4	2.8	
Goh et al	Prospective study	2017	228	**20-86	21	83.3	7.9	0.4	0.9	1.3		0.9	
<b>Current study</b>	<b>Retrospective</b>	<b>2019</b>	<b>216</b>	<b>*65.8 (12.2)</b>	<b>22 (11)</b>		<b>80.1</b>		<b>0</b>	<b>0</b>	<b>12.9</b>	<b>5.6</b>	<b>1.3</b>

0.0mm (IQR -1.0 – 0.8), in the metastasis group being 22.5mm (12.5-30.0) and in the myelolipoma group that of 0mm (IQR 0-0). In the ganglioneuroma group there was a median decrease in size of 5mm (IQR -6.0 – -2.5). The most significant change in size can be observed in the metastasis group, and this holds true despite the statistically shorter (P<0.001) follow up period in this group (median follow up of 11.2 months IQR 0-29.3) when compared to the adenoma group (median follow up of 20.9 months IQR 4.5-39.0), the myelolipoma group (median follow up of 21.3 months IQR 3.9-38.3) and the ganglioneuroma group (median follow up of 7.1 months IQR 3.8-11.2) (Table 1).

Left sided lesions were also found to be statistically more common than right sided lesions (P<0.001), with 58.8% of all lesions being left sided; 59.5% of patients having a left sided adenoma, 60.7% of metastasis being left sided metastasis, 50% of myelolipomas being left sided and 33% of the patients with a ganglioneuroma having a left sided lesion (Figure 4).

### Comparing Adrenal Adenomas With Adrenal Metastasis

When comparing the adenoma group with the metastasis group alone, change in size remained significantly different (P<0.001) despite no statistically significant difference in the duration of follow up in the adenoma group (median 20.9 months ICR 4.5–39.0) vs the metastasis group (median 11.2 months ICR 0-29.3) (P=0.084) (Table 1).

Unenhanced density was also significantly different (P=0.002) with the median unenhanced density of the adenoma group being 5HU (IQR -3 – 11) and 34HU (IQR 28 – 35) in the metastasis group. More males had adrenal metastasis (71.4%) as opposed to the adenoma group (49.1%) (P=0.028).

## DISCUSSION

From a total of 9100 CT scans, 216 incidentalomas were identified, with a frequency of 3.3%. The frequency of adrenal incidentalomas in the general population, as calculated from radiological series is suggested to be around 2-3% in those around the age of 50 years and increases to 10% in the elderly.<sup>1,4</sup>

From the identified 216 incidentalomas, 173 (80.1%) were confirmed adenomas, 28 (12.9%) were metastasis, 12 (5.6%) were myelolipomas and 3 (1.3%) were noted to be ganglioneuromas. These compare well to results from similar studies (Table 2). No phaeochromocytomas or adrenocortical carcinomas were detected during the study period. This could be attributed to the fact that the incidence of such conditions is low and we reviewed a finite amount of CT scans.<sup>9,10</sup> Our rate of metastasis was higher than that reported in the literature (Table 2). In most of the quoted literature, patients with previous or concurrent history of malignancy which are known to metastasize to the adrenal gland were excluded.<sup>2,5-6</sup> The authors argue that patients with

malignancies of the lung, breast, stomach, kidney, melanoma and lymphoma, which are known to metastasize to the adrenal gland, should be excluded from the definition of a true incidentaloma.<sup>6</sup>

Our study demonstrated no major male to female difference in the adenoma group (49.1% males), however, this cannot be extrapolated for the metastasis group; where a male preponderance of 71.4% was noted. Most studies report a higher female to male ratio.<sup>7-8</sup> In the meta-analysis by Barzon et al., there was a higher female to male ratio in the overall analysis including radiological, autopsy and surgical series, but when taking autopsy studies independently, this female preponderance was lost. This could be ascribed to a higher rate of imaging performed in females than in males.<sup>6</sup> In the study by Comlekci et al.,<sup>2009</sup>, there was also a female:male ratio of 2.9 in the adenoma group, with a ratio of 0.07 in the metastasis group, with 93% of patients with adrenal metastasis being males (n=14 patients; 3.7% of whole cohort).<sup>9</sup> The reason as to why more male patients were noted to have adrenal metastasis could be explained by the fact that most patients with adrenal metastasis in our cohort, and in the study by Comlekci, had primary lung cancer (39% in our cohort and 57.1% in the other cohort). Previously published data shows that lung cancer, internationally, has a higher prevalence in males rather than in females.<sup>10</sup>

More lesions were discovered on the left side and this was found to be in concordance with other studies where left sided tumours were more prevalent.<sup>11-12</sup> Older studies had shown a right sided predominance<sup>2</sup> but this may have been attributed to the predominant diagnostic modality used in these studies. Ultrasonography (US) was the diagnostic technique used in most cases and the right adrenal gland is known to be better visualised than the left adrenal gland by ultrasonography.

The mean age at presentation was 65.8 years ( $\pm 12.2$ SD). This age distribution might not be representative of the whole population as more diagnostic procedures are usually carried out in ageing patients.<sup>2</sup> Still, it is well documented that adrenal adenomas are more prevalent with increasing age.<sup>13-14</sup> Our cohort revealed an older mean age at presentation when compared to most meta-analyses. Once again, this could be attributed to the fact that in most published data, patients with metastasis were excluded and these tend to be older patients. In the study by Muth et al., patients with a history of extra adrenal malignancy, but no evidence of active disease at time of study were included in a separate arm of the study.<sup>15</sup> The mean age of those with no extra adrenal malignancy was 67 years, whereas the mean age of patients with a history of extra adrenal malignancy was 68 years. This compares better to our results, possibly because the cohort of patients included in the study was similar to our cohort. In the same study, the commonest reason for performing the initial CT scan was for

investigation of gastrointestinal symptoms (38% of patients). Similarly, in our cohort, gastrointestinal symptoms were the commonest trigger factor for the initial CT scan (34.1% of patients).

In the large Italian multicentric retrospective study published in 2000, including 1004 patients, the median size of adrenal incidentalomas was found to be 36mm<sup>2</sup> whereas in more recent studies performed in New Zealand<sup>12</sup> and Korea,<sup>11</sup> the median diameter was 21mm (IQR 10-83mm) and mean of 23mm ( $\pm 13$ SD) respectively. The latter figures are increasingly similar to our data, where the mean longest radiological tumour size at first scan was found to be 22.4mm ( $\pm 11.6$ SD). This may be attributed to increased awareness by reporting radiologists on adrenal incidentalomas reporting even smaller lesions and better imaging techniques leading to improved resolution of adrenal lesions.<sup>12</sup>

Our study revealed that half of the patients being followed up for malignancy were found to have an adrenal lesion consistent with an adrenal adenoma whilst being followed up for their primary malignancy. This may potentially justify the inclusion of all patients who had imaging of the adrenal region, including those with a history of malignancy, when characterising adrenal incidentalomas. Most studies in the literature exclude patients with underlying malignancy, on the basis that this cohort is at increased risk of harbouring adrenal metastasis.<sup>2,5</sup> However, given the high prevalence of adrenal adenomas in our study even in this cohort of patients, it effectively illustrates that patients with current malignancy may still have an adenoma irrespective of their malignancy.

We detected no malignant transformation in the 173 patients diagnosed with an adrenal adenoma, followed up for a median of 20.9 months (IQR 4.5-39.0). The mean change in size was that of 0.1mm ( $\pm 2.1$ SD) over a median follow up of 20.9 months in the adenoma group. In a recent systematic review, the natural course of an apparently benign adrenal incidentaloma developing malignancy was found to be very low at 0.2% (95% CI:0.0-0.4).<sup>1</sup> Out of the 906 patients included in the systematic review, only 2 patients were identified and the transformation was dubious in both scenarios; one patient had non-Hodgkin lymphoma and the initial radiological images were not consistent with benign characteristics in the first place, whilst in the second case there was a history of renal cell carcinoma and it was unclear whether the incidentaloma was found during the follow up of cancer or discovered incidentally.<sup>5</sup> Importantly, in the other 904 patients, there was no evidence of malignant transformation in a presumably benign adrenal incidentaloma. Based on these findings, the recently published guidelines suggest against repeated imaging if the lesion is confirmed to be a benign adrenal mass smaller than 4cm at diagnosis<sup>1</sup> because even a small increase in size does not seem to have significant clinical

implications. The cut-off of 4cm was based on clinical experience by panel members on the basis that repeated imaging might risk false positive results together with significant financial burden on the health system and psychological stress on patients. This data has been recently confirmed in a retrospective study including 1149 patients where the mean change in size was 14mm over a median of 4 years (IQR 2.0-6.0). The optimal cut-off value for diagnosing a benign lesion based on size was 3.4cm in the latter study, with a sensitivity of 100% and specificity of 95.0%. When using a cut-off value of 4cm to distinguish benign from malignant lesions, the sensitivity and specificity were 90.0% and 97.9% respectively.<sup>16</sup>

A larger mean change in size in the metastasis group was noted over a shorter median follow up period when compared to the adenoma group (p=0.001). Since most data in the literature excludes patients with extra adrenal metastasis it was rather difficult to compare our results with published data. In light of the fact of this significant difference, our data can therefore be useful in clinical practice when assessing incidentalomas, highlighting the possibility of a lesion being sinister if there is a significant increase in its size. Our finding that 52.4% of patients with underlying malignancy found to have an incidentaloma, had in fact a radiologically confirmed adenoma, proves the consistent rate of adenoma, thus highlighting the consistent rate of picking up incidentalomas in the course of imaging.

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### LIMITATIONS

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There is always a finite number of borderline cases when it comes to classification. This was the case when classifying adrenal incidentalomas into subtypes. To mitigate this all cases were re-reviewed, after been reported by radiologist in routine clinical practice, by the same team. Furthermore, equivocal cases were discussed by members of the research team.

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### CONCLUSION

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In conclusion, a snapshot of adrenal incidentalomas in Malta has been established together with the frequency of each subtype over a 6-month period. An important finding was that patients with underlying malignancy do indeed have a higher probability of being diagnosed with adrenal metastasis as expected. However, they may still be harbouring an incidental adrenal adenoma as half of our malignancy cohort had in fact an incidentaloma with radiological features consistent with an adenoma.

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### SUMMARY BOX

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- Adrenal incidentalomas are a common occurrence in abdominal imaging.
- Adrenal adenomas are the commonest adrenal lesion encountered in clinical practice and the majority, by far remain stable in size over time.
- Patients with underlying malignancy who present with an adrenal incidentaloma may still harbour an adrenal adenoma, rather than metastasis.

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