A Radiology-pathological Correlation of Renal Cell Carcinoma in a Tertiary Care Hospital - A Retrospective Study

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Abstract

Introduction: This study was conducted to understand the clinical algorithm of renal cell carcinoma (RCC). Correlation was done by a clinical presentation with radiological features and histopathology of RCC. The stress upon to understand the necessity for a team approach between clinician, radiologist, and pathologist and vice versa is emphasised.

Aim: The aim of this study was to correlate the histopathology of RCC with the radiological features.

Materials and Methods: The total number of renal tumors studied during the 8-year period was 45 cases, of which 25 cases were diagnosed by histopathology as various types of RCC conclusively. This is a retrospective study of renal tumors, diagnosed by histopathology as various types of RCC. All the relevant clinical data of the patients were searched from the ward records. The various radiological features were collected.

Results: The total number of renal tumors studied during the 8-year period was 45 cases, of which 25 cases were diagnosed by histopathology as various types of RCC conclusively. Magnetic resonance imaging provides molecular information with regard to RCC and potentially aid in biopsy planning. The total cases reported in the department are 25 cases out of which 16 cases are attending follow-up after 3 years.

Conclusion: The Fuhrman grading of RCC correlated grading of RCC. Pre-operative radiological classification can be used as a supplement to the histopathological grading. RCC needs correlation between radiologist, pathologist, and clinician.

Key words: Chromophobe renal cell carcinoma, Clear cell renal cell carcinoma, Magnetic resonance imaging, Multidetector computed tomography, Papillary renal cell carcinoma, Treatment protocols, Tumor staging (TNM)

INRODUCTION

Representing 2-3% of adult cancers, renal cell carcinoma (RCC) accounts for 90% of renal malignancies and is the most lethal neoplasm of the urologic system. RCC is a kidney cancer that originates in the lining of the proximal convoluted tubule, the 2004 World Health Organization Classification of adult renal tumors stratifies RCC into several distinct histologic subtypes of which clear cell, papillary, and chromophobe tumors account for 70%, 10-15%, and 5%, respectively. RCC accounts for 90% of adult renal malignancies and is the most lethal of all urologic cancers.¹ ¹ RCC is not a single entity but rather a heterogeneous group of neoplasms with varying histological findings, cytogenetic abnormalities, biologic behavior, prognosis, and response to therapy.² ¹⁴ Chromosome 3p deletions are found in up to 96% of clear cell RCCs including somatic inactivating mutations of the von Hippel–Lindau (VHL) gene.³ ¹ⁱ,¹² Cytogenetic abnormalities are associated with the papillary subtype include trisomies of chromosomes 3, 7, 12, 16, 17, and 20, c-MET mutations, and loss of the Y chromosome.³ ¹¹,¹³,¹⁴ Cytogenetic abnormalities associated with chromophobe RCC include loss of multiple chromosomes such as 1, 2, 6, 10, 13, 17, and 21.¹⁵ The clear cell subtype shows a less favourable outcome compared with papillary and chromophobe subtypes, and is more likely to be symptomatic, present at an advanced stage, and show a
greater propensity to metastasize.\textsuperscript{1,4,6,8,9,11,16} The 5-year survival rate is 44-69\% in clear cell tumors, 82-92\% in papillary tumors, and 78-92\% in chromophobe tumors.\textsuperscript{6,10,17} In advanced disease, a tailored management approach is recommended as the effectiveness of systemic therapy including the specific regime used may be influenced by the RCC subtype.\textsuperscript{3,18,25} Studies have suggested that clear cell, papillary, and chromophobe subtypes can be differentiated non-invasively on imaging.\textsuperscript{1} Studies have also found that RCCs that develop in patients with end-stage renal disease tend to be less aggressive than RCCs that occur in the general population.\textsuperscript{30-32} Hereditary RCCs account for 4\% and show a predilection toward early onset, bilaterality, and multicentricity.\textsuperscript{32} Around 25-60\% of VHL patients develop RCC with the risk of metastasis related to tumor size.\textsuperscript{33-35} Birt–Hogg–Dube (BHD) syndrome, an autosomal dominant condition caused by mutations in the folliculin gene, predisposes to cutaneous tumors, oncocytomas and clear cell, papillary, and chromophobe RCCs.\textsuperscript{33,36} Recently, it has been discovered that patients with hereditary succinate dehydrogenase mutations are at risk of developing aggressive early-onset RCCs in addition to pheochromocytomas and paraganglioma.\textsuperscript{36} Most RCCs are asymptomatic and discovered as unexpected findings on imaging performed for unrelated clinical indications.\textsuperscript{37,40} The classic triad of a palpable mass, flank pain, and hematuria is found in 6-10\% and portends a more aggressive histology and advanced disease.\textsuperscript{41,42} Clear cell RCC typically shows a heterogeneous consistency (secondary to necrosis, cystic change, or hemorrhage) has high signal intensity on T2-weighted magnetic resonance imaging (MRI), and is hypervascular on dynamic contrast-enhanced (DCE) computed tomography or MRI examinations. Most papillary RCCs (PRCC) are detected while at a low grade and small size, show low signal intensity on T2-weighted MRI, and are hypovascular following contrast administration. Chromophobe RCCs may have a homogeneous solid appearance even when large and may exhibit a central stellate scar and spoke-wheel enhancement. Clear cell RCC typically exhibits exophytic growth and has a tendency to be heterogeneous due to intratumoral necrosis, cystic change, or hemorrhage. Interruption of the tumor capsule has also been correlated with high tumor grade.\textsuperscript{43} Cystic PRCCs may show hemorrhagic fluid content and internal mural nodules or papillary projections while cystic clear cell RCCs typically show clear fluid content and irregular walls and septations.\textsuperscript{44} Chromophobe RCC tends to appear well-circumscribed and homogeneous (cystic change and necrosis are uncommon) even when large and perinephric infiltration and vascular involvement (<4\%) are rare.\textsuperscript{31} Most PRCCs demonstrate low T2 signal intensity.\textsuperscript{45,46} In contrast, most clear cell RCCs show high T2 signal intensity.\textsuperscript{11,47,48} Several preliminary studies have shown encouraging results in utilizing diffusion-weighted imaging (DWI) for characterizing RCCs into its main subtypes as well as into high-grade and low-grade tumors.\textsuperscript{49-52} DWI has been used to differentiate various subgroups of renal masses. MRI is also useful for imaging renal vein and IVC tumor thrombus and the rostral extension (important in pre-operative planning). The presence of enhancement in the thrombus is able to distinguish between bland and tumor thrombus.

Fuhrman et al. Grading of RCC
Specifically, grade I tumors consist of cells with small (approximately 10 mm), round, uniform nuclei with inconspicuous or absent nucleoli; grade II tumors have larger nuclei (approximately 15 mm) with irregular morphology and small nucleoli when examined under high power (400 magnification); grade III tumors have even larger nuclei (approximately 20 mm) with irregular outlines and large, prominent nucleoli that are evident even at low power (100 magnification); and grade IV tumors differ from grade III lesions in that they contain bizarre, multilobed nuclei, and heavy chromatin clumps.

The staging of RCC is the most important factor in predicting its prognosis. Staging can follow the TNM staging system, where the size and extent of the tumour (T), involvement of lymph nodes (N), and metastases (M) are classified separately. Furthermore, it can use overall stage grouping into stage I-IV, with the 1997 revision of AJCC described (Table 1).\textsuperscript{52}

Surgical and Further Management
Stage IA
Partial nephrectomy is a widely accepted treatment for RCC tumors of <4 cm in diameter. Nephron-sparing partial nephrectomy - with the objective being the complete surgical extirpation of the tumor while retaining sufficient healthy tissue for adequate renal function - is the preferred treatment option for stage IA. Over the past decade, the clinical indications for partial nephrectomy have been expanded to include most patients with low-stage tumors as studies have demonstrated that partial nephrectomy is as effective a therapeutic option as radical nephrectomy with comparable rates of tumor-free survival and overall survival.

Stage IB
The NCCN recommends that either partial nephrectomy or radical nephrectomy be performed for stage IB tumors.\textsuperscript{2} Both techniques show comparable oncologic control.

Stage II and III
The NCCN recommends that radical nephrectomy be performed for stage II and III tumors.\textsuperscript{2} Routine adrenalectomy and lymphadenectomy is not advocated in
the absence of radiologic disease at these sites as it does not improve survival. A laparoscopic approach is favored for stage II tumors while stage III tumors are usually treated by an open approach. Baseline abdominal computed tomography (CT) or MRI within 3-6 months, then CT, MRI, or US every 3-6 months for at least 3 years and then annually up to 5 years, (2) baseline chest CT within 3-6 months after surgery with continued imaging (CT or chest X-ray) every 3-6 months for at least 3 years and then annually up to 5 years.

### Stage IV
Renal cell cancers are typically treated with both local and systemic therapy. Local therapy consists of surgery to remove the entire affected kidney and any surrounding cancer. The surgery for Stage IV renal cell cancer is called a radical nephrectomy and involves removing the entire affected kidney, the attached adrenal gland, and any adjacent fat and involved lymph nodes or major blood vessels. Systemic therapy is directed at destroying cancer cells throughout the body and may include chemotherapy, targeted therapy, or immunotherapy. A randomized trial by Motzer et al. involving 750 patients with metastatic clear cell RCC showed that patients treated with sunitinib had longer progression free survival and overall survival compared with patients treated with interferon-1. Several studies have suggested that vascular endothelial growth factor (VEGF)-TKIs may be less effective in treating papillary and chromophobe RCCs compared with clear cell RCC. Potential agents include temsirolimus, sorafenib, sunitinib, pazopanib, axitinib, everolimus, bevacizumab, or erlotinib. Preliminary studies have suggested that temsirolimus has efficacy in treating PRCC. The NCCN guidelines for stage 4 patients are as follows: (1) Baseline abdominal computed tomography (CT) or MRI within 3-6 months, then CT, MRI, or US every 3-6 months for at least 3 years and then annually up to 5 years, (2) baseline chest CT within 3-6 months after surgery with continued imaging (CT or chest X-ray) every 3-6 months for at least 3 years and then annually up to 5 years.

### Aim
The aim of this study was to correlate the histopathology of RCC with the radiological features.

### MATERIALS AND METHODS
The total number of renal tumors studied during the 8-year period was 45 cases, of which 25 cases were diagnosed by histopathology as various types of RCC conclusively. This is a retrospective study of renal tumors, diagnosed by histopathology as various types of RCC. All the relevant clinical data of the patients were searched from the ward records. The various radiological features were collected. The clinical features examined included age, gender, smoking history, recent onset hypertension, performance status, and presenting symptoms. A comprehensive health checkup on general conditions were taken and stored in the computer server.

### RESULTS
Clear cell carcinoma was the most reported case and 16 cases were reported, other tumors were papillary carcinoma and chromophobe carcinoma in the study covering 8-year period was 45 cases, of which 25 cases were diagnosed by histopathology as various types of RCC conclusively at Thoothukudi Medical College (Tables 2-5).
MRIT1 shows often heterogeneous due to necrosis, hemorrhage, and solid components T2 shows appearances depend on histology clear cell RCC with hyperintense signal and PRCC with hypointense signal. Histopathology section shows clear cell carcinoma with increased vascularity and clear cytoplasm with four grades of Fuhrman nuclei, PRCC showing papillary architecture and chromophobe renal carcinoma showing the neoplastic cells have a fine reticular cytoplasm and bland nuclei some of which have “raisinoid” appearance.

### Clear Cell RCC

Clear cell renal carcinoma is derived from the proximal convoluted tubule - frequency 60-70%. Most commonly affects male patients in their sixties and seventies. Microscopically, the tumor cells are large, the appearance of the cytoplasm ranging from optically clear, with sharply outlined boundaries. Clear cell renal carcinoma (conventional) arises from proximal convoluted tubules large uniform cells with clear cytoplasm highly vascular.

#### Table 2: Histopathological subtypes of RCC and corresponding grades

<table>
<thead>
<tr>
<th>Grades</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Types</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear cell</td>
<td>10</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Papillary</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Chromophobe</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>8</td>
<td>3</td>
<td>0</td>
<td>25</td>
</tr>
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RCC: Renal cell carcinoma

#### Table 3: Histopathological age, sex, distribution, and signs and symptoms in the subtypes of RCC

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<th>Tumor type</th>
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<th>M: F ratio</th>
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<td>Females range from 66 to 74 years of age and the age involved in male was 69-74 years</td>
<td>7:9</td>
<td>Ten patients had complaints of fever, hematuria, and flank pain. Two patients had hematuria. Four patients had incidental findings</td>
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<td>Females range from 60 to 74 years of age and the age involved in male was 64-75 years</td>
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<td>Chromophobe carcinoma</td>
<td>Females range from 62 to 70 years of age and the age involved in male was 75 years</td>
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RCC: Renal cell carcinoma

#### Table 4: Correlation study of RCC

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<td>Grade I</td>
<td>Renal cell cancer (RCC) lower pole of left kidney. Arterial (40 s) contrast-enhanced CT shows areas of tumor with low intake of contrast surrounded by areas of increased contrast uptake</td>
<td>Section studied shows clear cell carcinoma with features of tumor cells have mild nuclear pleomorphism with occasional small nucleoli and stippled chromatin typical of Fuhrman grade 2 nuclei</td>
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<td>An arterial phase CT will show enhancement of a tumor thrombus due to neovascularization of the tumour, as in this case</td>
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PRCC: Papillary renal cell carcinoma

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Based on nuclear features, these tumors are graded into four grades. Fuhrman grade 1 nuclei which are uniform, lack, or have inconspicuous nucleoli. The tumor cells have mild nuclear pleomorphism with occasional small nucleoli and stippled chromatin typical of Fuhrman grade 2 nuclei. Fuhrman grade 3 nuclei may be patchy, show moderate pleomorphism, and large nucleoli. The marked nuclear enlargement of grade 4 nuclei is obvious when compared to the scattered inflammatory cells. Prominent cherry-red nucleoli, with some nuclei harboring two or three nucleoli. Sixteen cases clear cell renal carcinoma of were reported. Nine cases involving females and seven case involving males. The age group involved in females range from 66 to 74 years of age and the age involved in male was 69-74 years.

**Clear Cell RCC**

The histopathology and radiology correlation was perfect in all the cases (Figures 1-8).

**PRCC**

Majority of tumors occur sporadically, but some may develop in members of families with hereditary. PRCC arises from distal convoluted tubules can be multifocal and bilateral most common form in dialysis-associated RCC type I is sporadic, generally good prognosis type II is inherited, bilateral, and multifocal. Microscopically, type I have papillae covered by a single layer of cuboidal or low columnar cells with scanty cytoplasm and low-grade nuclei and carry a better prognosis than type II tumors. Microscopically, type II are of a higher nuclear grade and contain more than one layer of cells with abundant eosinophilic cytoplasm. Six cases papillary cell renal carcinoma of were reported. Three cases involving females and three case involving males. The age group involved in females range from 60 to 74 years of age and the age involved in male was 64-74 years.

### Table 5: Final outcome of the study

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Surgery done</th>
<th>Cure rate measured after 3 years (%)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell renal carcinoma</td>
<td>Ten cases were stage I. Four cases were stage II. Two cases were stage III. Partial nephrectomy was done treatment for RCC tumors of&lt;4 cm in diameter. Partial nephrectomy or radical nephrectomy was done for stage IB tumors. Radical nephrectomy be performed for stage II and III tumors</td>
<td>75</td>
<td>Eleven cases attend regular follow-up. One case died of multiple organ failure</td>
</tr>
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<td>PRCC</td>
<td>Three cases were stage I. Two cases were stage II. One case was in stage III. Partial nephrectomy was done treatment for RCC tumors of&lt;4 cm in diameter. Partial nephrectomy or radical nephrectomy was done for stage IB tumors. Radical nephrectomy be performed for stage II and III tumors</td>
<td>50</td>
<td>Three cases are attending the follow-up</td>
</tr>
<tr>
<td>Chromophobe RCC</td>
<td>One case were stage I. Two cases were stage II. Partial nephrectomy was done treatment for RCC tumors of less than 4 cm in diameter. Radical nephrectomy was done for stage IB tumors. Radical nephrectomy be performed for stage II</td>
<td>66</td>
<td>Two cases are attending the follow-up</td>
</tr>
</tbody>
</table>

**Figure 1:** CT scan shows heterogeneously enhancing mass at the upper pole of the right kidney after administration of contrast

**Figure 2:** Section studied shows small uniform nuclei with evenly distributed chromatin and the absence of nucleoli, all of which are features of Fuhrman grade 1 nuclei
Figure 3: Renal cell cancer (RCC) lower pole of left kidney. Arterial (40sec) contrast enhanced phase.

Figure 4: Section studied shows clear cell carcinoma with features of Fuhrman grade 2 nuclei, typical of Fuhrman grade 2 nuclei.

Figure 5: An arterial phase CT will show enhancement of a tumour thrombus due to neovascularisation of the tumour, as in this case.

Figure 6: Section studied shows clear cell carcinoma with features of Fuhrman grade 3 nuclei, patchy, and show moderate pleomorphism and large nucleoli.

Figure 7: Left heterogenous enhancing mass in the mid-pole of the left kidney. This is well illustrated on this 4 phase renal angiogram CT study.

Figure 8: The marked nuclear enlargement of grade 4 nuclei is obviously seen. Prominent cherry-red nucleoli, with some nuclei harbouring two or three nucleoli.
PRCC, Type 1
The histopathology and radiology correlation was perfect in all the cases (Figures 9 and 10).

RCC (Type II Papillary)
The histopathology and radiology correlation was perfect in all the cases (Figures 11 and 12).

Chromophobe RCC: The frequency of incidence among overall RCC is chromophobe is derived from the cortical collecting duct. Chromophobe RCC has a much better prognosis than clear cell and PRCC, with 5-year survival rate of >90%. Most cases arise sporadically, whereas some familial cases are associated with BHD syndrome. Microscopically, the neoplastic cells have a fine reticular cytoplasm and bland nuclei some of which have “raisinoid” appearance. The cells have distinct, thick nuclear membranes, and perinuclear halos. Some cells have no nuclei in the plane of section due to the voluminous cytoplasm. This RCC arises from intercalated cells of collecting ducts, similar histologically to renal oncocytomas best prognosis. Three cases were reported. The age group involved in two females range from 62 to 70 years and the age involved in male was 75 years.

The histopathology and radiology correlation was perfect in all the cases (Figures 13 and 14).

Metastatic RCC
The most common sites for metastasis are the lymph nodes, lung, bones, liver, and brain. Average survival time in 2008 for the metastatic form of the disease was under a year and by 2013, this improved to an average of 22 months. From 2007 to 2013, seven
The PRCC and chromophobe RCC responded moderately to the treatment. The clear cell renal carcinoma did not respond to treatment to the expected mark.

Baseline abdominal CT or MRI within 3-6 months, then CT, MRI, or US every 3-6 months for at least 3 years and then annually up to 5 years; baseline chest CT within 3-6 months after surgery with continued imaging (CT or chest X-ray) every 3-6 months for at least 3 years and then annually up to 5 years.

**DISCUSSION**

RCC, in our study, the common subtypes were clear cell RCC, PRCC, and chromophobe RCC were the common subtypes observed. The PRCC and chromophobe RCC responded moderately to the treatment. The total cases reported in the department are 25 cases out of which 16 cases are attending follow-up after 3 years. The clear cell renal carcinoma did not respond to treatment to the expected mark. RCC is not a single uniform entity but a group of related neoplasms in which the histologic findings, cytogenetic abnormalities, biologic behavior, and imaging appearances of the tumors are subtype dependent. The 3 main subtypes - clear cell, papillary, and chromophobe - can often be differentiated non-invasively based on characteristic radiologic appearances. Based on the hypothesis that the diffusion of water to and from the cells is highly dependent on the ratio of intracellular and extracellular space, DWI MRI scan is used to differentiate the tumor grades. Organ-sparing treatment can be entertained in selected cases. This ranges from adrenal sparing nephrectomy to partial nephrectomy, performed both open or laparoscopically. In addition, percutaneous radiofrequency or cryoablation (typically under CT guidance), which can be carried out with only local anesthetic and sedation, has been introduced in selected cases. Avastin is a targeted therapy that blocks a protein known as VEGF. Votrient is a targeted oral medication known as an angiogenesis inhibitor. Sutent is an oral multitargeted tyrosine kinase inhibitor that targets proteins responsible for stimulating cancer cell growth. 5-fluorouracil appears to be the most effective chemotherapeutic agent currently available for kidney cancer.

**CONCLUSION**

Imaging remains the primary tool for the detection and screening of RCC. Perfusion MRI and diffusion MRI play important roles in tumor characterization, prediction, and early detection of therapeutic response and used to differentiate the histology of renal masses in some new treatments have been approved specifically for metastatic RCC (sunitinib, temsirolimus, bevacizumab, sorafenib, everolimus, pazopanib, and axitinib). These new treatments are based on the fact that RCCs are very vascular tumors - they contain a large number of blood vessels. The drugs aim to inhibit the growth of new blood vessels in the tumors, hence slowing growth and in some cases reducing the size of the tumors. Paraneoplastic syndromes are seen in about 25% of RCC patients will develop a paraneoplastic syndrome. They are hypercalcemia (20%), hypertension (20%), and polycythemia: From erythropoietin secretion (~5%), Stauffer Syndrome: Hepatic dysfunction not related to metastases, feminization, and limbic encephalitis.

The prognosis is influenced by several factors, including tumor size, degree of invasion and metastasis, histologic type, and nuclear grade. The PRCC and chromophobe RCC responded moderately to the treatment. The clear cell renal carcinoma did not respond to treatment to the expected mark.
preliminary studies. DCE and perfusion MRI can also be used to estimate the morphologic grading of RCC. Histopathology provided the final diagnosis. The prognostic significance of tumor necrosis in clear cell RCC has been confirmed by other groups. More aggressive RCC tumors, which are likely to exhibit necrosis, also harbor increased numbers of tumor-infiltrating T-cells. Tumor necrosis has garnered increasing attention over the past few years, in part because a number of studies have now shown that tumor necrotic tissues can be successfully targeted to facilitate both external tumor imaging and to foster a therapeutic antitumoral response by the host. Coagulative tumor necrosis represents a significant prognostic marker for clear cell and chromophobe RCC. The landscape for RCC treatment has changed dramatically in recent years, with the addition of three new FDA-approved agents this year. This brings our arsenal to seven drugs: Interleukin-2, the VEGF receptor TKI’s sunitinib, sorafenib, and pazopanib, the VEGF neutralizing antibody bevacizumab in combination with interferon, and the mTOR inhibitors temsirolimus and everolimus. Pre-operative radiological classification can be used as a supplement to the histopathological grading. This study provides the importance of other medical faculty the surgeon, radiologist, and oncologist to work as a team for a successful outcome. We correlated the histopathological findings with radiological findings. This resulted in perfect correlation between the histopathology study and radiology study.

REFERENCES