Radiomics: a new tool to differentiate adrenocortical adenoma from carcinoma

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Abstract

Background: The main challenge in the management of indeterminate incidentally discovered adrenal tumours is to differentiate benign from malignant lesions. In the absence of clear signs of invasion or metastases, imaging techniques do not always precisely define the nature of the mass. The present pilot study aimed to determine whether radiomics may predict malignancy in adrenocortical tumours.

Methods: CT images in unenhanced, arterial, and venous phases from 19 patients who had undergone resection of adrenocortical tumours and a cohort who had undergone surveillance for at least 5 years for incidentalomas were reviewed. A volume of interest was drawn for each lesion using dedicated software, and, for each phase, first-order (histogram) and second-order (grey-level colour matrix and run-length matrix) radiological features were extracted. Data were revised by an unsupervised machine learning approach using the K-means clustering technique.

Results: Of operated patients, nine had non-functional adenoma and 10 carcinoma. There were 11 patients in the surveillance group. Two first-order features in unenhanced CT and one in arterial CT, and 14 second-order parameters in unenhanced and venous CT and 10 second-order features in arterial CT, were able to differentiate adrenocortical carcinoma from adenoma (P < 0.050). After excluding two malignant outliers, the unsupervised machine learning approach correctly predicted malignancy in seven of eight adrenocortical carcinomas in all phases.

Conclusion: Radiomics with CT texture analysis was able to discriminate malignant from benign adrenocortical tumours, even by an unsupervised machine learning approach, in nearly all patients.

Introduction

Adrenal incidentalomas discovered during abdominal imaging for other indications are not uncommon findings¹, with a prevalence rising with age from around 3 per cent at the age of 50 years to 10 per cent in the elderly². The diagnostic work-up of adrenal incidentalomas includes endocrine evaluation to evaluate hormone function and radiological imaging to differentiate malignant from benign masses³,⁴. Identifying malignancy is critical, as the surgical strategy and approach may be influenced by the nature of the mass⁵. Adenomas usually have an increased lipid content that gives rise to a low attenuation mean value at unenhanced CT (less than 10 Hounsfield units (HU)), high absolute and relative washout percentages on contrast-enhanced CT (over 60 per cent and more than 40 per cent respectively), and signal drop-off in in-phase and opposition-phase MRI sequences⁶,⁷. With large masses, however, heterogeneity in intracellular lipid content, along with areas of necrosis, haemorrhage and calcification, can lead to neither CT nor MRI being able to define the nature of the lesion¹. As around 10–40 per cent of all adrenal incidentalomas are lipid-poor adenomas, the accuracy of suggested thresholds may be inadequate⁸, potentially leading to surgical overtreatment. Malignant adrenal lesions present with increased metabolic activity⁹ that may be revealed by increased uptake at [¹⁸F]FDG PET–CT, but the accuracy of the technique remains under debate.
because of controversies concerning correct cut-off points for maximum standardized uptake values (SUVmax)\(^9\).

Radiomics is an emerging area of radiology that uses a variety of computational methods to obtain quantitative parameters from CT and MRI, potentially allowing automated analysis even for heterogeneous tumours\(^10,11\). Texture analysis is a computational quantitative technique that provides a measure of lesion heterogeneity on the basis of local variations in image brightness, discriminating between pathologically different regions. Statistical texture analysis is based on first- and second-order techniques; the former determine how many pixels have a specific attenuation within a mass, and the latter determine whether those pixels are clustered inside the tumour volume.

Few studies have evaluated radiomic approaches to differentiate between benign and malignant adrenal masses\(^12,13\). The aim of this pilot study was to investigate whether CT texture analysis could be a suitable method for distinguishing benign from malignant adrenocortical non-secreting lesions in order to strengthen the indication for surgery, even with an unsupervised machine learning approach.

### Methods

The present study included a selection of patients recruited between 2012 and 2018 at Padua University Hospital, Italy, with indeterminate functionally inactive adrenal lesions discovered incidentally at imaging in patients without other neoplasms.

The study group included patients who underwent adrenalectomy at a single centre and who had an adrenal mass with a mean CT densitometry value in unenhanced acquisition of more than 10 HU and a reduced relative or absolute washout on contrast-enhanced CT (less than 40 per cent and below 60 per cent respectively), without clinically evident and overt laboratory signs of hypercortisolism or virilization, with no radiological signs of local invasion to adjacent structures or distant metastases, and with CT performed by a standardized protocol. A comparator group of non-operated patients diagnosed and followed up at the same centre, with clinically asymptomatic and functionally inactive adrenal lesions discovered incidentally at imaging in patients without other neoplasms.

From a database of 336 operated patients, 19 (9 adenomas, 10 carcinomas) met the inclusion criteria and were included in the study. In accordance with the selection criteria, all patients with adrenocortical carcinomas had disease confined to the gland (stage I-II according to European Network for the Study of Adrenal Tumours classification\(^15\)). Eleven patients comprised the unoperated cohort of adrenal incidentalomas. Clinical characteristics of the patients and imaging features of the tumours are summarized in Table 1. The mean size of the adrenal lesions was

### Images acquisition and analysis

All CT examinations were performed with a 128-slice scanner (Somatom Definition\(^\text{TM}\); Siemens Healthineers, Erlangen, Germany), including unenhanced and contrast-enhanced scans after intravenous injection of 2 ml/kg iohexol 350 mg iodine per ml (Omnipaque\(^\text{TM}\); GE Healthcare, Milwaukee, Wisconsin, USA) followed by a 50-ml saline flush. There was cranio-caudal image acquisition with 120 kV tube voltage, 250 mAs effective dose, 0.5 s rotation time, 0.6 mm detector collimation, and 0.75 pitch. Slice thickness was 5 mm for unenhanced acquisition and 3 mm for arterial and venous scans; all images analysed had soft-tissue reconstruction with a 30B kernel. The arterial-phase image was acquired 15 s after the achievement of 100 HU within the aortic lumen, and the venous-phase image 80 s after contrast administration. The mean densitometry value in unenhanced, venous, and delayed phases was calculated by drawing a region of interest (ROI) along the margins of the maximum diameter of the adrenal mass in the axial slice.

Absolute and relative washouts were calculated as reported previously\(^15\). When \([^{18}F]\)FDG PET-CT was available, SUVmax was assessed as described previously\(^9\).

In each CT slice of the three phases (unenhanced, arterial, and venous), two radiologists in consensus drew a ROI along the margin of the adrenal lesion using FMD (FMD Group, Zurich, Switzerland), a specific software for image texture analysis. A volume of interest (VOI) for each lesion in each phase was created (Fig. 1). Each voxel inside the VOIs measured 0.744 × 0.744 × 5.000 mm for unenhanced scans, and 0.742 × 0.742 × 3.000 mm for contrast-enhanced acquisitions. Densitometry data in HU for each voxel inside the VOIs were extracted automatically by the software, which obtained 32 radiomic features from the image texture of each VOI. The radiomic features analysed were five first-order parameters, and 27 second-order grey-level co-occurrence matrix (GLCM) and second-order run-length matrix (RLM) parameters\(^16\), as described in detail in Table S1 and Fig. S1.

### Statistical analysis

Data from adenomas, carcinomas, and patients with unoperated incidentalomas were compared using \(\chi^2\) and Student’s t tests, as appropriate. The level of significance was taken as \(P < 0.050\).

Principal component analysis (PCA)\(^17\) was applied to the radiomic features extracted by dedicated software. PCA is a mathematical transformation providing a set of new components (principal components), which are obtained by a linear combination of the original ones. Principal components are ordered according to their contribution to the total variation of the data set. Features that had \(P < 0.050\) in the differentiation between adrenocortical carcinoma and the other two groups were selected. A receiver operating characteristic (ROC) curve was built for each parameter selected, and the area under the ROC curve, and sensitivity and specificity at Youden’s index, were calculated. Data for the lesions were analysed using a K-means clustering technique\(^18\), an unsupervised machine learning approach. The detection rate of adrenocortical carcinoma versus adenoma and incidentaloma was calculated, regardless of pre-test classification of the disease. Statistical analysis was done using R software (R Foundation for Statistical Computing, Vienna, Austria).

### Results

From a database of 336 operated patients, 19 (9 adenomas, 10 carcinomas) met the inclusion criteria and were included in the study. In accordance with the selection criteria, all patients with adrenocortical carcinomas had disease confined to the gland (stage I-II according to European Network for the Study of Adrenal Tumours classification\(^15\)). Eleven patients comprised the unoperated cohort of adrenal incidentalomas. Clinical characteristics of the patients and imaging features of the tumours are summarized in Table 1.
significantly larger for carcinomas and adenomas compared with incidentalomas (mean(s.d.) 62.3(35.2) versus 25.9(1.4) mm, \(P = 0.003\); 56.6(42.4) versus 25.9(1.4) mm, \(P = 0.027\)).

In accordance with the selection criteria, mean unenhanced densitometry, and relative and absolute washout values for both carcinomas and adenomas were suggestive of malignancy (more than 10 HU, and less than 40 per cent and below 60 per cent respectively), although higher unenhanced values and lower washout values were detected in carcinomas. Values for the incidentaloma group were always indicative of benign lesions (Fig. 2). \([^{18}F]FDG\) PET–CT was available for 10 patients (6 carcinoma, 4 adenoma), and mean SUVmax was no different between carcinomas and adenomas (mean(s.d.) 14.9(7.2) versus 15.8(22.2); \(P = 0.905\)).

**Table 1 Clinical and radiological features of patients evaluated for adrenal mass**

|                  | ACC (n = 10) | Adenoma (n = 9) | AI (n = 11) | \(P^\) |
|------------------|-------------|----------------|------------|--------|
| Age (years)*     | 53.5(14.4)  | 66.2(6.4)      | 71.4(9.4)  | 0.537  |
| Sex ratio (M : F)| 4 : 6       | 4 : 5          | 5 : 6      | 0.265\*|
| Lesion side      |             |                |            | 0.625\*
| Right            | 6           | 5              | 4          | 0.713\*|
| Left             | 4           | 4              | 7          | 0.854\*|
| Axial maximum diameter (mm)* | 62.3(35.2)  | 56.6(42.4)     | 25.9(1.4)  | 0.753  |
| Mean densitometry value (HU)* | 33.4(4.7)   | 20.2(9.2)      | 2.8(9.4)   | 0.001  |
| Relative washout (%)* | 16.5(0.2)   | 23.7(0.4)      | 46.5(0.5)  | < 0.001 |
| Absolute washout (%)* | 30.0(0.2)   | 32.2(0.1)      | 63.3(0.3)  | < 0.001 |
| SUVmax*          | 14.9(7.2)\*| 15.8(22.2)\*   | –          | 0.905  |

*Values are mean(s.d.). PET–CT performed in \*six and \*four patients. ACC, adrenocortical carcinoma; AI, adrenal incidentaloma; HU, Hounsfield units; SUVmax, maximum standardized uptake value. \*Student’s \(t\) test, except \(^\chi^2\) test.

**Fig. 1 Volume of interest of an adrenal mass delineated using PMOD software**
Volume of interest of adrenal mass on venous-phase CT: a axial, b sagittal, and c coronal views, and d volume rendering reconstruction.
Texture analysis showed that two first-order features in unenhanced CT and one in arterial CT, and 14 second-order parameters in unenhanced and venous CT and 10 in arterial CT, were able to differentiate adrenocortical carcinomas from adenomas and incidentalomas ($P < 0.050$).

Among the first-order parameters, the histogram mean in unenhanced CT acquisition showed a sensitivity of 95 per cent and specificity of 100 per cent using the identified Youden index cut-off of 22.5 HU (Fig. 3). Specificity and sensitivity of 90 and 50 per cent respectively for the histogram mean in arterial-phase CT acquisition was also observed. Histogram entropy in the unenhanced CT phase had a specificity of 90 per cent and a sensitivity of 65 per cent.

In the analysis of second-order features, a specificity of 100 per cent and a sensitivity of 95 per cent was found for 10 parameters in unenhanced CT images (GLCM autocorrelation, entropy, difference entropy, sum average, sum entropy, maximum probability, homogeneity inverse difference moment, RLM short run low grey-level emphasis, short run high grey-level emphasis, grey-level non-uniformity), in eight features of arterial-phase images (GLCM autocorrelation, entropy, difference entropy, sum average, sum entropy, maximum probability, homogeneity inverse difference moment, RLM short run high grey-level emphasis), and in 10 parameters for venous-phase CT images (GLCM autocorrelation, entropy, difference entropy, sum average, sum entropy, maximum probability, homogeneity inverse difference moment, RLM long run low grey-level emphasis, short run high grey-level emphasis, grey-level non-uniformity). A specificity of 100 per cent and sensitivity of 90 per cent for RLM long run low grey-level emphasis, and RLM short run high grey-level emphasis was observed. A specificity of 100 per cent and sensitivity of 85 per cent for RLM long run low grey-level emphasis was found in three second-order features in the venous phase. The specificity was 90 per cent and sensitivity 85 per cent for RLM short run low grey-level emphasis in unenhanced images, and RLM long run low grey-level emphasis in arterial acquisitions was observed. A specificity of 100 per cent and sensitivity of 85 per cent was found in three second-order features in the venous phase. The specificity was 90 per cent and sensitivity 85 per cent for RLM short run low grey-level emphasis in unenhanced images, and RLM long run low grey-level emphasis in arterial acquisitions was observed. A specificity of 100 per cent and sensitivity of 85 per cent was found in three second-order features in the venous phase. 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Using the whole data set for each phase (unenhanced, arterial, and venous), a K-means analysis was undertaken to search for
Adrenal incidentalomas are frequent unexpected findings in imaging studies. After excluding hormone hypersecretion, the critical point for each incidentally detected adrenal mass is to establish whether it is benign or malignant, in order to assess the further strategy and potential surgical approach. Several features have been studied to predict the nature of adrenal mass at imaging, but inaccuracy is often reported. Although size alone is often used as an indicator of the risk of malignancy, it is generally adopted as first-cut-off, overlap between benign and malignant lesions can result in unnecessary surgery for diagnostic purposes.

Increased attenuation values equal to or higher than 10 HU on unenhanced CT, indicating a lipid-poor adrenal lesion, have a high sensitivity (95 per cent c.i. 91 to 100 per cent) but poor specificity (72 (60 to 82) per cent) for detecting malignancy. A cut-off of 20 HU has been proposed as a threshold for differentiating between benign and malignant adrenal masses. Several parameters among first- and second-order features had high diagnostic accuracy (sensitivity and specificity over 90 per cent), and may therefore be suitable for clinical purposes. Several unenhanced CT textural parameters also may be used to distinguish adenoma from carcinoma. The advantage of extracting images from the unenhanced CT image is that this is easier to control, imaging is easier to obtain, and the texture data extracted depend only on the inherent density of the tumour. On the other hand, enhanced CT images are affected by many factors, including differences in contrast materials and injection rates, as well as the scan delay time. For these reasons, only data from the same CT scanner acquired at the same institution with the same protocol were included in the present study.

Radiomics allows extracted quantitative data to be used as the input to a machine learning process. Combining data and using a machine learning unsupervised approach, two clusters of patients were clearly identified, achieving a detection rate of seven of eight for adrenocortical carcinoma, and 19 of 20 for adrenal adenoma and incidentaloma in all three phases.

**Discussion**

Adrenal incidentalomas are frequent unexpected findings in imaging studies. After excluding hormone hypersecretion, the critical point for each incidentally detected adrenal mass is to establish whether it is benign or malignant, in order to assess the further strategy and potential surgical approach. Several features have been studied to predict the nature of adrenal mass at imaging, but inaccuracy is often reported. Although size alone is often used as an indicator of the risk of malignancy, it is generally adopted as first-cut-off, overlap between benign and malignant lesions can result in unnecessary surgery for diagnostic purposes.

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Supplementary material

Supplementary material is available at BJS Open online.

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