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Use of DWI in the Differentiation of Renal Cortical Tumors

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Abstract

OBJECTIVE—The purpose of this study was to differentiate clear cell renal cell carcinoma (RCC) from other common renal cortical tumors by use of DWI.

MATERIALS AND METHODS—The study included 117 patients (mean age, 60 years) with 122 histopathologically confirmed renal cortical tumors who underwent 1.5-T MRI that included DWI before they underwent nephrectomy between 2006 and 2013. For each tumor, two radiologists independently evaluated apparent diffusion coefficient (ADC) values on the basis of a single ROI in a nonnecrotic area of the tumor and also by assessment of the whole tumor. The concordance correlation coefficient (CCC) was calculated to assess interreader agreement. The mean ADC values of clear cell RCC and every other tumor subtype were compared using an exact Wilcoxon rank sum test.

RESULTS—Interreader agreement was excellent and higher in whole-tumor assessment (CCC, 0.982) than in single-ROI analysis (CCC, 0.756). For both readers, ADC values for clear cell RCC found on single-ROI assessment (2.19 and $2.08 \times 10^{-3} \text{ mm}^2/\text{s}$) and whole-tumor assessment (2.30 and $2.32 \times 10^{-3} \text{ mm}^2/\text{s}$) were statistically significantly higher than those for chromophobe, papillary, or unclassified RCC ($p < 0.05$) but were similar to those for oncocytoma found on single-ROI assessment (2.14 and $2.32 \times 10^{-3} \text{ mm}^2/\text{s}$) and whole-tumor assessment (2.38 and $2.24 \times 10^{-3} \text{ mm}^2/\text{s}$). ADC values were also higher for clear cell RCC than for angiomyolipoma, but the difference was statistically significant only in whole-tumor assessment ($p < 0.03$).

CONCLUSION—ADC values were statistically significantly higher for clear cell RCC than for chromophobe, papillary, or unclassified RCC subtypes; however, differentiating clear cell RCC from oncocytoma by use of DWI remains especially challenging, because similar ADC values have been shown for these two tumor types.

Keywords

cancer; DWI; kidney neoplasms; MRI; renal cell carcinoma

The incidence of renal cell carcinoma (RCC) in the United States has increased in recent years [1]. This increase is partly attributed to the more widespread use of imaging and the resulting increase in the detection of small (< 4 cm) mostly asymptomatic lesions [2]. In the past, incidentally found RCC lesions have been treated more or less as a single tumor entity, with radical surgical resection considered the only potentially curative therapeutic option. However, it has become evident that RCC represents a very heterogeneous family of tumors with different histopathologic subtypes, which differ not only in their genomic profiles but also in their metastatic potential and outcomes. Clear cell RCC, for example, accounts for the vast majority of all metastatic tumors and is associated with a worse outcome than RCC subtypes such as papillary or chromophobe RCC, which are more indolent [3, 4].

The understanding that nearly half of all patients with diagnosed renal cortical tumors will prove to have disease of a benign or indolent subtype (i.e., papillary or chromophobe RCC) has provided an incentive for the use of more conservative treatment approaches, with kidney-sparing resection performed whenever possible. Partial nephrectomy is preferred for healthy and young patients, but active surveillance or focal ablation is recommended for elderly and frail patients with serious medical comorbidities, such as renal impairment, which increase the risk of renal failure after surgery [5].

Because the role of renal biopsies is still evolving [6] and because the incidence of RCC in the United States continues to rise, a strong clinical need has developed for new imaging techniques that can help characterize renal cortical lesions preoperatively. At present, 10–30% of all incidentally found renal lesions that are resected are identified as benign by means of histopathologic analysis [7], and better preoperative characterization of lesions could help prevent unnecessary operations by identifying benign or indolent disease. At the same time, to avoid undertreatment of patients and to assist the surgeon with the process of surgical planning (especially the choice between the use of radical and kidney-sparing approaches), it is essential to be able to identify aggressive subtypes such as clear cell RCC.

Different imaging modalities, including CT [8], ultrasound [9], and MRI [10, 11], have been assessed for their ability to characterize renal cortical tumors. Although statistically significant differences between different tumor subtypes have been found with the use of certain imaging metrics (e.g., the degree of contrast enhancement on different imaging phases), the ranges of values for these metrics have generally overlapped for different tumor subtypes. As a result, these metrics have limited practical value for assisting in making decisions about routine clinical care, and additional imaging methods are still needed.

DWI is an emerging oncologic imaging method that provides insights into the tissue microenvironment by assessing the restriction of free water movement caused by the increased cell density of a tumor and changes in the local tissue architecture. The degree of restriction can be quantified by calculating the apparent diffusion coefficient (ADC). Several authors have used MRI with DW sequences to characterize both cystic and solid renal cortical lesions [12–24]. However, their analyses have mostly been based on the ADC values of either a single ROI or a small number of ROIs drawn somewhere in the lesion, or their analyses have included relatively small numbers of patients. Because RCC tumors, especially clear cell RCC tumors, often have areas of necrosis and intratumoral heterogeneity with respect to both their radiologic and genomic features [25], it remains unclear whether single-ROI measurements are reproducible and truly representative of whole tumors. To our knowledge, the value of whole-tumor assessment in calculating ADC metrics has not been investigated.

The purpose of this study was therefore to investigate the usefulness of DWI in differentiating the various histologic subtypes of renal cortical tumors with the use of both single-ROI and whole-tumor ADC assessment. We were particularly interested in the identification of clear cell RCC, and we hypothesized that ADC values for this aggressive tumor subtype would differ from those of other renal cortical tumors, thereby allowing preoperative characterization of such tumors.

Materials and Methods

Patients, Inclusion Criteria, and Reference Standard

The institutional review board at Memorial Sloan Kettering Cancer Center approved this retrospective HIPAA-compliant study and waived the requirement for informed consent. A retrospective search for patients with renal cortical tumors who underwent preoperative MRI examinations was performed using the databases of the urology, radiology, and pathology departments for the period from March 2006 through April 2013. For inclusion in the study, patients had to meet the following criteria: they had to have undergone an MRI examination performed using a dedicated renal MRI protocol, including a DW sequence, at our institution; they had to have undergone a total or partial nephrectomy at our institution; and the results of histopathologic analysis of the resected specimen had to have indicated the presence of a renal cortical tumor.

The database search identified 119 patients who fulfilled the inclusion criteria. Two patients were excluded from analysis because their DW images were affected by heavy distortion. The final cohort therefore consisted of 117 patients with 122 renal cortical lesions. The mean interval between MRI examination and surgery was 34 days (range, 1–250 days). The reference standard was histopathologic analysis of the surgically resected specimen.

Five of 117 patients in our study had been included in a previous study [12] that focused on preliminary comparison of ADC values associated with renal cortical tumors and benign cysts. In the present study, we evaluated the use of DWI in the differentiation of renal cortical tumors, including the different subtypes of RCC.

MRI Technique and Analysis

All 117 examinations were performed at a field strength of 1.5 T on the following MRI units manufactured by GE Healthcare: Optima MR450w ($n = 7$), Signa Excite ($n = 83$), Signa HDx ($n = 12$), and Signa HDxt ($n = 15$). The dedicated MRI protocol used in the examinations included a DW sequence with b values of 0 and 500 s/mm² (echo-planar imaging sequence with breath-holding, TR/TE of 1800–6000/59.2–84.3, matrix of 96 × 96 to 128 × 128, FOV of 440–460 mm, slice thickness of 7 mm, and intersection gap of 1 mm). ADC maps were generated voxelwise with the use of a monoexponential model. Other sequences, including a T1-weighted fat-saturated multiphase contrast-enhanced series and a T2-weighted sequence, were also performed and were available for tumor localization.

Two readers, both of whom had more than 4 years of experience in the interpretation of genitourinary MR images, were blinded to all histopathologic and clinical patient information and independently assessed each tumor (Fig. 1) with the use of the following method. First, they used all available sequences to correctly identify and localize a tumor. Then, using ImageJ software (version 1.47 m, National Institutes of Health), they drew a freehand single ROI on the ADC map [26], encircling a nonnecrotic area of the tumor (which was defined as tissue that enhanced on late-phase contrast-enhanced images), taking care not to include any surrounding tissue. ADC values for whole-tumor assessment were generated in a similar way, with both readers encircling the entire tumor on every slice with the use of a freehand ROI. For predominantly cystic tumors, only the solid parts were included in analysis. The data from all of these ROIs were then analyzed using in-house software written in Matlab, version R2014a, (Mathworks), which calculated the corresponding ADC values for each tumor on a voxel-by-voxel basis.

The median number of voxels included in single-ROI analysis was 387.5 voxels (range, 5–5458 voxels), for reader 1, and 238.5 voxels (range, 20–5370 voxels), for reader 2. The median number of voxels included in volumetric tumor assessment was 4565.5 voxels (range, 49–209,110 voxels), for reader 1, and 4516.5 voxels (range, 34–160,071 voxels), for reader 2.

Statistical Methods

We summarized the mean ADC values in single-ROI assessment and whole-tumor assessment as median and range values. To assess interreader agreement between the ADC values measured by the two readers (readers 1 and 2), the concordance correlation coefficient (CCC) was estimated. A CCC of 1 indicates perfect concordance, and a CCC of –1 indicates perfect discordance. The Wilcoxon signed rank test was used to compare the single-ROI ADC and the whole-tumor ADC for each subtype, for the two readers individually.

Because the numbers of angiomyolipoma, oncocytoma, and unclassified RCC lesions were small, the exact Wilcoxon rank sum test, based on the method proposed by Mehta and Patel [27] was used to compare the mean ADC values of clear cell RCC and every other tumor subtype. No multiple-comparison adjustment was applied, given the hypothesis-generating

purpose of this study. Statistical significance was denoted by $p < 0.05$. Statistical analyses were performed using SAS software (version 9.2, SAS Institute).

Results

Patient and Tumor Characteristics

A total of 117 patients (mean age, 60 years; range, 17–83 years) with 122 renal cortical lesions were included in the study. Eighty-two of the patients (70%) were men (mean age, 61 years; age range, 31–80 years), and 35 (30%) were women (mean age, 57 years; age range, 17–83 years). On the basis of findings from histopathologic evaluation, seven of the 122 tumors (5.7%) were characterized as angiomyolipoma, four (3.3%) as oncocytoma, 79 (64.8%) as clear cell RCC, 12 (9.8%) as chromophobe RCC, 12 (9.8%) as papillary RCC, and eight (6.6%) as unclassified RCC. Mean tumor size was 7.2 cm (range, 1.0–20.5 cm). Detailed patient information, including tumor stage, is provided in Table 1.

Interreader Agreement on Apparent Diffusion Coefficient Measurements

Overall interreader agreement on measured ADC values reached a CCC of 0.756 (95% CI, 0.679–0.832) for single-ROI assessment. It improved across all tumor types in whole-tumor assessment (CCC, 0.982 [0.976–0.988]).

Apparent Diffusion Coefficient Values in the Differentiation of Renal Cortical Tumors

For readers 1 and 2, measured ADC values for clear cell RCCs in both single-ROI assessment (2.19 and $2.08 \times 10^{-3} \text{ mm}^2/\text{s}$) and whole-tumor assessment (2.30 and $2.32 \times 10^{-3} \text{ mm}^2/\text{s}$) were statistically significantly higher than those for chromophobe RCCs (for single-ROI assessment, 1.31 and $1.29 \times 10^{-3} \text{ mm}^2/\text{s}$; for whole-tumor assessment, 1.59 and $1.53 \times 10^{-3} \text{ mm}^2/\text{s}$), papillary RCCs (for single-ROI assessment, 1.39 and $1.47 \times 10^{-3} \text{ mm}^2/\text{s}$; for whole-tumor assessment, 1.51 and $1.47 \times 10^{-3} \text{ mm}^2/\text{s}$), or unclassified RCCs (for single-ROI assessment, 1.66 and $1.55 \times 10^{-3} \text{ mm}^2/\text{s}$; for whole-tumor assessment, 1.70 and $1.73 \times 10^{-3} \text{ mm}^2/\text{s}$) ($p < 0.05$, for all comparisons) (Tables 2 and 3 and Figure 2). For the two readers, the ADC values for oncocytomas were similar to those for clear cell RCC on both single-ROI assessment (2.14 and $2.32 \times 10^{-3} \text{ mm}^2/\text{s}$) and whole-tumor assessment (2.38 and $2.24 \times 10^{-3} \text{ mm}^2/\text{s}$). The statistical significance of the difference between ADC values in clear cell RCC and oncocytoma could not be analyzed because of the small number of oncocytomas ($n = 4$).

Measured ADC values of clear cell RCC were also higher than those of angiomyolipoma; however, the difference was only statistically significant in whole-tumor assessment (Tables 2 and 3). In the clear cell RCC group, there was a statistically significant difference between ADC values from the single-ROI and whole-tumor assessments of both readers (Table 2). However, the ranges of ADC values measured using the two approaches overlapped greatly, and the absolute difference was small (for reader 1, $0.11 \times 10^{-3} \text{ mm}^2/\text{s}$; for reader 2, $0.24 \times 10^{-3} \text{ mm}^2/\text{s}$).

Discussion

This study investigated the potential usefulness of DWI in differentiating clear cell RCC from other renal cortical tumors, testing the hypothesis that the ADC values of clear cell RCC differ significantly from those of other malignant RCC subtypes and benign tumors. Assessment of ADC values was conducted using a single ROI in a nonnecrotic tumor area and was also performed using whole-tumor assessment, with the latter method generally having superior interreader agreement. For both types of assessment, ADC values of clear cell RCC were found to be statistically significantly higher than those of other malignant RCC subtypes (chromophobe, papillary, and unclassified RCC). This is an unusual finding because most malignant tumors tend to show more restricted diffusion with lower ADC values. However, our findings also suggest that DWI may not be useful in differentiating clear cell RCC from oncocytoma because the ADC values of the small number of oncocytomas in our study were all within the range of ADC values of clear cell RCC. We also found higher ADC values in clear cell RCC than in angiomyolipoma, although the difference was only statistically significant in whole-tumor assessment. This finding may have been a result of the fact that all the angiomyolipomas in our study were surgically resected and did not have typical imaging features (such as gross fat) that usually aid in the distinction of these tumors and that may render resection unnecessary [28].

The understanding of RCC has changed considerably during the past 2 decades. The discovery of separate tumor subtypes with distinctively different genomic profiles, metastatic potential, and outcome has supported new emerging concepts that help to exclude resection for a selected group of patients (e.g., elderly and frail patients) in favor of active surveillance or focal ablation. However, it is important to correctly characterize a newly discovered renal cortical tumor before a treatment approach is selected. To address this growing clinical need and to assist in surgical planning (radical vs kidney-sparing approaches), various cross-sectional imaging modalities (e.g., CT, ultrasound, and MRI) have been assessed. Although some statistically significant differences between the parameters used for imaging of clear cell RCC and other renal cortical tumors have been found, the ranges of the reported imaging parameters have overlapped substantially, making it difficult to apply the study findings to clinical practice.

DWI could be of particular value for characterizing renal cortical neoplasms, because it allows visualization and quantification of cell density, the integrity of cell membranes, and tissue architecture, and because its ability to assess the tumor microenvironment has already been proven to be of value in other areas of oncologic imaging. Furthermore, no application of contrast agent is necessary for its acquisition, which is an additional benefit for patients with impaired renal function.

Several groups have investigated the use of DWI for characterization of renal cortical neoplasms. To date, analyses have been based on either a single ROI or a limited number of ROIs in each tumor [12–21, 24]. It is uncertain whether a single ROI drawn in a heterogeneous lesion can be considered representative of a whole tumor. This issue is of particular concern for RCC, in which areas of macro- and microscopic necrosis and hemorrhage are abundant. Furthermore, many previous studies included smaller numbers of

patients [13, 29] or a limited number of histopathologic subtypes [13, 19]. Other studies have based their conclusions on comparisons between malignant and benign lesions [15] or have included all nonclear cell RCC subtypes in one group for statistical analysis [16, 17, 29], thus disregarding the broad clinical and biologic differences between the subtypes.

Wang et al. [19] examined 85 malignant RCCs (49 clear cell, 22 papillary, and 14 chromophobe RCCs) but did not include benign tumors in their study. They found that the mean ADC for clear cell RCC was significantly higher than that for papillary or chromophobe RCC, which is in accordance with our findings. However, our study expanded on that of Wang and colleagues in several ways. In our study, analysis was performed by two independent readers, with the use of both single-ROI and whole-tumor assessment, whereas Wang and colleagues relied on a single reader drawing a single ROI on the tumor. Because we included a broader range of RCC subtypes in our study, we were able to show that the ADC values for clear cell RCC were also significantly different from those associated with rare unclassified RCC, a category that comprises all tumors that cannot be categorized as any other subtype [30] and that therefore contains tumors of both high and low malignant potential. Furthermore, the inclusion of a small number of benign oncocytomas in our study allowed us to compare their ADC values to those for clear cell RCC. Our finding that the ADC values for oncocytomas and clear cell RCCs were similar is consistent with other studies that have revealed difficulties in distinguishing these two tumor subtypes with the use of other imaging approaches [10, 31].

In contrast to our study, an investigation by Taouli et al. [18] found significantly higher ADC values in oncocytomas than in a group of solid RCCs (which included clear cell, chromophobe, papillary, and unclassified RCC). The explanation for this discrepancy between their findings and ours might lie in the smaller number of tumors in their study (28 RCCs, of which 20 were solid RCCs) and that their sample included more papillary RCCs ($n = 12$) than clear cell RCCs ($n = 11$). Given the relatively low ADC values of papillary RCCs, the inclusion of all RCCs in one group for statistical analysis might have made the distinction of RCC from oncocytoma possible in their study population.

The underlying biologic causes for our finding of higher ADC values in clear cell RCC than in other malignant RCC subtypes remain unclear. At a b value of 500 s/mm², the influence of the perfusion fraction on ADC values is relatively low but not totally eliminated. Therefore, it could be hypothesized that strongly increased blood perfusion and intratumoral angiogenesis, as found in clear cell RCC [32], could contribute to the high ADC values in clear cell RCC. This hypothesis is supported by the results of preliminary studies [22, 33] that used intravoxel incoherent motion imaging to assess tumor perfusion and also reported higher values for perfusion parameters in clear cell RCC. However, these hypotheses need to be investigated in future studies.

In our study, whole-tumor assessment resulted in better interreader agreement than did single-ROI analysis. In the clear cell RCC group, a statistically significant difference between the two approaches was found for both readers; however, the great overlap between generated ADC values from both approaches limits the importance of this finding for clinical routine care.

Our study had a number of limitations. Although, compared with prior preliminary studies, we included a larger group of patients with various RCC subtypes, the number of benign lesions in our surgical cohort was still small. Therefore, our findings regarding the differentiation of RCC from benign tumors will need to be validated by larger, ideally prospective, studies. Furthermore, there was some overlap among the ranges of ADC values of clear cell RCC and other types of renal cortical tumors in our study, which makes it difficult to apply the findings to individual patients. Our findings are especially unlikely to aid the differentiation of clear cell RCC from oncocytoma. Future studies that possibly combine DWI with additional modalities of multiparametric MRI (dynamic contrast-enhanced and chemical-shift sequences) are therefore needed to achieve a better preoperative characterization of renal cortical lesions in these patients. However, by alerting radiologists to the high ADC values found in clear cell RCC, our findings should help in the characterization of renal cortical lesions. In addition, because of the retrospective nature of our study, we could not account for slight differences in MRI parameters. Finally, even though our results show that assessment of renal cortical lesions benefits from whole-tumor ADC analysis, this method requires increased time and effort when compared with single-ROI analysis. In the future, this disadvantage could be lessened by the development of dedicated software solutions that help to segment the tumor.

In summary, clear cell RCC had significantly higher ADC values than did chromophobe, papillary, or unclassified RCC. This finding could provide additional diagnostic information to help differentiate among malignant RCC subtypes. However, because measured ADC values were similar in clear cell RCC and oncocytoma, ADC analysis may not lessen the challenge of differentiating between those two tumor subtypes. Whole-tumor ADC assessment of renal cortical tumors allows superior interreader agreement compared with analysis based on a single ROI alone.

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Fig. 1. Clear cell renal cell carcinoma (RCC)

A–D, Centrally necrotic clear cell RCC in 48-year-old man (**A** and **B**) and heterogeneous but solid clear cell RCC in 55-year-old woman (**C** and **D**) are seen on contrast-enhanced T1-weighted fat-saturated images (**A** and **C**). On DWI apparent diffusion coefficient maps (**B** and **D**), two different ROIs were used in whole-tumor analysis (*red outline*), with same procedure performed on all slices with visible tumor, and in single-ROI analysis (*yellow outline*). ROI used for single-ROI analysis excluded necrotic areas.

Fig. 2.

Apparent diffusion coefficient (ADC) values (expressed as millimeters squared per second) for renal cortical tumors, as derived from single-ROI and whole-tumor assessments performed by both readers. Figure shows median value (*line in box*); interquartile range (*height of box*); lowest and highest data points still within 1.5 times interquartile range (*whiskers*), outliers (*circles*), and extreme outliers (more than three times interquartile range) (*asterisks*). RCC = renal cell carcinoma.

TABLE 1**Patient and Renal Cell Carcinoma (RCC) Characteristics**

Characteristic	Value
Sex, no. (%) of patients	
Female	35 (30)
Male	82 (70)
All	117 (100)
Tumor type, no. (%) of patients	
Angiomyolipoma	7 (5.7)
Oncocytoma	4 (3.3)
Clear cell RCC	79 (64.8)
Chromophobe RCC	12 (9.8)
Papillary RCC	12 (9.8)
Unclassified RCC	8 (6.6)
All	122 (100)
Tumor category of RCC, no. (%) of patients	
pT1	35 (31.5)
pT2	11 (9.9)
pT3	65 (58.6)
pT4	0
Fuhrman grade for clear cell RCC, no. (%) of individuals	
1	2 (2.5)
2	19 (24.1)
3	41 (51.9)
4	17 (21.5)
Age (y), mean $\pm$ SD	60.0 $\pm$ 12.1
Tumor size (cm), mean $\pm$ SD	
Angiomyolipoma	4.4 $\pm$ 3.8
Oncocytoma	4.35 $\pm$ 1.65
Clear cell RCC	7.42 $\pm$ 3.61
Chromophobe RCC	10.12 $\pm$ 5.27
Papillary RCC	5.55 $\pm$ 5.61
Unclassified RCC	6.38 $\pm$ 4.29
All	7.16 $\pm$ 4.19

TABLE 2
Apparent Diffusion Coefficient (ADC) Values According to Histopathologic Tumor Type

Assessment and Reader	Angiomyolipoma (n = 7)	Oncocytoma (n = 4)	Clear Cell RCC (n = 79)	Chromophobe RCC (n = 12)	Papillary RCC (n = 12)	Unclassified RCC (n = 8)
Single ROI						
Reader 1	1.78 (1.21–3.16)	2.14 (1.69–2.53)	2.19 (0.98–4.14)	1.31 (0.80–3.61)	1.39 (0.81–2.34)	1.66 (0.82–2.45)
Reader 2	1.93 (1.20–3.05)	2.32 (1.66–2.50)	2.08 (0.76–3.21)	1.29 (0.66–3.59)	1.47 (0.80–2.52)	1.55 (0.60–2.71)
Whole tumor						
Reader 1	1.85 (1.40–2.76)	2.38 (2.17–2.50)	2.30 (1.03–3.06)	1.59 (0.91–3.28)	1.51 (0.83–2.61)	1.70 (0.89–2.72)
Reader 2	2.00 (1.20–2.90)	2.24 (2.18–2.45)	2.32 (1.07–3.18)	1.53 (0.93–3.28)	1.47 (1.01–2.62)	1.73 (0.74–2.75)
<i>p</i> , single-ROI vs whole-tumor assessments						
Reader 1	0.578	0.250	0.001	0.151	0.083	0.109
Reader 2	0.938	0.875	< 0.001	0.266	0.151	0.055

Note—Except for *p* values, data are median (range) of ADC values ($\times 10^{-3}$ mm²/s). RCC = renal cell carcinoma.

TABLE 3

Comparison of Apparent Diffusion Coefficient Values for Clear Cell Renal Cell Carcinoma (RCC) and Other RCC Histopathologic Types, Determined by Use of Exact Wilcoxon Rank Sum Test

Assessment and Reader	Angiomyolipoma vs Clear Cell RCC	Chromophobe RCC vs Clear Cell RCC	Papillary RCC vs Clear Cell RCC	Unclassified RCC vs Clear Cell RCC
Single ROI				
Reader 1	0.1401	0.0001	< 0.0001	0.0063
Reader 2	0.3271	0.0001	0.0001	0.0119
Whole tumor				
Reader 1	0.0067	< 0.0001	< 0.0001	0.0025
Reader 2	0.0283	< 0.0001	< 0.0001	0.0021

Note—All data are *p* values. No test involving oncocytoma was performed because of the small sample size ($n = 4$).