Needle Core Biopsy of Renal Neoplasms: the Winnipeg Experience and Comparison with the Literature

by

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Abstract

Renal cell carcinoma is the seventh most common malignant neoplasm in the western countries. Renal tumour core biopsy is a procedure to provide histopathological information and guide treatment. The main objective of this study was to determine the diagnostic rate and accuracy of renal core biopsy in the diagnosis of renal cell carcinoma type, subtype, and nuclear grade. We also hypothesized that clear cell subtype and high grade cases would be more likely to undergo nephrectomy than any other subtypes and low grade cases. This study included 163 cases from 2007 to 2016. By comparing the renal biopsy pathology reports with the subsequent nephrectomy reports, the diagnostic rate was 84% and non-diagnostic rate was 9.2%. Histologic type and subtype were 100% concordant. The data from this study shows excellent accuracy of renal core biopsy in diagnosing histology subtypes. Therefore, the application of renal core biopsy should be expanded. However, histologic subtype and grade did not affect clinical decision making.

Acknowledgements

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

AJCC	American Joint Committee on Cancer
AMACR	α-methylacyl-CoA racemase
AUA	American Urological Association
CA IX	carbonic anhydrase IX
CK	cytokeratin
CT	Computed tomography
DSM	Diagnostic Services of Manitoba
EMA	epithelial membrane antigen
FG	French gauge
FNA	fine needle aspiration
GH	Grace Hospital
H&E	hematoxylin and eosin
HSC	Health Science Centre
IHC	immunohistochemistry
ISUP	International Society of Urological Pathology
MRI	magnetic resonance imaging
PET	Positron emission tomography
RCC	renal cell carcinoma
SBGH	St. Boniface General Hospital
UICC	Union for International Cancer Control
US	ultrasound
WHO	World Health Organization

1. Introduction

1.1. Renal cell carcinoma

In adults, the two most common renal malignant tumours are renal cell carcinoma (RCC) and urothelial carcinoma and of these two, RCC constitutes more than 90% of renal malignancies [1, 2]. In children, nephroblastoma or Wilms tumour is the most common [2]. The common types of benign kidney tumour are oncocytoma, angiomyolipoma and papillary adenoma [9].

RCC is defined as a group of carcinomas which originate from the epithelium of the renal tubules [1]. RCC, constituting 1% to 3% of all the malignant neoplasms of the internal organs, is the seventh most common malignant neoplasm in the western countries[3, 17]. North America and the Czech Republic have the highest incidence rate [2]. In Canada, the approximate incidence of RCC was 5900 cases and the death resulting from RCC was 1700 cases in 2012 [5]. Over the last few decades, the incidence of RCC in Canada and the United States has tended to increase steadily probably due to the incidental discovery through imaging technology [5, 10]. Evans et al, (2015) stated that of these unexpected findings, benign tumours comprise approximately 20-30% and malignant tumours, specifically RCC about 50-55% [15]. The RCC patients' age ranges from 40 to 75 and the individuals in their sixtieth and seventieth are mostly affected [1, 9, 10]. Males are usually 2 to 3 times more susceptible than females [1].

1.2. Etiology and clinical features of RCC

The main cause of renal malignancies is tobacco smoking, which has been found in 39% of male cases [1, 10]. Obesity, especially in females, is another factor that is positively related to RCC [1, 10]. Bergstrom's study, (2001) showed that the incidence of RCC is 2 times more likely when body mass index is greater than 29 kg/m^2 [1]. In addition to tobacco smoking and obesity, history of hypertension is the third factor that can increase the incidence of RCC, in which the diuretics or

renin could play a role [1, 10]. Some other medical conditions, such as chronic renal failure, acquired renal cystic disease and tuberous sclerosis can also increase the likelihood of developing RCC [2, 9, 10]. Further, a few environmental chemicals have been studied for potential carcinogenesis, such as arsenic, asbestos, pesticides and fungal toxins [1]. However, only arsenic has been confirmed to be carcinogenic [1]. Most of the RCC cases are acquired with a few being autosomal dominant familial, which is more common in young patients [9].

The classic symptoms are haematuria, pain and flank mass and only 5% of patients have all three symptoms [1, 10]. Of these three, haematuria is the most reliable one; however it does not occur continuously and is not easy to identify visually [9]. Thus, the tumour could be asymptomatic for a relatively long period until the tumour grows larger or metastasis occurs [1, 9, 10]. Approximately 40% of patients present with nonspecific symptoms, such as weight loss and abdominal pain [1]. RCC can also produce a variety of systematic symptoms as well as paraneoplastic syndromes, hypercalcemia, hepatic dysfunction and feminization or masculinization [9]. Half of the patients have an increased erythrocyte sedimentation rate and raised erythropoietin level [1]. One third of patients have normocytic anaemia, which may not result from haematuria [1]. One distinctive feature of RCC is that the tumour cells can metastasize to other organs even before the presence of renal or local symptoms [9]. RCCs commonly metastasize to lungs, bone, regional lymph nodes, liver, adrenal gland and brain, which are listed in order from the most frequent to the least frequent [9]. The 5 year survival rate of RCC patients is approximately 45% and increases to 70% when metastases are absent [9]. When the tumour cells are identified in the renal vein or perinephric fat, 5 year survival rate can decrease to 20% [9].

1.3. Imaging evaluation of RCC

Imaging plays a pivotal role in diagnosing renal tumour [5]. Computed tomography (CT) is the primarily utilized imaging technology for renal masses due to its staging accuracy being higher than 90% [5]. Plain CT is suitable for diagnosing benign lesions and contrast CT for malignant lesions [1, 5]. During the CT procedure, the contrast medium is injected and information regarding the masses can be provided, such as tumour size, lymph node involvement and any other organs involvement in the abdomen, thorax or even brain [5]. Besides CT, magnetic resonance imaging (MRI) is the second option for patients who are not suitable for CT and those who could be pregnant or have allergy to the contrast medium [5]. MRI and ultrasound (US) can be applied if the tumour masses extend into the inferior vena cava [5]. Positron emission tomography (PET) is not used as a primary tool to assess RCC; it can be applied when the tumour recurs [5].

Advances in imaging technology have allowed the identification and characterization of small renal masses, which are defined as less than 4 cm in greatest dimension [1, 5, 15]. Additionally, more renal tumours are being diagnosed incidentally when doing radiologic examinations for other conditions [3, 15, 17]. Currently, the incidental finding of RCCs or renal masses, especially small renal masses is an increasing trend with approximately 70% of renal masses being incidental finding [1, 3, 10, 13, 17]. Thus, the management of renal masses has changed as well [1, 3, 10, 13], as will be discussed in the “renal tumour biopsy” section.

1.4. Staging and grading of RCC

The TNM staging system guides clinicians in providing patients with appropriate treatment options [5]. In addition, TNM staging can predict prognosis for individual cases [5, 11]. The details of

the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) TNM staging are described as follows.

T stands for primary tumour and has TX, T0, T1, T2, T3 and T4 categories [1, 5, 11]. T1 and T2 are further divided into a and b subcategories and T3 is divided into a, b and c subcategories respectively [1, 5, 11]. In short, T1 and T2 are defined as tumour masses located within the kidney parenchyma [1, 5, 11]. In contrast, T3 and T4 are tumour masses extending beyond the kidney parenchyma and T4 has more extension than T3 [1, 5, 11]. N stands for regional lymph node invasion and has N0, N1 and N2 categories [1, 5, 11]. N0 does not have lymph node involvement while N1 or N2 does [1, 5, 11]. M stands for distant metastasis and has M0 and M1 categories [1, 5, 11]. M0 has no metastasis at all compared to the positive metastasis in M1 [1, 5, 11]. Therefore, staging I to IV can be determined according to the combined conditions of TNM. For example, stage I can be T1N0M0, stage II can be T2N0M0, stage III can be T1/T2N1M0 or T3N0/N1M0 and stage IV can be T4 any N M0 or any T any N M1[1, 5, 11].

Nuclear grade, as well as staging can provide prognostic information [1, 6, 11]. Currently, the commonly used grading systems are 4-tiered or 3-tiered and 4-tiered Fuhrman grading system has been the most common one in clinical practice [1, 6, 11]. The grading system focuses on the nuclei of the tumour cells and evaluates their size and shape [6]. The grading system uses the 10x objective and the details of 4-tiered grading system are described as follows. The nuclei in grade 1 have slightly more chromatin and the nucleoli are not visible [1, 11]. In grade 2, the chromatin has a granular appearance and the nucleoli are not obvious [1, 11]. Conversely, the nucleoli in grade 3 and 4 are easily recognized under the low power [1, 11]. The additional nuclear features of grade 4 include nuclear pleomorphism and increased chromatin as well as a sarcomatoid morphology[1, 11].

The diagnosis of grade is decided on the highest grade observed and when sarcomatoid dedifferentiation is observed, it clearly indicates grade 4 [1, 2, 6, 11].

Fuhrman grading system focuses on assessing 3 different aspects [8, 18, 20, 22, 23, 24]. Studies have shown that it is difficult to examine these 3 aspects at same time, especially when contradictory information is present [8, 22]. Due to the lack of clear or detailed grading criteria, high interobserver variation occurs [22, 23, 24]. Therefore, the prognostic utility of the Fuhrman system is questionable [8, 22]. In order to improve grading accuracy, the new International Society of Urological Pathology (ISUP) grading system was proposed in 2012 [15, 18]. The ISUP grading system assesses nucleolar prominence only and this parameter has shown to be prognostically significant in clear cell and papillary carcinomas [15, 22, 23].

1.5. Treatment management of RCC

On the basis of the staging, treatment options include conservative treatment or active surveillance, nephron sparing partial or traditional radical nephrectomy, and neoadjuvant or adjuvant treatments [5, 14, 16]. Active surveillance is defined as possible treatment or intervention at a later time with close clinical and imaging follow up [14]. Treatment options are based on three main factors: histopathologic diagnosis and stage of the renal mass, surgeon's viewpoint and the patient's individual condition and the final decision should balance above three factors [14, 16]. Generally, for pT1aN0M0, the patients can undergo short or long term active imaging follow-up when the tumour is stable [5]. When the tumour is growing, the surgery option could be considered [5]. In this case, partial nephrectomy is highly recommended and the advantage of this procedure is to prevent the loss of the renal function and possible chronic renal failure, leading to increased survival rate [5, 17]. In Canada, if the patients' health condition does not permit the surgery or the

tumour masses are identified on both sides, ablation treatment can be utilized [5, 15]. Ablation treatment is either radiofrequency or cryoablation, both of which are minimally invasive [15]. A renal biopsy is recommended to establish tumour diagnosis before performing the ablation procedure [5, 14].

For pT1bN0M0, partial nephrectomy is the current trend in clinical practice, while if the partial nephrectomy is not possible, the radical nephrectomy through laparoscope or abdomen-opening is the next option [5]. The treatment for pT2N0M0 is similar to pT1bN0M0 except the kidney preserving therapy is debatable and the current recommendation is for such procedures to be performed by experienced urologists only [5]. When the staging increases to pT3, treatment options should be discussed according to the extension of the tumour mass [5]. If the surgery option is considered, radical nephrectomy through laparoscope or abdomen-opening is preferable over partial nephrectomy [5]. The only treatment for pT4N0M0 is limited to surgical removal, including not only kidney but also nearby organs that tumour cells extend to [5]. Therefore, radical nephrectomy is recommended for more aggressive tumours, such as collecting duct carcinoma [15].

In the management of renal malignancies, neoadjuvant and adjuvant treatments are newly developed [5]. Neoadjuvant treatment is defined as treatment prior to scheduled surgery and the purposes are to reduce the tumour size to make it resectable, to reduce the possibility of a positive resection margin as well as to reduce the recurrence rate [5]. Adjuvant treatment is defined as treatment after surgery with complete surgical resection, and would apply to patients who have high Fuhrman grade, high T stage, and involvement of lymph nodes [5]. The common adjuvant treatments are radiotherapy, chemotherapy, immunotherapy and antiangiogenic therapy [5]. However, at present, both neoadjuvant and adjuvant therapies are experimental, and available only in clinical trials [5]. Advanced RCC is defined as non-resectable or metastatic and it is treated

primarily with newly developed drugs including tyrosine kinase and check point inhibitors [10, 21]. For clear cell RCC with metastasis, systemic therapy has been shown to improve the tumour outcome. On the basis of the limited studies on the management of non-clear cell RCC, the effectiveness of the targeted therapies has not been fully confirmed [35, 36]. In detail, non-clear cell RCC does not respond to either cytokine therapy or check point inhibitors. Antiangiogenic therapy seems to benefit a small number of patients, but more clinical trials should be conducted to verify the effectiveness [35, 36].

1.6. Histological classification of RCC

Pathologically, RCC is classified mainly on the basis of morphology, growth pattern, genetic features and cell of origin [2, 10]. The histological classification has an important role on predicting prognosis and treatment [3]. Advancements in basic science research and immunohistochemistry (IHC) technology have helped to expand the understanding of renal neoplasms [7]. According to 2016 World Health Organization (WHO)'s renal tumour classification, the main subtypes of RCC are clear cell, papillary, chromophobe, clear cell papillary, and the above four subtypes comprise approximately 95% of all the RCC cases [20]. The rare ones include, but are not limited to collecting duct, medullary, and unclassified RCC [2, 3]. In 2013, ISUP updated the classification by adding 5 new subtypes of renal neoplasm, for example clear cell papillary renal cell carcinoma [3, 7]. In addition, 3 new provisional or emerging entities are added as well, for example, thyroid –like follicular renal cell carcinoma [3, 7]. These entities were integrated into the WHO 2016 classification [20].

1.6.1 Clear cell RCC

Clear cell RCC is the most common subtype, constituting 70% to 75% of all RCC cases [3]. Five percent of the clear cell RCCs are related to inherited disorders, such as von Hippel-Lindau disease and tuberous sclerosis, and the remaining 95% are sporadic [3]. Clear cell RCC, originating from the proximal tubules, is so called due to the presence of malignant cells with clear and eosinophilic cytoplasm [1, 3]. Macroscopically, the tumour mass is usually solitary and can occur at any location of the renal cortex [1, 11]. More than 95% of cases have a unilateral mass, with less than 5 % involving both sides [1]. Grossly, the tumour mass is typically globular or bosselated with a golden yellow color because of abundant lipids in the cells [1, 11]. The tumour is usually well circumscribed from the adjacent kidney parenchyma and common complications include varied degree of necrosis, hemorrhage, cystic degeneration and calcification [1, 3, 11]. RCC is usually low grade when the mass is less than 2 cm [14]. When the tumour mass is greater than 4 cm, necrotic change is often present [3]. Extensive necrosis correlates with higher nuclear grade [3, 11]. The average tumour size is 7 cm in diameter and larger size is associated with the increased chance of metastasis [1]. Microscopically, tumour cells can form different architectural patterns, such as solid, alveolar or acinar structures and characteristically, a prominent microvascular network surrounds the tumour cells [1, 11, 15]. The microscopical features of clear cell RCC with grade 1 to 4 are shown in Figure 1.1 to 1.3.

Clear cell RCC has the tendency to invade the renal sinus and perinephric fat and further into the renal venous circulation [3]. As a result, lung, liver and bone are the common sites of metastases [1, 3]. An unusual feature of clear cell RCC is to metastasize to uncommon organs and this metastasis can occur more than ten years after the tumour detection [1]. Approximately half of the clear cell RCC cases are diagnosed as stages 1 and 2, 45% stage 3 and less than 5% stage 4 [1]. The

prognosis of clear cell RCC is usually worse than other two common subtypes: papillary and chromophobe RCCs [3]. The immunoprofile includes positive immunoexpression of low molecular weight cytokeratins: cytokeratins 8, 18, 19 (CK 8, 18, 19) and vimentin [1, 11].

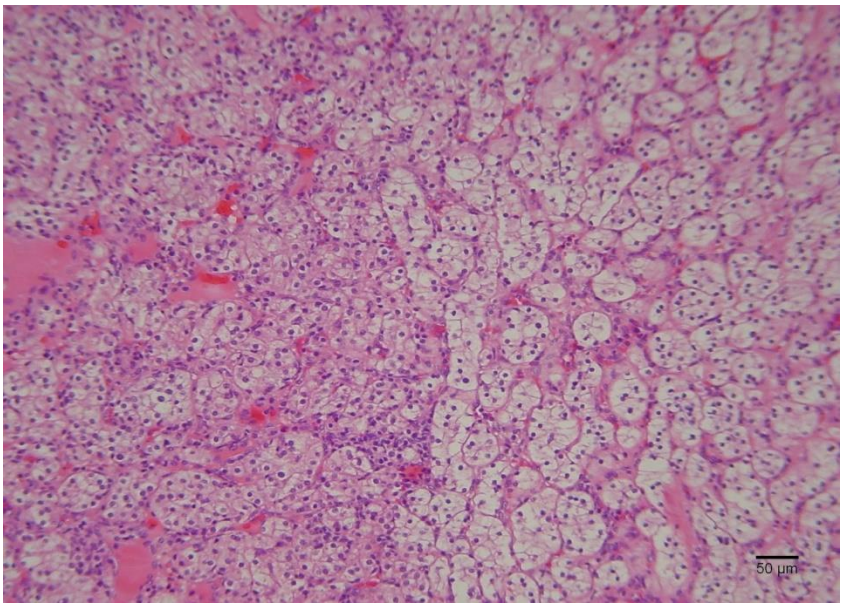

Figure 1.1. Clear cell RCC with grade 1 on right side and grade 2 on left side, x 100. The nuclei in grade 1 are round and have slightly more chromatin; and the nucleoli are not visible, as shown on right side. In grade 2, the chromatin has a granular appearance and the nucleoli are small and not obvious under the low power, as shown on left side. Image is courtesy of Dr. H. R. Wightman.

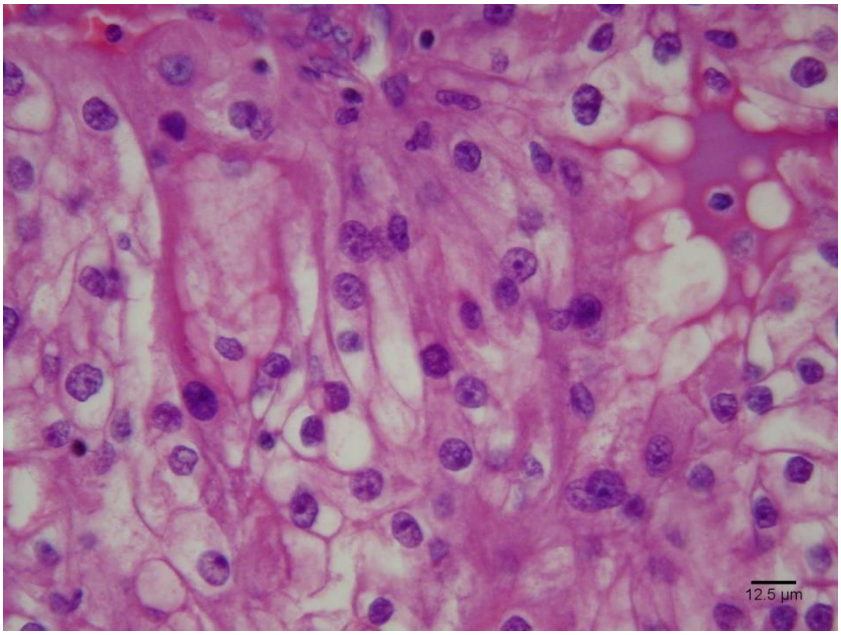

Figure 1.2. Clear cell RCC with grade 3, x 400. The nuclei have irregular shape. The nucleoli are large and easily recognized. Image is courtesy of Dr. H. R. Wightman.

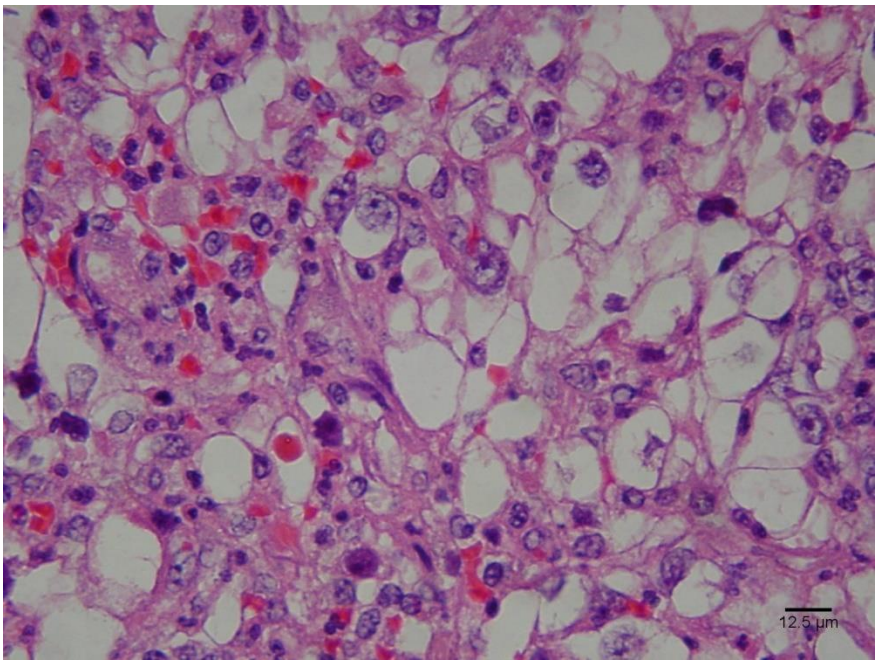

Figure 1.3. Clear cell RCC with grade 4, x 400. The nuclei have irregular shape with nuclear pleomorphism and increased chromatin. The nucleoli are large and easily recognized. Image is courtesy of Dr. H. R. Wightman.

1.6.2. Papillary RCC

Papillary RCC is the second most common subtype, constituting 10 -15 % of all RCC cases [1, 3, 11]. It could occur either genetically or sporadically [3]. The macroscopical features are similar to clear cell RCC except the slightly more common complications of hemorrhage, necrosis and cystic degeneration [1, 7]. Further, unlike the solitary and unilateral mass in clear cell RCC, bilateral or mutilfocal masses are more common in papillary RCC [1, 7, 10]. Microscopically, tumour cells form varied degree of papillary and tubular structures and the centre of the papilla contains fibrovascular tissue [1, 7, 11, 15].

On the basis of the biological, pathological features and clinical behaviour, papillary RCC has further subcategorized into two types: type 1 and type 2 [1, 3, 7, 15]. In type 1, papillae are formed and lined by one layer of small basophilic cells which have less cytoplasm but hyperchromatic nuclei, as shown in Figure 2.1 [1, 3, 7, 11]. In contrast, tumour cells of type 2 have abundant eosinophilic cytoplasm with higher nuclear grade, as shown in Figure 2.2 [1, 7, 11]. Type 2 usually has higher grade and stage than type 1 [1, 11]. Consequently, type 2 has a worse prognosis than type 1 [3, 11]. Five year survival rate can be as high as 84% for both types, and as low as 49% with sarcomatoid change [1]. The immuoprofile includes the positive CK 7, which is usually positive in type 1 [1, 7, 11]. In comparison with CK7 positivity in type 1, positive CK20 and E-cadherin are usually observed in type 2 [7].

1.6.3. Clear cell papillary RCC

Clear cell papillary RCC is a new entity proposed by ISUP in 2013 and added by WHO in 2016 [4, 20]. Macroscopically, clear cell papillary RCC is small in size and has a well circumscribed border and intact capsule [4, 7]. The characteristic golden yellow color of clear cell RCC may not

present in this entity, instead, the cut surface could be white tan or reddish brown [4]. Histologically, the tumour cells are usually low grade and nuclei are situated adjacent to the gland lumen [4, 7, 15]. In addition to the features of the nuclei, the cytoplasm is usually clear [8]. The above two features can help with the histological diagnosis [8]. According to the Crumley's review, (2013), metastasis has not been reported based on clearly diagnosed cases, suggesting a better prognosis than other RCC subtypes [4]. This may be better considered as a tumour of low malignant potential [7]. The immunoprofile includes positive CK7, carbonic anhydrase IX (CA IX) and high molecular weight cytokeratin, and negative expression include CD10 and α-methylacyl-CoA racemase (AMACR) [7, 8].

1.6.4. Chromophobe RCC

Chromophobe RCC constitutes approximately 5% of all renal malignancies [3, 11]. Chromophobe RCC, originating from the intercalated cells of collecting duct, is defined as large pale cells with a prominent cell membrane [1, 11]. Similar to the above two subtypes, chromophobe RCC also occurs either genetically or sporadically [1]. Morphologically, the mass is solid and well demarcated with homogeneously tan color prior to fixation and light grey color after fixation [1, 11]. Microscopically, tumour cells are polygonally shaped with transparent or granular cytoplasm and the nuclei are irregular with perinuclear clearance, as shown in Figure 3 [1, 11, 15]. Eighty-six percent of the cases are diagnosed as stages 1 and 2 and 14% as stage 3 [1]. Chromophobe RCC has an excellent prognosis of all the RCCs with the mortality rate being lower than 10% [1, 3]. However, if sarcomatoid change is identified, the prognosis will become much worse [3]. The immunoprofile includes diffusely positive CK7 and CD117, positive pan-cytokerain, lectins and epithelial membrane antigen (EMA), with EMA having positive expression diffusely [1, 11, 15]. The negative immunoexpressions are vimentin and CD 10 [1].

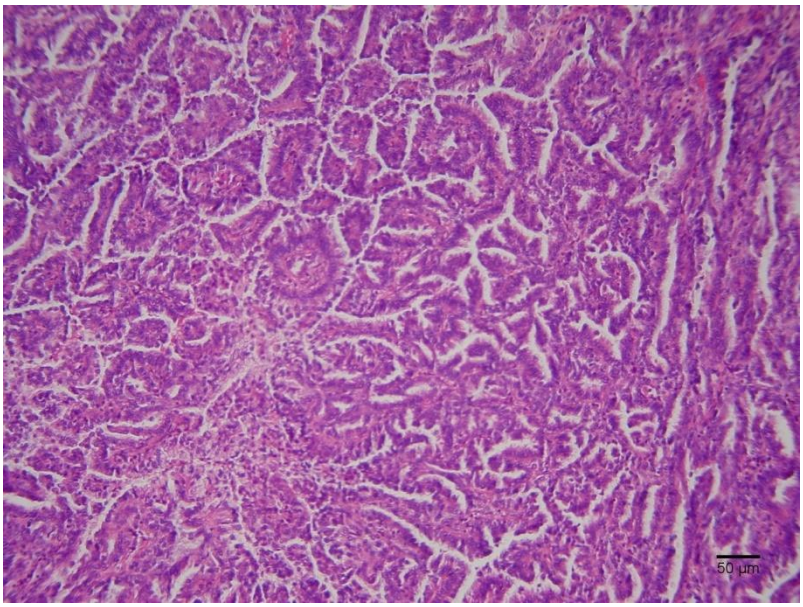

Figure 2.1. Papillary RCC type 1 with grade 2, x 100. In type 1, papillae are formed and lined by one layer of small basophilic cells which have less cytoplasm but hyperchromatic nuclei. Image is courtesy of Dr. H. R. Wightman.

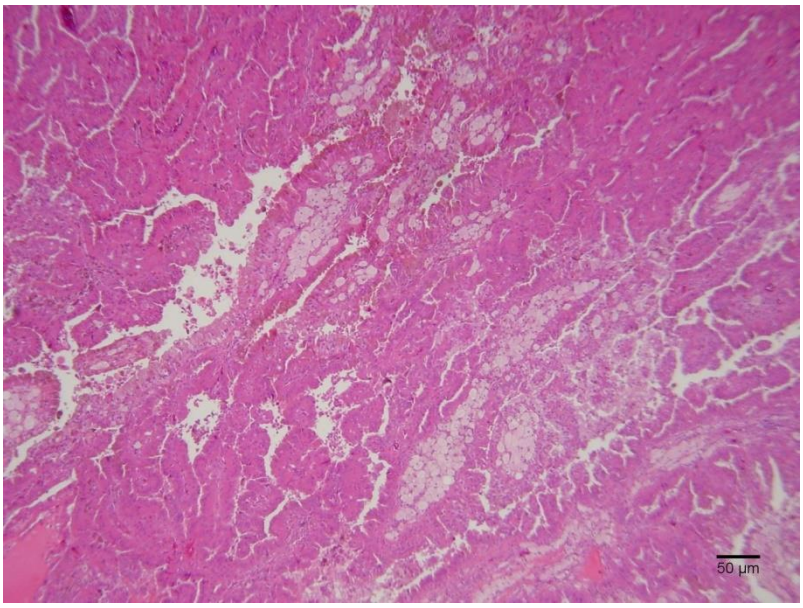

Figure 2.2 Papillary RCC type 2 with grade 2, x 100. In type 2, papillae are formed by tumour cells with abundant eosinophilic cytoplasm and higher nuclear grade. Image is courtesy of Dr. H. R. Wightman.

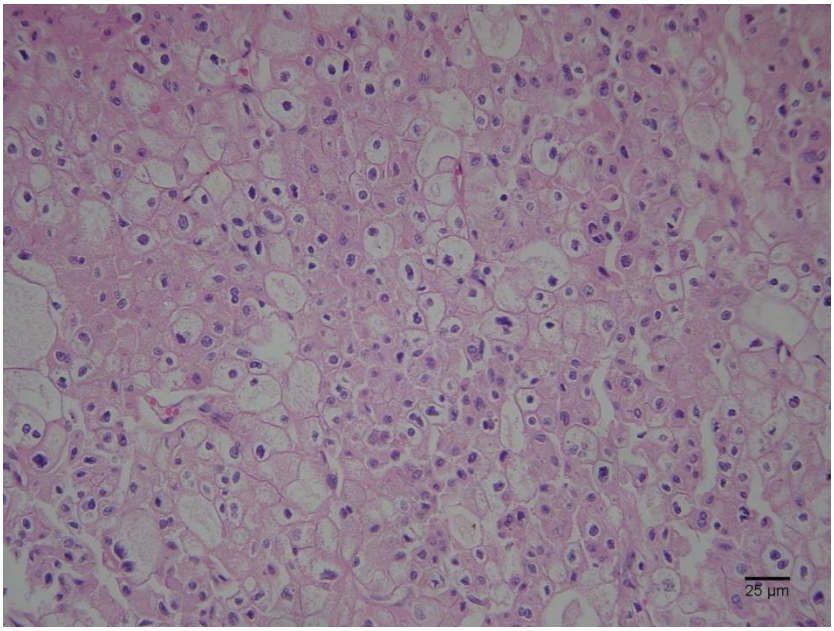

Figure 3. Chromophobe RCC, x 200. Tumour cells are polygonally shaped with transparent cytoplasm and prominent cell membrane. The nuclei are irregular with perinuclear clearance. Image is courtesy of Dr. H. R. Wightman.

1.6.5. Collecting duct carcinoma

Collecting duct carcinoma which is also called Bellini duct carcinoma, constitutes less than 1% of all renal malignancies [3, 10]. Collecting duct carcinoma is related to the cells of the medullary collecting duct of Belini [1, 10]. The central area of the kidney is the common location for collecting duct carcinoma and the tumour masses are characterized by firm texture, white grey color and ill-defined edge [1]. Histologically, the tumour cells form nestlike or tubular structures in the fibrotic stroma and the diagnosis is usually not easy [9, 10]. The tumour cells are Fuhrman grade 3 to 4 and it is common to find the extension of tumour cells into perinephric and renal sinus fat [1, 10]. Approximately 33% of cases have metastases at the time of diagnosis and 66% of patients do not survive more than 2 years [1]. Therefore, the prognosis of the collecting duct carcinoma is poor [1]. Immunoprofiles include positive PAX 8 in most cases and positive p 63 in 14% of cases [7].

1.6.6. Medullary carcinoma

Medullary carcinoma was a newly added subtype in 1995 and it is also considered as a variant of collecting duct carcinoma [1, 3]. It is a rare subtype and constitutes less than 1% of all the renal malignancies [1]. Medullary carcinoma is defined as an exceptionally aggressive renal cell carcinoma arising from the renal medulla and being associated with the sickle cell trait and sickle cell disease [1, 10]. Similar to collecting duct carcinoma, the tumour mass in medullary carcinoma is also located centrally and has ill-defined border [1]. The size of the mass is from 4 cm to 12 cm and hemorrhage and necrosis are common [1]. Microscopically, the tumour cells could form reticular or adenoid cystic structures in a poorly differentiated pattern [1]. The initial manifestation is usually vascular or lymphatic metastases and therefore, the prognosis is poor [1]. The patients

usually die within 15 weeks after the tumour mass removal [1]. Immunoprofiles include positive keratin AE1 or AE3, EMA and CEA [1].

1.6.7. RCC, unclassified

RCC, unclassified is a renal neoplasm which does not fall into any of the above categories and constitutes approximately 4% to 6% of all renal malignancies [1, 3]. The tumour cells are usually high grade and sarcomatoid change is often found [1]. This subtype has the worst prognosis amongst all of the subtypes of RCC [3].

1.6.8. Oncocytoma and oncocytic neoplasm

Oncocytoma is a benign renal neoplasm originating from intercalated cells [1, 10]. Approximately 5% of all primary renal neoplasms are oncocytoma [1, 10]. Current studies support that most oncocytoma are sporadic [1]. Most of the patients do not have any symptom at the time of diagnosis and are usually discovered incidentally by radiological examination due to non renal medical conditions [1]. Macroscopically, oncocytoma has classical mahogany-brown color and one third of cases have a stellate scar located centrally [1]. Microscopically, the oncocytes are large sized cells with eosinophilic cytoplasm and a large number of mitochondria inside [1, 15]. Tumour cells also form the acinar, tubular or microcystic structures and the stroma has hyaline change, as shown in Figure 4.1 and 4.2 [1].

Oncocytic neoplasms, arising from the intercalated cells of collecting ducts, can be either oncocytoma or chromophobe RCC [3, 4]. The relationship of the oncocytic lesions is very close and sometimes it is difficult to distinguish between the two of them [3]. ISUP has developed a new concept, that of hybrid oncocytoma/chromophobe tumour, which is defined when one tumour has mixed characteristics from the above two tumours [4, 7]. Most hybrid cases are low stage, T1

or T2 at initial diagnosis and retrospective studies found that this entity develops slowly clinically [4, 7].

1.7. Renal tumour biopsy

A diagnostic biopsy is defined as a procedure to provide patients with histopathological information and guide treatment [15]. Percutaneous renal biopsy has been used to diagnose and manage medical renal conditions for a long time and the application of renal biopsy on renal neoplasm was first reported in the 1970s [8]. Historically, the role of renal biopsy for tumours was debated because of its potential danger, unreliable results and lack of treatment implication, and such concerns prevented its regular application in clinical practice [8, 12, 15, 16, 18]. This situation has changed over the past 10 years, in which period the application of renal biopsy has increased significantly due to the advancement of imaging technology in detecting small renal masses and its diagnostic role in preventing unnecessary surgery [8, 12, 15]. In other words, renal biopsy has modified renal tumour management as active surveillance is becoming more acceptable for small renal masses detected incidentally [12, 15]. According to the study by Delahunt et al, (2014), renal biopsy has great advantages for small renal tumours undergoing conservative treatment, especially benefiting those patients whose renal function is impaired or who might not survive for the surgery [8]. Active surveillance of small renal malignancies after biopsy is more cost-effective than immediate surgery and no difference in survival rate has been identified between the two treatment options [8]. Most importantly, biopsy reports can provide histological diagnosis to differentiate benign or malignant and subtypes of malignancies, which can guide clinicians to make appropriate treatment decisions [8, 12, 13, 14, 15, 16, 17, 19]. For example, benign or less aggressive tumours can be considered for active surveillance [12, 16, 17].

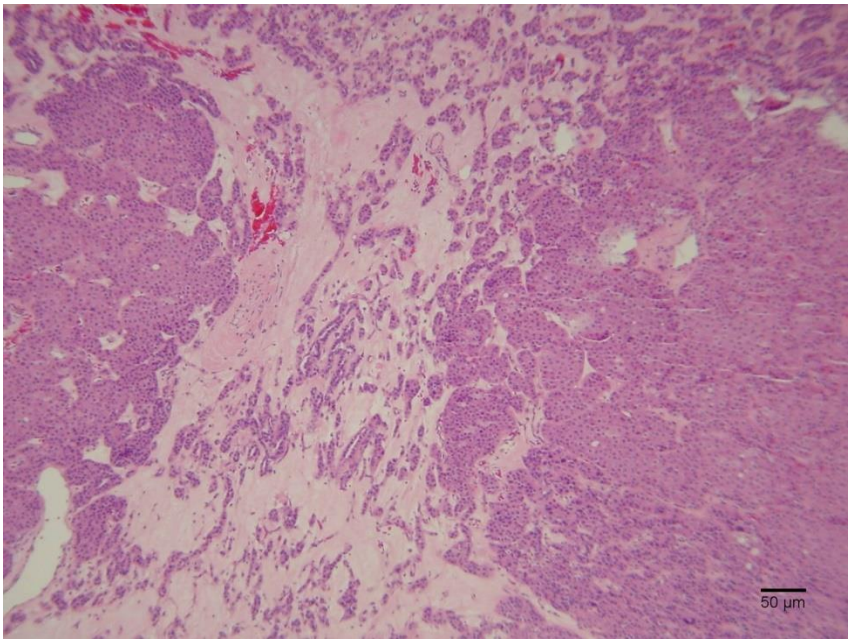

Figure 4.1. Oncocytoma, x 100. Tumour cells form the acinar structure and the stroma has hyaline change. Image is courtesy of Dr. H. R. Wightman.

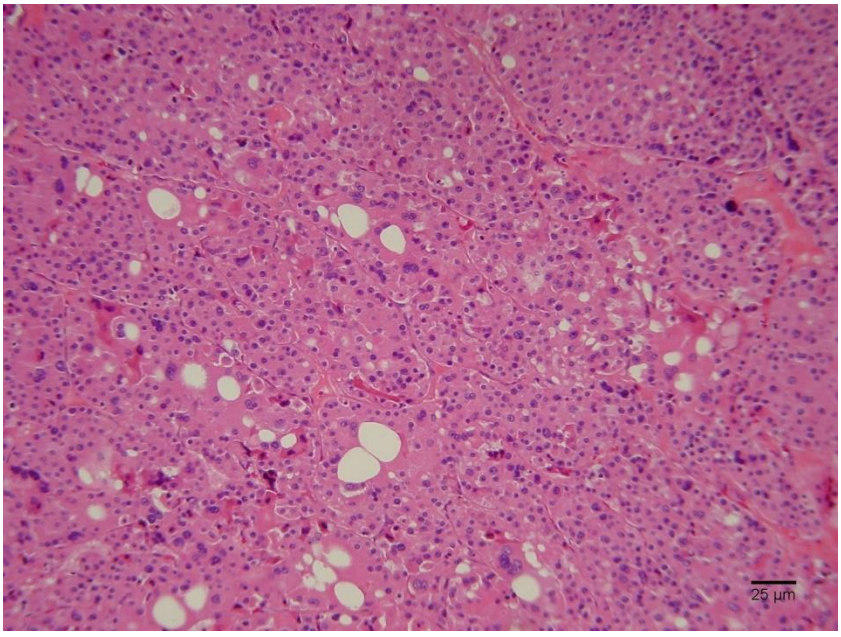

Figure 4.2. Oncocytoma, x 200. Tumour cells form the acinar or tubular structures. Tumour cell are large sized with eosinophilic cytoplasm. Image is courtesy of Dr. H. R. Wightman.

1.8. Renal tumour biopsy procedure and indications

Before renal tumour biopsy, a patient history is taken and coagulation status is checked if necessary [8, 13]. On the basis of above information, the operator will decide which type of imaging to use and how to approach the renal tumour [8]. Anticoagulant treatments should be paused if the patient is taking one [8]. The imaging types include US, CT and MRI. The decision is made according to the available imaging equipment and the operators' own preference [8, 12, 13]. US can provide the operators with the real time imaging, but US is not the best choice for overweight patients because fat and needle are not easily distinguishable [8]. CT does the opposite compared to the US, distinguishing fat and needle for overweight patients, but not providing real time imaging [8]. The optimal approach is to reach the lesion in the shortest path and avoid touching other organs or large vessels [12]. Tumour size may affect the biopsy accuracy as shown by several studies that tumour masses less than 3 cm in greatest dimension cause decreased biopsy efficacy [8]. Tumour size affects not only biopsy accuracy but also biopsy procedure as necrosis is likely related to the larger size of the mass [8]. Therefore, during the procedure, two peripheral biopsies are required for tumour size greater than 4 cm [8]. If the tumour size is smaller than 4 cm, one peripheral biopsy and one central biopsy are recommended [8].

Needle size is another consideration when performing the biopsy procedure [8]. As a larger needle increases the tissue yield and diagnosis accuracy, 18 French gauge (FG) is the most widely used one in clinical practice [8, 19]. The number of cores taken during the procedure varies from 1 to 5 and at least two satisfactory cores are recommended [8, 17]. A satisfactory core is defined as being at least 1 cm long and intact with no visible necrosis or hemorrhage [8]. When bleeding occurs in the procedure or sampling is difficult, fewer or shorter cores may be obtained[15]. After obtaining the satisfactory cores, the cores are placed in 10% buffered formalin [8, 15]. It is recommended that

each core is to be submitted separately in each cassette [8, 15]. The main reason for this is to preserve tissue in case multiple immunostains have to be performed [8, 15].

There are 3 major scenarios in which renal biopsy should be considered for renal masses. In all of these scenarios, the result should guide or potentially change treatment options [5, 14, 16, 19]. In other words, when either surgery or conservative management is the only option, renal biopsy is not necessary [14, 19]. The first scenario relates to solitary or bilateral primary renal masses of uncertain nature [8]. In this scenario, distinguishing between benign neoplasm and carcinoma is obviously crucial [8]. A very common example is to distinguish between oncocytoma and RCC. Additionally, distinguishing between different types of carcinoma is important as low grade or less aggressive types of RCC are more likely to be followed conservatively than resected immediately [8]. The second scenario is a patient with a renal mass and wide spread metastatic disease [8, 12]. In this scenario, confirmation of a primary renal cell carcinoma and its subtype are important in determining appropriate chemotherapy [8, 12]. Targeted systemic therapies can differ between clear cell RCC and non-clear cell RCC both in preferred therapy and overall effectiveness [35, 36]. Finally, the third scenario is a renal mass in a patient with history of another primary carcinoma, either concurrent or remote [8,12]. In this scenario, it is important to distinguish between a primary RCC or a metastasis to kidney from the other carcinoma [8, 12].

2. Literature Review

Sampling is one of the most important technique factors when applying renal tumour biopsy, especially dealing with small renal masses and this procedure is performed by either radiologists or urologists [15, 16]. Two methods are available for gathering renal mass tissue: fine needle aspiration (FNA) or core biopsy [14]. When comparing these two, core biopsy is better in terms of its higher tissue yield with important structures to facilitate the histological diagnosis and a couple of studies confirmed that 5 to 16% of FNA cases had insufficient sample tissue [12, 14]. However, FNA could improve the diagnostic accuracy when both two methods were applied at the same time [14, 30]. According to the consensus meeting of the 5th International Symposium on Focal Therapy and Imaging in Prostate and Kidney Cancer in 2012, FNA should not be used alone but be used together with core biopsy [14]. As discussed in the Introduction, needle size, number of cores and sampling location are issues that must be addressed during tissue sampling [14]. 18 FG is the commonly used needle size and 18 FG has better diagnostic yield than 20 FG [8]. A coaxial method is also suggested and probably is the best for improving biopsy performance [15]. During coaxial method, a larger guiding needle or cannula 17 FG is stabilized in the mass and a smaller cutting one 18 FG is placed via the larger cannula to sample the tissue [12, 15]. The advantages of such method are twofold: the first one is to provide tissues for FNA to correlate with the core biopsy, and the second one is to reduce the possibility of the most severe complication: tumour seeding [15]. Increasing the number of cores has been found to be related to the better diagnostic yield [14]. However, Tsivian et al, (2014) stated that it was not the number of cores but the amount or quality of tissue played an essential role [14]. In regards to the sampling location to be obtained, either central or peripheral options could be considered [14]. Though no optimal site has been identified, the operators need to keep in mind not to sample necrotic tissue

which is common in the centre of the larger masses [14]. Therefore, 18FG, minimum two satisfactory cores with high quality and no gross necrosis were recommended by the panel of the consensus meeting (the panel of the consensus meeting of the 5th International Symposium on Focal Therapy and Imaging in Prostate and Kidney Cancer in 2012) [8, 14].

US, CT and MRI are the available imaging choices [14], as mentioned in the Introduction. Each of them has their own advantages and none of them has been labeled as the best choice [14]. Because of US's low cost, easy accessibility and no ionizing radiation, it was given the preference by the panel of the consensus meeting [14]. The biopsy approach could be either subcostal or supracostal, depending on the anatomical location of the mass [14]. Though supracostal path has elevated risk of causing pneumothorax and adjacent organ puncture, severe complications are uncommon [14]. The panel of the consensus meeting agreed that both paths should be equally considered and special cases needed to be treated on an individual basis [14].

It is still a controversial topic whether or not tumour size affects tissue yield [14]. Some studies, which are consistent with the previous one in the Introduction, support such a statement, while Wang et al, (2009) and Barwari et al, (2011) oppose it with no association established [8, 14]. The panel of the consensus meeting indicated that in small masses, the tissue yield could be lower [14]. Tumour seeding is the severe possible complication, but when using the coaxial method with better equipment and improved technique, this complication should be reduced to minimal [14, 17]. Several studies reported that the rate of such incidence is less than 0.01% and it occurred more in urothelial carcinoma than RCC [8, 16, 19]; however this figure could be underestimated because no follow up had been monitored or recorded [14]. The panel of the consensus meeting suggested conducting more detailed research on the complications [14].

One important parameter to evaluate the role of renal biopsy is its non-diagnostic rate [14]. The rate of non-diagnostic tissue varied ranging from 0 - 47% from reviews and observational studies [8, 12, 13, 15, 16, 17, 18, 19] (Table 1.1). In contrast, the diagnostic rate was from 62% to 96% with the mean being calculated as 83% [5]. The study by Evans et al, (2015) summarized 529 cases from 2001 to 2013 and calculated the initial non-diagnostic rate at 10%, and then the rate decreased to 6.2% when the data from the initial and repeated biopsies were added together [15]. Of these non-diagnostic cases, 72% sampled renal parenchyma [15]. The study by Gellert et al, (2014) retrieved 218 cases from 2006 to 2011 and the non-diagnostic rate was 11% [16]. Similarly, the findings in the non-diagnostic cases were either benign renal parenchyma or fibrosis [16]. The study by Maturen et al, (2007) collected 152 cases from 1999 to 2005 and the non-diagnostic rate was 4% [13]. When analyzing the non-diagnostic cases, by imaging two were solid, two cystic and remaining two mixed [13]. On the basis of the previous studies, non-diagnostic samples are mainly caused by not having enough sampled tissue [12]. Masses small than 2.5 cm and cystic lesions are more likely to have non-diagnostic results [15, 16]. The experience of the operator can also affect the quality of the sampled tissue and it is estimated that the non-diagnostic rate by experienced operators could be around 12.5% [15, 16]. The panel of the consensus meeting recommended standardizing the term of “non-diagnostic biopsy” which should include not only insufficient tissue but also those biopsies that a definite diagnosis is not established [14].

Diagnostic accuracy for malignancy, especially histological subtyping and grading are other factors to evaluate in the role of renal biopsy [14]. After slices of core tissue are stained with hematoxylin and eosin (H&E), a pathologist will make a histologic diagnosis on morphologic grounds [15]. If the initial diagnosis is not easily determined, the IHC panels can be ordered to help with the differential diagnoses[15]. In 2012, ISUP developed guideline for using IHC to classify

renal tumours and the pathologists can refer this guideline for best practice [15]. Radiologic features can also be reviewed to help with the diagnoses [15]. When a subsequent nephrectomy is performed, both diagnoses of core tissue and surgical specimen are compared, and then the histologic concordance rate can be calculated [8, 15]. The studies by Evans et al, (2015), Gellert et al, (2014) and Maturen et al, (2007) achieved 93%, 97% and 97.7% concordance rates in histologic typing respectively [13, 15, 16]. The histologic concordance of other review papers achieved relatively high rates from 74 -100 % [8, 12, 14, 18, 19] (Table 1.1). Tissue from renal biopsy is smaller in comparison to the nephrectomy specimen. Unlike the surgical specimen, some cases may not have enough tissue for further sections or IHC staining [15]. Furthermore, the heterogeneity of RCC makes the challenging cases more difficult on core biopsy materials [14, 15]. Challenging cases include, but are limited to tumours having both clear cell and papillary features, papillary RCC subtyping, tumours having oncocytic features, cystic lesions and poorly differentiated tumours having sarcomatoid change [15, 16]. The panel of the consensus meeting's recommendation for such cases is to seek opinions from experienced urological pathologists [14]. Even with encountering the above difficulties, the histologic concordance should reach the relatively high rate noted [16].

As mentioned in the Introduction, the role of Fuhrman grading system is controversy because it is not as robust as the histology accuracy and is not routinely utilized in core biopsies in some practice settings [8, 13]. Grading accuracy ranges from 43% to 78% (Table 1.1) when a 4-tiered Fuhrman grading system is used. According to the study by Blumenfeld et al, (2010) 55% of graded cases were under graded when comparing to the nephrectomy specimens [8]. However, the grading accuracy can be improved if a 2-tiered Fuhrman grading system or collapsed method is applied [15]. Evans et al, (2015) defined the collapsed method as converting Fuhrman grades 1 or 2

to low grade and Fuhrman grades 3 or 4 to high grade [15]. In his study, the concordance rate of grading was 61.4% prior to using collapsed method [15]. After applying this method, the grading accuracy increased to 94.3% [15]. The review paper by Tsivian et al, (2014) also confirmed that the grading accuracy could be better if using a 2-tiered Fuhrman grading system [14]. The discrepancy of grading accuracy could be explained by the following two reasons. First, the grade of the renal tumours in even small renal masses is heterogeneous [15]. During renal biopsy, the sampled tissue may not be obtained from the highest grade area, which causes lower grading concordance [14]. Second, the judgements from different examiners can vary [14]. This variability can be due to both intraobserver and interobserver variation and such variability can be reduced when a 2 grade system is used [14, 15]. The urologists prefer having as much information as possible to help with choosing treatment option, even though they realize the fact that the renal biopsy report could be under graded [15]. The panel of the consensus meeting's opinion on grading is that it can be applied and the 2-tiered system is preferable [14].

As mentioned before, the application of better IHC markers contributes to the relatively high diagnostic accuracy of the percutaneous renal core biopsy [15], [16]. When the differential diagnoses are raised for the common four subtypes of renal tumours: clear cell RCC, papillary RCC, chromophobe RCC and oncocytoma, 5 IHC markers are recommended and these 5 markers are CA IX, CD117, CK7, CD10 and AMACR [16, 17]. The CA IX expression is on the membrane and the diffuse positivity is observed in approximately 85% of the clear cell RCC [17]. Furthermore, the positivity of this marker in other subtypes of RCC is usually focal or near necrosis [17]. For clear cell subtype, membranous CD 10 positivity is also expressed diffusely [17]. The expression of CD 117 and CK7 is in the cytoplasm and these two markers can be used to differentiate oncocytic lesions [17]. Chromophobe RCC has positivity of both markers while oncocytoma only

has diffuse positivity of CD117 but negativity of CK7 [17]. The CD 117 reactivity in chromophobe subtype is characterised by more expression at peripheral cytoplasm than central area [17]. Even with the aid of IHC markers, oncocytic neoplasm is still difficult to be interpreted on the basis of small amount of tissue [37]. On such cases, the argument exists on whether to make the definitive diagnosis or oncocytic neoplasm instead [37]. The combination of AMACR and CK7 are used to diagnose papillary subtype and both markers have diffuse positivity[17]. In contrast to the diffuse CD 10 positivity in clear cell, the CD 10 has sporadic expression in papillary subtype [17]. Al-Ahmadie et al, (2011) designed a study in which 2 cores were sampled from the nephrectomy specimens and the diagnoses were made before and after IHC staining [17]. Then both diagnoses from the cores were compared with the diagnosis from the resected specimen [17]. In their study, 87% of the total cases fell into the group of four common subtypes and after staining with the above 5 markers, the diagnostic accuracy could be increased from 90% to 99% [17]. In the study by Gellert et al, (2014), the mentioned 4 common subtypes constitute 65% of all the cases [16]. IHC markers were applied in 69% of total cases and in 34% of these cases, the recommended 5 markers were ordered, resulting in a diagnostic accuracy of 97% [16].

Renal core biopsy can provide histological diagnosis to differentiate benign or malignant masses and subtypes of malignancies. Figure 5 shows clear cell RCC on a renal core case. Based on such information, the clinicians can make the appropriate management strategy [8, 12, 13, 14, 15, 16, 17, 19]. The study by Gellert et al, (2014) recruited 218 renal biopsy cases with 181 cases having diagnostic results [16]. Of these 181 cases, 81 cases were clear cell RCC, 23 case were the other 3 subtypes with 7 cases papillary RCC, 11 cases chromophobe RCC and 5 cases clear cell papillary RCC [16]. In terms of clinical management, 14 cases of clear cell RCCs underwent active surveillance. Contrarily, 12 cases of other 3 subtypes underwent active surveillance with 2 cases

of papillary RCCs, 6 cases of chromophobe RCCs, and 4 cases of clear cell papillary RCCs [16]. In order to test if clear cell RCCs are less like to undergo active surveillance than the other 3 subtypes of RCCs, a p value is calculated, as shown in Table 1.2. P value is 0.002, which is considered to be very statistically significant. Results indicate that the subtypes of RCC can guide treatment decisions.

Table 1.1. Literature sources

Non-diagnostic rate %	Histologic concordance %	Grading accuracy %	Benign lesion %	References
4-21	89.7-100	46-78	1-40	8. Delahunt, B., et al 2014
5-16	88-94	64-70	Not provided	12. Caoili, EM. and Davenport, MS. 2014
0-47	86-98 (subtype)	46-76	36	14. Tsivian, M., et al 2014
0-36	74-100	43-75	Not provided	18. Marconi, L. et al 2015
14.1	77.5-100	51.5-75.9	Not provided	19. Patel, HD. et al 2015
4	97.7	Not routinely reported	40	13. Maturen, KE., et al 2007
10 (initial) 6.2 (together with repeat biopsy)	93	61.4 to 94.3 when grades were collapsed (grades 1 -2 and 3-4 converted into low grade and high grade	20-30	15. Evan, AJ. et al 2015
11	97	54	Not provided	16. Gellert, L. et al 2014

Table 1.2. Active surveillance rate

Number of clear cell RCCs undergoing active surveillance	Number of clear cell RCCs not undergoing active surveillance	
14	67	P value=0.002
Number of other 3 subtypes of RCCs undergoing active surveillance	Number of other 3 subtypes of RCCs not undergoing active surveillance	
12	11	

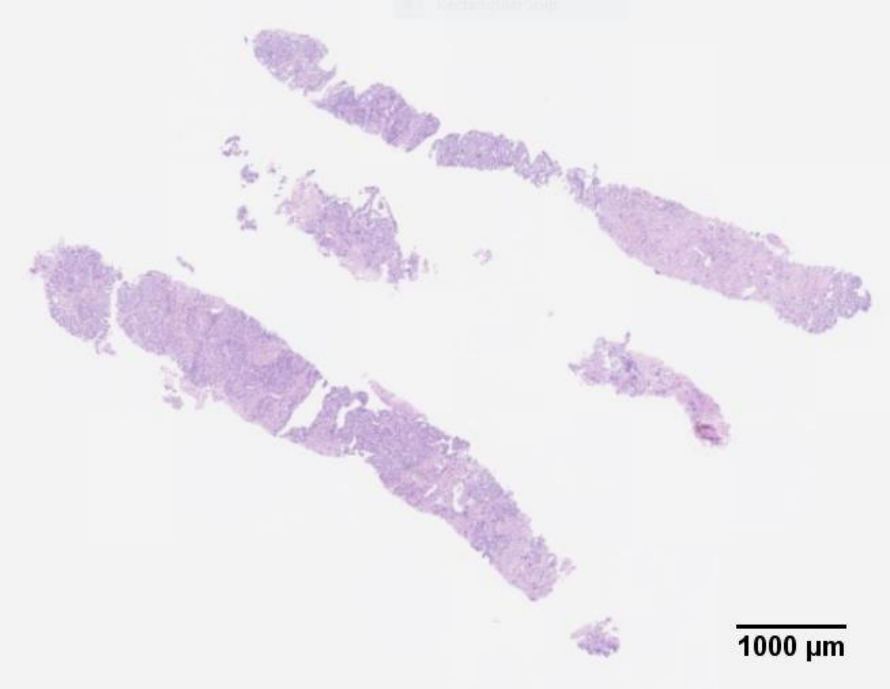

Figure 5.1. Clear cell RCC, x 5. The renal core biopsy tissue shows clear cell RCC at lower power (x 5). Image is courtesy of Dr. H. R. Wightman.

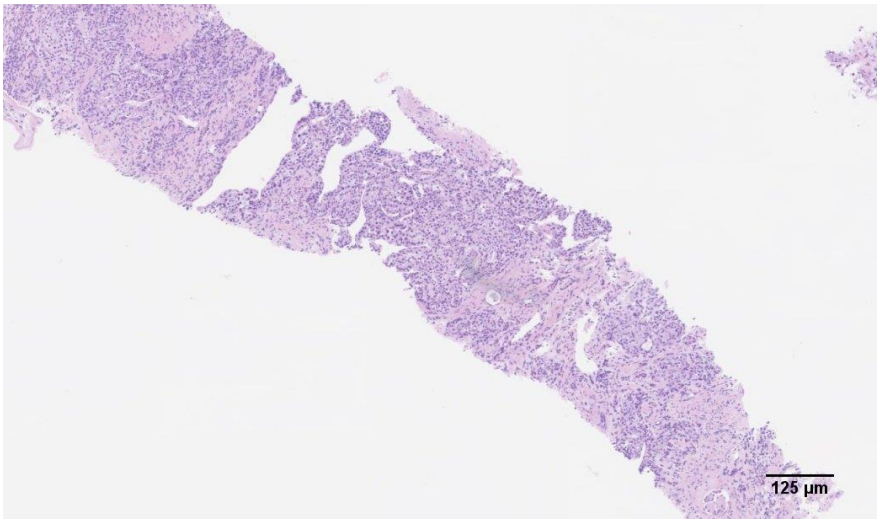

Fig 5.2. Clear cell RCC, x 40. The renal core biopsy tissue shows clear cell RCC at lower power (x 40). Image is courtesy of Dr. H. R. Wightman.

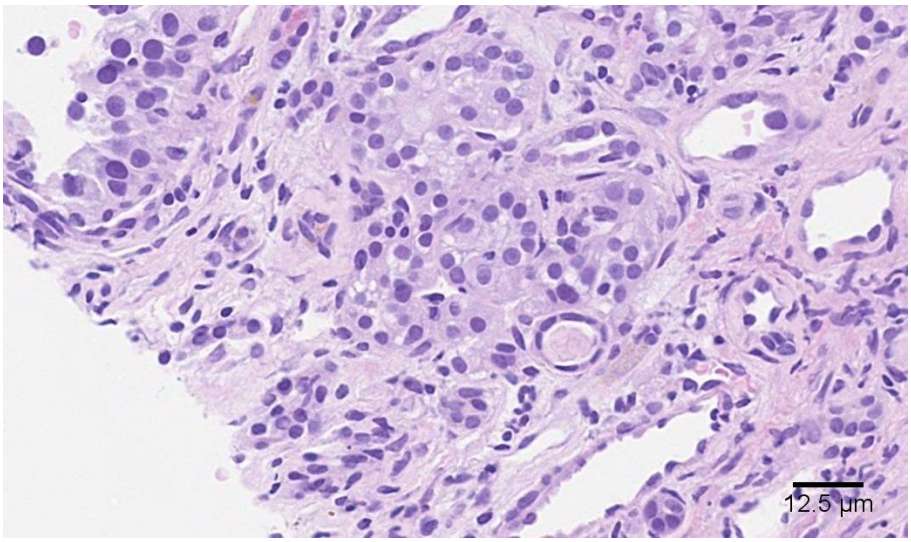

Figure 5.3. Clear cell RCC with macronuclei, x 400. The renal core biopsy tissue shows clear cell RCC with macronuclei at high power (x 400). Image is courtesy of Dr. H. R. Wightman.

3. Objectives

1. Determination of number of core biopsies from 2007 to 2016.

2. Determination of patients' demographics, hospital site, and core biopsies gauge size.

3. Determination of specific histologic diagnoses including RCC subtypes and nuclear grade in the renal core biopsy samples. This includes determination of non-diagnostic and satisfactory rates.

4. Correlation of renal core biopsy and nephrectomy specimens to determine diagnostic accuracy in relation to carcinoma type, subtype and nuclear grade (4 and 2 tiered grade) with nephrectomy specimens being the gold standard.

5. Assessment of the role of FNA and its contribution to overall diagnosis to be assessed.

6. Assessment of the role of IHC.

7. Assessment of the role of subtype of RCC and grade in surveillance of renal masses. We hypothesize that clear cell RCCs and high grade cases would be more likely to undergo nephrectomy than any other subtypes of RCCs and low grade cases.

8. Assessment of the role of case volume in radiologist and pathologist performance.

4. Methods

4.1. Data collection

A retrospective search and data collection were performed through the Diagnostic Services of Manitoba (DSM) database. The search was executed and the keywords used were “kid*” and “bx” for specimen, and “carcinoma”, “neoplasm”, “oncocytoma”, “oncocytic” and “negative” within text. On the basis of the above searching criteria, 279 cases were retrieved. Then, all of 279 cases were reviewed carefully by Dr. H. R. Wightman and the PA student to choose the cases originating from the renal parenchyma by imaging and to exclude the cases from the renal pelvis or ureter. As a result, total 163 cases, ranging from Mar 2007 to May 2016, were included in this study.

Clinical information of each case was extracted including gender, age, indication and hospital site. Indications were grouped into 4 categories: primary tumour, metastatic tumour, differential diagnosis and bilateral tumour. The definitions of each group are described as follows. Primary tumour was defined as a solitary renal mass without tumour elsewhere; metastatic tumour was defined as a renal mass with documented metastatic disease by imaging; differential diagnosis was a renal mass with history of previous carcinoma or localized concurrent carcinoma, and bilateral tumour was bilateral renal masses with or without tumour elsewhere.

4.2. Review of reports

The pathology reports were reviewed and diagnoses placed into one of the following four groups: benign tumour, malignant tumour, suspicious group and non-diagnostic group. In the malignant tumour group, RCC cases and other types of carcinoma were grouped separately. Additionally, RCC subtype and grade information were collected when present.

4.3. Case analysis

All cases with a related nephrectomy in DSM database were analyzed. The histological diagnosis, grading and T stage of each nephrectomy report were recorded. By comparing the pathology report of renal biopsy with the report of the nephrectomy specimen, the concordance rates of type and subtype were calculated respectively. Type was defined as RCC or urothelial carcinoma and subtype was defined as any subtype of RCC. The concordance rate of grading was calculated by utilizing the collapsed method, as discussed in the Introduction[15].

4.4. Identification of FNA cytology reports

The DSM database was searched to identify all related FNA cytology reports. If the report was available, the information was collected and compared with the report of the renal biopsy. All cases with cytology were assessed as to the role of cytology in establishing a more exact diagnosis than related core biopsy alone. Regarding the application of IHC, the number of IHC was summarized for each of the available cases, as well as the common subtypes of RCC: clear cell RCC, papillary RCC and chromophobe RCC.

Clinical information related to the renal core biopsy procedure was collected including gauge size, number of cores, type of imaging guidance and operator name.

4.5. Statistical analysis

P values were calculated by GraphPad software, using Fisher's exact text (two-tailed) in a 2x2 contingency table.

5. Results

The distribution of 163 cases was 1 case in 2007, 2008 and 2010 each, 4 cases in 2009 and 2012 each, 3 cases in 2011, 26 cases in 2013, 36 cases in 2014, 62 cases in 2015 and 25 cases in 2016.

5.1. Patients Characteristics

5.1.1. Gender distribution

Of 163 cases, male cases were 111, comprising 68% of the total cases. Female cases were 52, comprising 32% of the total cases. The male to female ratio was 2.13.

5.1.2. Age distribution

The patients' age ranged from 11 to 90 years old. The details of age distribution with percentage of each age group and with gender composition are displayed in Figure 6 and Table 2 respectively. From Figure 6, three groups, 50-59, 60-69 and 70-79 were the groups having the most patients with the sum of three groups comprising 83% of the total cases. When calculating the male to female ratio in these three groups, the results were 3, 1.76 and 1.92 respectively.

5.1.3. Indication

Of 163 cases, only one case did not have clinical information and the remaining 162 cases included indication for biopsy. The primary tumour group included 127 cases; metastatic tumour group 17 cases; differential diagnosis group 12 cases and bilateral tumour group 6 cases.

5.1.4. Site where the pathology reports were signed out

All the cases were submitted to the Pathology Department of three hospitals: Health Science Centre (HSC), St. Boniface General Hospital (SBGH) and Grace Hospital (GH). SBGH had the most cases 118 in comparison with HSC having 44 cases and GH having 1 case.

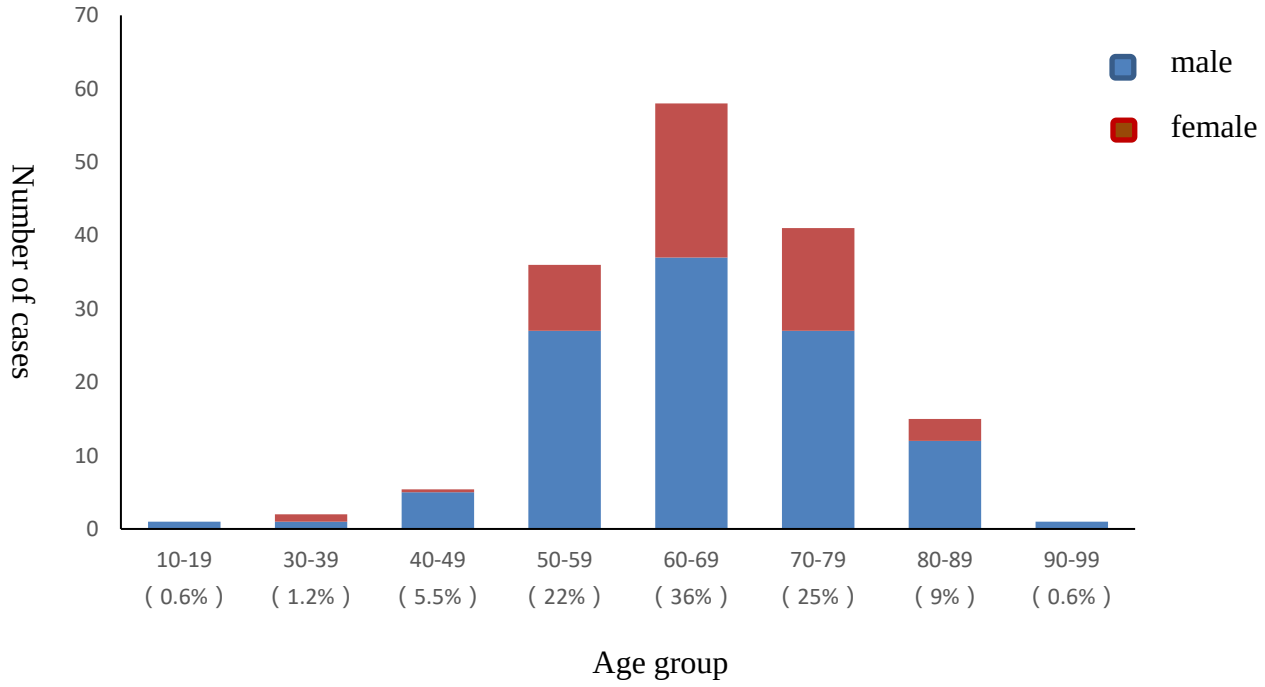

Figure 6. Age distribution. This figure shows number of cases at different age groups. Three groups: 50-59, 60-69 and 70-79 were the groups having the most patients with the sum of three groups comprising 83% of the total cases. When calculating the male to female ratio in these three groups, the results were 3, 1.76 and 1.92 respectively.

Table 2. Age distribution with gender composition

Age group (years)	Male cases	Female cases	Total
10-19	1	0	1
30-39	1	1	2
40-49	5	4	9
50-59	27	9	36
60-69	37	21	58
70-79	27	14	41
80-89	12	3	15
90-99	1	0	1

5.2. Histology and grading of renal core biopsy

Benign tumour group had 20 cases; malignant tumour group had 117 cases; suspicious group had 11 cases and non-diagnostic group had 15 cases. The percentage of each group is shown in Figure 7. The details of each group are specified in Table 3. In the benign tumour group, 18 out of 20 cases were oncocytoma. In the malignant tumour group, 103 out of 117 were RCC, 6 out of 117 were urothelial cell carcinoma, 6 out of 117 were poorly differentiated carcinoma, 1 out of 117 was B cell lymphoma and 1 out 117 was squamous cell carcinoma. In terms of subtypes of RCC, clear cell RCCs constitute 71% of the total RCC cases, papillary RCC 12%, chromophobe 2%, clear cell papillary 2% and subtype not stated 11%.

The non-diagnostic group was further categorized into 3 subgroups which included the subgroups of “atypical cells”, “too limited for evaluation” and “other”. The subgroup of “atypical cells” had 4 cases which had tiny clusters of neoplastic or atypical cells and were insufficient for histology assessment. The subgroup of “too limited for evaluation” had 10 cases which were entirely non-diagnostic, with limited tissue or benign renal parenchyma only. The subgroup of “other” had 1 case which had differential diagnoses between Wilms and metanephric adenoma. The diagnostic rate was calculated as 84% and non-diagnostic rate was 9.2%. No repeat biopsy was performed on any of the unsuccessful cases.

Of 57 total graded cases, 53 cases were RCC, 2 cases were urothelial carcinoma, 1 case was oncocytic renal neoplasm and 1 case was carcinoma, not otherwise specified. Further, when the 57 cases were categorized by Fuhrman grading system, 33 cases utilized grade number out of 4 or the 4-tiered Fuhrman grading system and the remaining 24 cases utilized low or high or the 2-tiered Fuhrman grading system. The details of graded cases are summarized in Table 4.1. The above cases were further converted into groups of low and high grade. The group of low grade

had 39 cases, the group of high grade had 17 cases, and 1 case was excluded due to undetermined high or low grade.

In the primary tumour group of 127 cases, 74 cases were RCCs which had definite subtypes with 58 cases being clear cell RCCs. The remaining subtypes of RCCs are shown in Table 3.2.3. Of 127 primary tumour cases, 47 cases were graded with the details of grade cases being shown in Table 4.2. Similarly, these cases were converted into groups of low and high grade. The group of low grade had 33 cases, the group of high grade had 13 cases and 1 case was excluded due to the undetermined high or low grade.

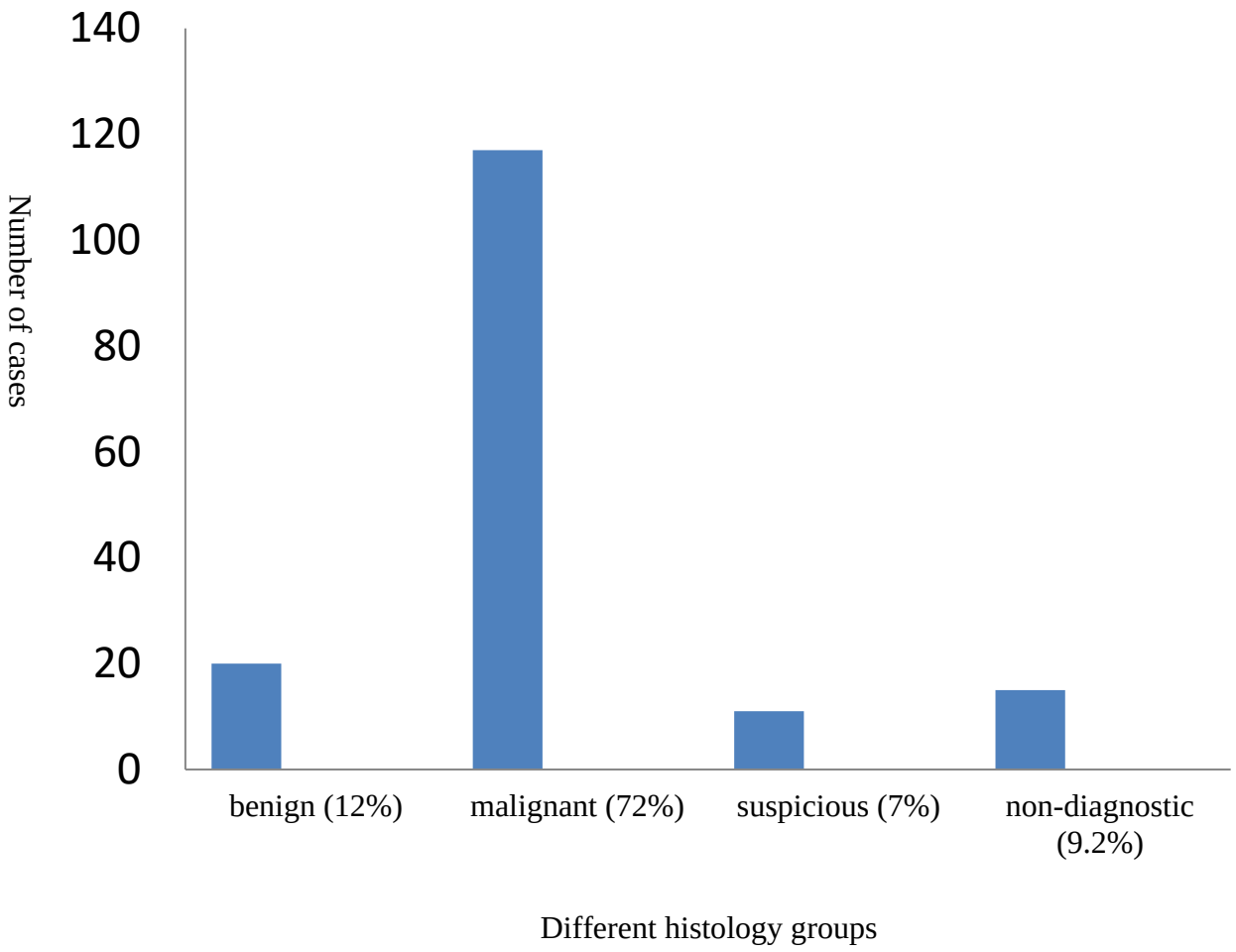

Figure 7. Distribution of benign, malignant, suspicious and non-diagnostic groups. This figure shows the number of cases in different histology groups. Benign tumour group had 20 cases, comprising12%; malignant tumour group had 117 cases, comprising 72%; suspicious group had 11 cases, comprising 7% and non-diagnostic group had 15 cases, comprising 9.2%.

Table 3. Groups of renal core biopsy histological report

3. 1. Benign tumour group

Benign tumour cases	Number of cases
oncocytoma	18
Metanephric adenoma	1
Benign tissue	1
	Total 20

3. 2.1. Malignant tumour group

Malignant tumour cases	Number of cases
Renal cell carcinoma	103
Urothelial cell carcinoma	6
B cell lymphoma	1
Squamous cell carcinoma	1
Poorly differentiated carcinoma / high grade carcinoma	6
	Total 117

3.2.2. Subtypes of RCC in total population

Subtypes of RCC	Number of cases	Percentage %
Clear cell	73	71
Papillary	12	12
Chromophobe	2	2
Clear cell papillary	2	2
Clear cell or clear cell variant of papillary	1	1
Papillary with clear cell feature	2	2
RCC subtype not stated	11	11
	Total 103	

3.2.3. Subtypes of RCC in primary tumour group

Subtypes of RCC	Number of cases
Clear cell	58
Papillary	10
Chromophobe	2
Clear cell papillary	1
Clear cell or clear cell variant of papillary	1
Papillary with clear cell feature	2
RCC subtype not stated	11
	Total 85

3.3. Suspicious group

Suspicious group	Number of cases
Oncocytic neoplasm with oncytoma vs chromophobe RCC	5
Suspicious RCC	5
Suspicious low grade carcinoma	1
	Total 11

3.4. Non-diagnostic group

Non-diagnostic group	Number of cases
Atypical cell	4
Too limited for evaluation	10
Other	1
	Total 15

Table 4.1. 4-tiered Fuhrman grade (total)

Different grade	Number of cases
Grade 1	2
Grade 2	17
Grade 3	11
Grade 4	2
Grade 1 to 2 or low grade	20
High grade	4
Grade 2 to 3	1
	Total 57

Table 4.2. 4-tiered Fuhrman grade (primary group)

Different grade	Number of cases
Grade 1	2
Grade 2	13
Grade 3	9
Grade 4	2
Grade 1 to 2 or low grade	18
High grade	2
Grade 2 to 3	1
	Total 47

5.3. Histology and grading of subsequent nephrectomy

Of total 163 cases, 54 cases underwent nephrectomy. The distribution of nephrectomies by year is displayed in Figure 8. When categorized by pathology report, 2 cases were urothelial carcinoma and the remaining 52 cases were RCCs. Of 52 RCC cases, 37 cases were clear cell RCC. The subtypes of the remaining of RCCs are included in Table 5.

In the primary tumour group, of 58 clear cell RCCs, 32 cases underwent nephrectomy. Of 16 other RCCs subtyped, 9 cases underwent nephrectomy. In testing the hypothesis that clear cell was more likely to undergo nephrectomy than any other subtypes of RCC, a p value was calculated by using the data from the primary tumour group, as shown in Table 6.1. P value was 1.0 which was not statistically significant.

When reviewing the pathology diagnoses of initial renal core biopsy, 44 cases were both typed and subtyped, 5 cases only had type without subtype and 5 cases did not have either type or subtype. In comparing renal core biopsy to nephrectomy specimen, all 44 cases with type and subtype were concordant (100% concordance rate). Of 44 surgical specimen cases, 12 cases were signed out from HSC, 31 cases from SBGH and 1 case from GH. Of the concurrent renal core biopsy diagnoses, 13 cases were signed out from HSC and 31 cases from SBGH. Comparing these 44 pairs, 9 pairs were reported by the same pathologist, and the remaining 35 pairs by different pathologists. Additionally, the highest volume pathologist reported 32 out of 163 biopsy cases and all of 32 cases fell into diagnostic group. The non-diagnostic rate for all additional pathologists was 11%. In testing whether high or low volume made a difference in diagnosing RCCs and histological subtypes, p value was 0.04 which was considered to be statistically significant (see Table 6.2.).

Of these 54 cases, 27 cases were graded with 25 being RCCs and 2 being urothelial carcinoma. After ruling out 2 urothelial carcinoma and 1 RCC due to the presence of 2 tumours, the remaining 24 pairs were left for calculating concordance rate of grade. Another 2 cases were further excluded due to the use of an "overlap" grade (i.e. 2 - 3 of 4) in either the core biopsy or nephrectomy specimen, leaving 22 paired cases. Prior to utilization of the collapsed method, 13 pairs had the same grade and concordance rate was 59% and 9 pairs upgraded from low to high. After applying the collapsed method, 16 pairs had the same grade; 6 pairs upgraded from low to high. Therefore, concordance rate of the collapsed grade increased to 73%.

Of these 54 cases, 38 cases were staged at T1. The details of all the T1 were as follows: 20 cases of T1a, 15 cases of T1b, 1 case of T1a and T1b and 2 cases of T1a or T1b not being specified. Apart from T1, 1 case was staged at T2 and 15 cases were staged at T3.

Of these 54 cases, 24 cases underwent partial nephrectomy. All of the 24 case were RCCs with 17 cases being clear cell. The subtypes of the rest of RCCs are listed in Table 7.1. The tumour dimensions of these cases varied from 1.5 cm to 6.2 cm and the average dimension was calculated at 3.40 cm. The T stages of these cases are summarized in Table 7.2, with 21 cases of T1 and 3 case of T3.

In contrast, the remaining 28 RCC cases underwent radical nephrectomy and the tumour dimensions ranged from 2 cm to 14.5 with the average dimension of 5.8 cm. The T stages of 28 RCCs are summarized in Table 7.2, with 16 cases of T1, 1 case of T2, and 11 cases of T3. Table 7.2. also compares percentage of different T stages in both partial and radical nephrectomy cases.

Of 15 non-diagnostic cases, 3 cases underwent nephrectomy and all of them were RCC cases with one clear cell with cystic change, one papillary and one chromophobe. The tumour's greatest dimensions of these 3 cases were 5 cm, 5 cm and 6 cm respectively.

In the primary tumour group, 24 graded cases underwent nephrectomy and the details of grade cases are shown in Table 8.1. After converting these cases into low and high grade, the group of low grade had 19 cases, the group of high grade had 4 cases and 1 case was excluded due to the undetermined high or low grade.

In testing the hypothesis that high grade carcinoma would be more likely to under nephrectomy, a p value was calculated by using the data from the primary tumour group, as shown in Table 8.2. P value was 0.19 which was not statistically significant.

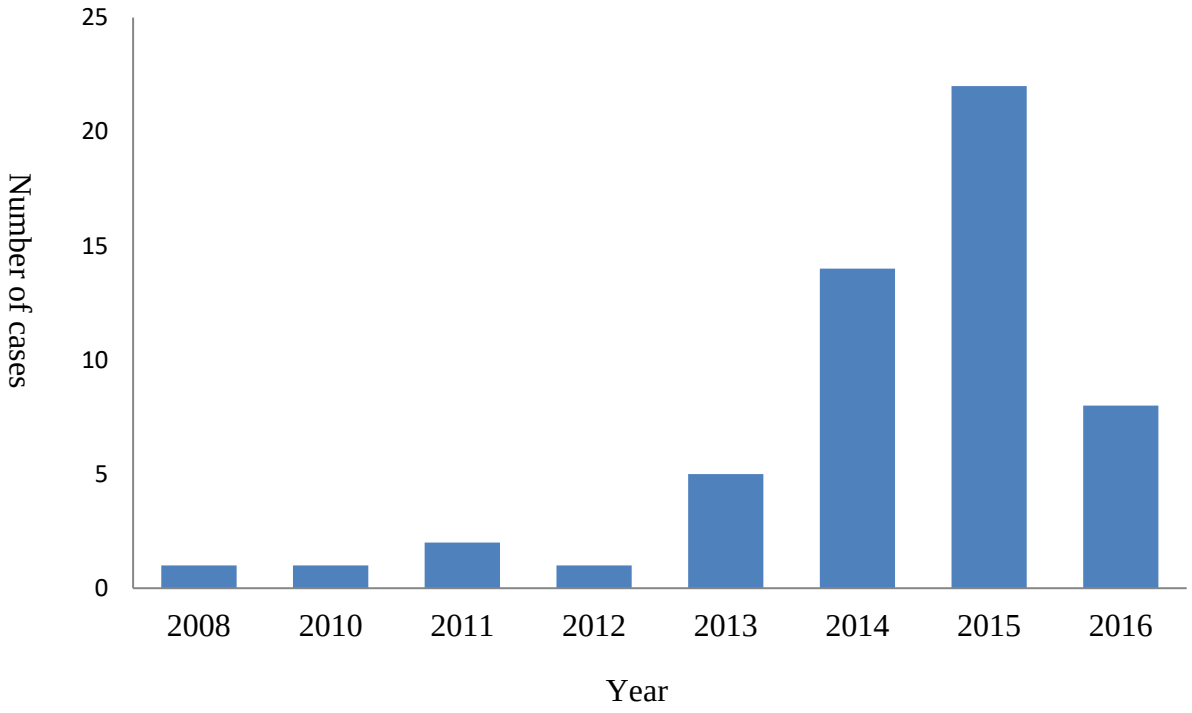

Figure 8. Distribution of nephrectomies by year. The distribution of nephrectomies by year is as follows. 2008, 2010 and 2012 had 1 case in each year. 2011 had 2 cases. 2013 had 5 cases. 2014 had 14 cases. 2015 had 22 cases. 2016 had 8 cases.

Table 5. Nephrectomy subtypes

Subtypes of RCCs	Number of cases
Clear cell	37
Papillary:	11
Type 1	2
Type 2	7
Not stated	2
Papillary with clear cell change	1
Clear cell papillary	1
Chromphobe	1
Unclassified	1
	Total 52

Table 6.1. Nephrectomy rates (subtypes). In the primary tumour group, of 58 clear cell RCCs, 32 cases underwent nephrectomy; of 16 other definitely subtyped RCCs, 9 cases underwent nephrectomy. P value was 1.0 which was not statistically significant.

Number of clear cell RCCs undergoing nephrectomy 32	Number of clear cell RCCs not undergoing nephrectomy 26	P value=1.0
The remaining RCCs undergoing nephrectomy 9	The remaining RCCs not undergoing nephrectomy 7	

Table 6.2. Diagnostic rates (pathologists). The highest volume pathologist reported 32 cases and all of the cases were in the diagnostic group. The remaining pathologists reported 131cases and 15 cases were in the non-diagnostic group. P value was 0.04 which was statistically significant.

	Number of cases in groups of diagnostic and suspicious	Number of cases in non-diagnostic group	
One pathologist	32	0	P value=0.04
The remaining pathologists	116	15	

Table 7.1. Partial nephrectomies with subtypes

Subtypes of RCCs	Number of cases
Clear cell	17
Papillary:	5
Type 1	1
Type 2	4
Papillary with clear cell change	1
Clear cell papillary	1
	Total 24

Table 7.2. T stages for partial and radical nephrectomies

	Number of cases underwent partial nephrectomy and percentage	Number of cases underwent radical nephrectomy and percentage
T1a	14 /58.3%	5/ 17.9%
T1b	5/20.8%	10/35.8%
T1	2/8.3%	0
T1a and T1b	0	1/3.6%
T2	0	1/3.6%
T3	3/12.5%	11/39.2%
Total	24	28

Table 8.1. Nephrectomy grades (primary group)

Different grade	Number of cases
Grade 1	2
Grade 2	5
Grade 3	0
Grade 4	4
Grade 1 to 2 or low grade	12
Grade 2 to 3	1
	Total 24

Table 8.2. Nephrectomy rates (grade). In the primary tumour group, of 33 low graded cases, 19 cases underwent nephrectomy; of 13 high graded cases, 4 cases underwent nephrectomy. P value was 0.19 which was not statistically significant.

	Number of cases undergoing nephrectomy	Number of cases not undergoing nephrectomy	
Low grade cases	19	14	P value=0.19
High grade cases	4	9	

5.4. Cytology reports

Of 163 cases, 100 cases had a corresponding cytology report. Firstly, these 100 available cases were categorized into 3 groups: unsatisfactory group, descriptive and diagnostic. The definitions of each group are described as follows. “Unsatisfactory” was defined as an entirely non-diagnostic aspirate. “Descriptive” was defined as a microscopic description without a definite diagnosis of carcinoma. “Diagnostic” was defined as all diagnoses of carcinoma as well as suspicious, suggestive or compatible carcinoma diagnoses. Each of the above 3 groups had 31, 38 and 31 cases respectively. Secondly, these 100 cytology reports were compared with pathology reports of the renal core biopsies. Five pairs were non-diagnostic; 32 pairs carried same or similar diagnostic information; 59 cases had less information and 4 cases had more information. Table 9 lists the details of the 4 pairs in which cytology reports had more information than renal core biopsy report.

Table 9. FNA data

Case number	Renal core biopsy report	Cytology report
13S069666	Non-diagnostic	Type and subtype
14S045591	Non-diagnostic	Carcinoma cell present
14S024502	Non-diagnostic	Type
14S003149	Type	Type and subtype

5.5. IHC

Of 163 cases, IHC was ordered in 93 cases. Table 10 presents the number of cases ordered by year and Table 11 summarizes number of IHC ordered for each case. On the basis of the data, the average was calculated at 5.2 IHC ordered per case. When considering the application of IHC in subtypes, Table 12 concludes that information.

Of 92 RCCs subtyped, IHC was ordered in 40 cases. Of 15 non-diagnostic cases, IHC was ordered in 8 cases. In testing the hypothesis that the application of IHC was associated with increased diagnosis of RCC and subtype, p value was 0.58 which was not statistically significant, as shown in Table 13.1.

Of 32 cases signed out by the highest volume pathologist, IHC was ordered in 18 cases. In testing the hypothesis that IHC was ordered more frequently by the highest volume pathologist than the remaining pathologists, p value was 1 which was not statistically significant, as shown in Table 13.2.

Table 10. IHC volume and percentage

Year	Number of cases ordered IHC	Total case number	Percentage %
2007	1	1	100
2008	1	1	100
2009	4	4	100
2011	1	3	33
2012	4	4	100
2013	18	26	69
2014	20	36	56
2015	28	62	45
2016	16	25	64

Table 11. Summary of number of IHC ordered per case

Number of IHC ordered	Number of cases
1	6
2	10
3	18
4	11
5	12
6	10
7	9
8	5
9	3
10	5
12	1
13	2
23	1

Table 12. IHC (subtypes)

Challenging cases	Total case number	Number of cases IHC ordered
RCCs subtyped	92	40
RCCs unclassified	11	9
Clear cell RCC	73	30
Papillary RCC	12	9
Chromophobe RCC	2	1
Suspicious oncocytic neoplasm	5	4
oncocytoma	18	9

Table 13.1. IHC (subtype versus non-diagnostic). Of 92 RCCs subtyped, IHC was ordered in 40 cases. Of 15 non-diagnostic cases, IHC was ordered in 8 cases. P value was 0.58 which was not statistically significant.

Number of RCCs subtyped with IHC 40	Number of RCCs subtyped without IHC 52	P value=0.58
Number of non-diagnostic cases with IHC 8	Number of non-diagnostic cases without IHC 7	

Table 13.2. IHC (high volume versus low volume pathologists). Of 32 cases signed out by the highest volume pathologist, IHC was ordered in 18 cases. Of 131 cases signed out by the remaining pathologists, IHC was ordered in 75 cases. P value was 1 which was not statistically significant.

Number of cases with IHC by the highest volume pathologist 18	Number of cases without IHC by the highest volume pathologist 14	P value=1
Number of cases with IHC by the remaining pathologists 75	Number of cases without IHC by the remaining pathologists 56	

5.6. Renal core biopsy operators

Of 163 cases, 139 cases included requesting doctor information. Of 15 non-diagnostic cases, 6 cases were performed by a radiologist who did 49 cases, 3 by a radiologist who did 35 cases. Five cases were performed by 5 different radiologists who performed between 1 to 9 cases respectively and one case did not have requesting doctor's information. The non-diagnostic rates of the 2 high volume radiologists versus the remaining radiologists were 10.7% and 7.6% respectively. In testing the hypothesis that high volume radiologists would have a lower non-diagnostic rate than low volume radiologists, p value was 0.60 which was not statistically significant, as shown in Table 14.1.

5.7. Renal core biopsy characteristics

Of 163 cases, 110 cases included information on gauge size. Gauge 20 was used in 90 cases (82%). Gauge 18 was used in 18 cases (16%). The gauge size of the remaining 2 cases was as follows; one used 19 and the other one used both 16 and 18. Of cases using gauge 20, 70 cases fell into the diagnostic group and 12 cases into the non-diagnostic group. Contrarily, of cases using gauge 18, all of the 18 cases were in the diagnostic group. The diagnostic rate was 100% using gauge 18, and the rate decreased to 85% using gauge 20. In testing the hypothesis that large gauge size would increase the diagnostic rate, p value was 0.12 which was not statistically significant, as shown in Table 14.2. Of interest, the high volume radiologists used 20 gauge only, as shown in Table 15.

Regarding the number of cores taken, Figure 9 shows the distribution of core numbers. The average cores taken per case was 2.9, the median and mode were calculated at 3 for each.

In terms of imaging guidance, 138 cases or 85% used CT guided method. Six cases used U/C guided method and in the remaining 19 cases, imaging information was absent.

Table 14.1. Radiologist diagnostic rate (high volume versus low volume). Of 84 cases performed by the 2 high volume radiologists, the non-diagnostic cases were 9. Of 79 cases performed by the remaining radiologists, the non-diagnostic cases were 6. P value was 0.60 which was not statistically significant.

	Number of cases by high volume radiologists	Number of cases by low volume radiologists	
Total cases	84	79	P value=0.60
Non-diagnostic cases	9	6	

Table 14.2. Gauge size (diagnostic rate). Of cases using gauge 20, 70 cases were in the diagnostic group and 12 cases in the non-diagnostic group. Of cases using gauge 18, all of the cases were in the diagnostic group. P value was 0.12 which was not statistically significant.

	Number of diagnostic cases	Number of non-diagnostic cases	
Gauge 20	70	12	P value=0.12
Gauge 18	18	0	

Table 15. Summary of gauge size

Doctor	Total cases performed	Gauge 18	Gauge 20	Size not known
Radiologist 1	49	0	49	0
Radiologist 2	35	0	20	15
Radiologist 3	10	3	2	5
Radiologist 4	9	3	2	4
Radiologist 5	8	0	6	2
Radiologist 6	8	0	7	1

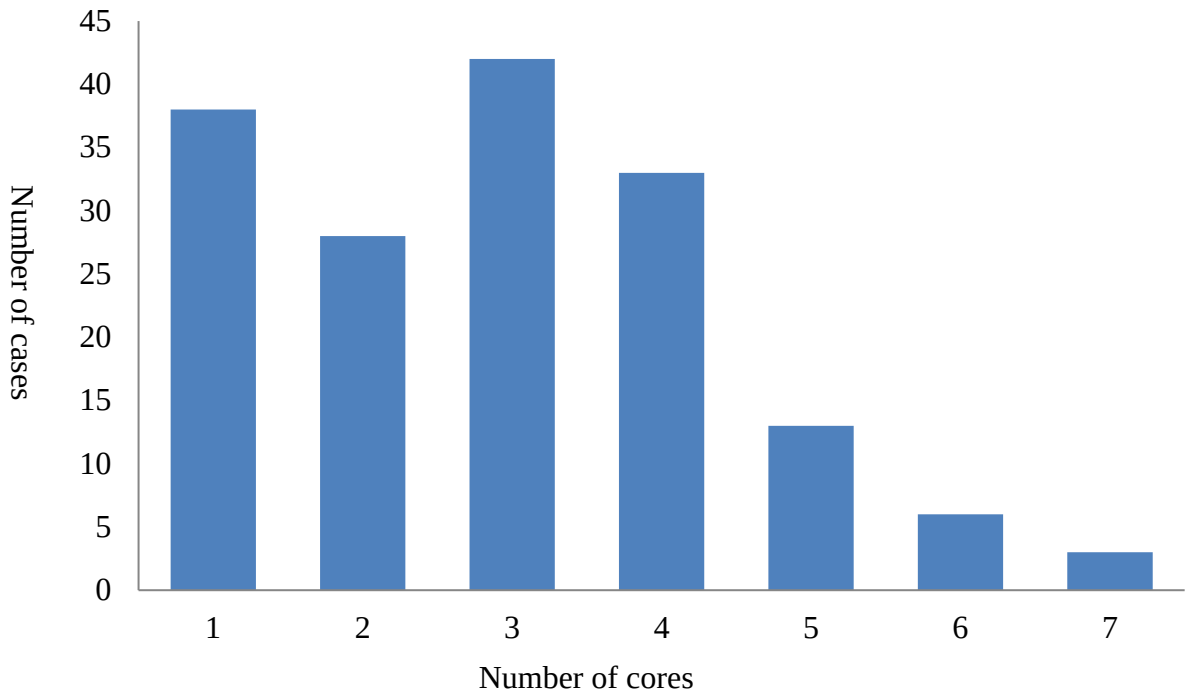

Figure 9. Summary of number of cases in relation to the number of cores taken. 38 cases had 1 core. 28 cases had 2 cores. 42 cases had 3 cores. 33 cases had 4 cores. 13 cases had 5 cores. 6 cases had 6 cores. 3 cases had 7 cores.

6. Discussion

6.1. Diagnostic and grading accuracy in renal core biopsy

Renal core biopsy has been increasingly utilized as a tool in diagnosis of renal masses in the past decade. The main objective of this study was to determine the diagnostic role of renal core biopsy in terms of its accuracy in histological type, subtype and grade. From the recent literature which was published from 2007 to 2015, histological concordance rates ranged from 74 to 100% [8, 12, 13, 14, 15, 16, 18, 19]. For example, the study by Sofikerim et al, (2010) analysed 42 patients, and these patients had renal core biopsies with subsequent surgical resections between 2001 and 2008 [31]. The pathology diagnoses for both procedures were blindly reported by one pathologist. Histological subtype was evaluated at 31 out of 40 or 77.5% concordant and histological type was 36 out of 40 or 90% [31]. In a more recent study, Millet et al, (2012) retrieved 187 renal core biopsies performed between 2006 and 2011 [32]. Of these 187 cases, 61 underwent surgery and the histological subtype from surgical specimen was completely consistent with the renal biopsy result, which meant that the concordance rate of histological subtype was 100% [32]. There are different methods to calculate concordance rate of histological subtype. The studies by Sofikerim et al, (2010), Schmidbauer et al, (2008) and Richard et al, (2015) calculated histology concordance rates by including the diagnosis of RCC unclassified as discordant [31, 33, 34]. In the current study, 163 cases ranging from Mar 2007 to May 2016 were recruited. On the basis of 44 pairs which reported type and subtype in the pathology diagnoses of renal core tissue and surgical specimens, histologic type and subtype between two procedures were 100% concordant. When including additional 5 cases of RCC unclassified at renal biopsy report, concordance decreased to 89%. Therefore, the results from this study are similar to the published data.

This high accuracy in histological typing and subtyping is probably due to the following factors. Firstly, renal core biopsy has been applied in Winnipeg's hospitals for at least 10 years. The operators have accumulated ample experience to master biopsy techniques. Secondly, with the increasing number of renal core biopsy cases, especially in the last few years, the surgical pathologists have increased experience in interpreting the limited amount of renal core biopsy tissue.

In comparison to the high diagnostic accuracy for subtype, the concordance rate of grading in this study was 59% when using a 4-tiered grading system. After applying the collapsed method, the concordance rate increased to 73%. In addition, all of the discordant cases were upgraded from biopsy tissue to nephrectomy specimens. The grading accuracy from published data between 2007 and 2015 ranged from 43% to 78%, and these data were based on the 4-tiered system [8, 12, 13, 14, 15, 16, 18, 19]. In the study by Evans et al, (2015) the grading accuracy improved from 61% to 94% after collapsed method was used [15]. Comparing to the published data, results from the current study fall into the midrange and also confirm that the collapsed method improves the grading accuracy. Under grading may be explained by the following factors. First, RCC is often intrinsically heterogeneous [14, 15]. The limited tissue from core biopsy may not have sampled the highest grade area [14, 15]. Second, the Fuhrman grading system as initially described lacked detailed grading criteria and clear rules on defining highest grade [22, 23, 24]. Recently, ISUP has instituted more objective criteria for grading based on focal nucleolar prominence [8, 18, 20]. In order to define the highest grade, ISUP requires prominent nucleoli at 20 x power with at least 50% of nucleoli displaying the required features in at least one high power field [8, 18, 20]. Use of ISUP grading criteria may minimize grading disagreement between pathologists. However,

current ISUP criteria may also result in upgrading of the nephrectomy specimens, which would increase grade discordance.

6.2. Non-diagnostic rate

In this study, 15 out of 163 cases were non-diagnostic and the non-diagnostic rate was 9.2 %. None of these cases had repeat biopsies performed. This could be explained by the controversial utility of repeat biopsy. Two studies showed that repeat biopsies increased the diagnostic accuracy, while several other studies showed that repeat biopsies had similar results to the initial biopsies [8, 14, 15, 19]. From the data published between 2007 and 2015, the rate of non-diagnostic results varied from 0 - 47% [8, 12, 13, 14, 15, 16, 18, 19]. Therefore, the non-diagnostic rate of this study is at the low range compared to the published data. Of these non-diagnostic cases, 10 cases were entirely non-diagnostic, all with limited tissue or tissue sampled from renal parenchyma only. Four cases had tiny clusters of neoplastic or atypical cells which were insufficient for histology evaluation. One case had a differential diagnosis between Wilms and metanephric adenoma. The nature of the non-diagnostic group was similar to the studies by Evans et al, (2015), Gellert et al, (2014) and Maturen et al, (2007) [13, 15, 16]. When there is only limited amount of tissue for histological examination, the pathologists usually write a descriptive report instead of providing a definite diagnosis [15].

One of our hypotheses was that high volumes would decrease the non-diagnostic rate for pathologists. In the current study, the highest volume pathologist reported 32 cases which were all diagnostic. The non-diagnostic rate for all additional pathologists was 11%, with a p value of 0.04, as shown in table 6.2. However, the numbers are relatively small.

Tumour size and subtype of RCC are possible factors causing unsuccessful biopsy [15, 16, 29]. In this study, only 3 out of 15 non-diagnostic cases underwent subsequent nephrectomy and the greatest tumour dimensions were 5 cm, 5 cm and 6 cm respectively. Due to majority of cases lacking information on tumour size, we cannot state that the non-diagnostic rate is related to smaller masses. The subtype of RCC may also play a role in causing the non-diagnostic result [29]. The study by Al-Ahmadie et al, (2011) indicated that clear cell subtype was more likely to be non-diagnostic probably due to the common presence of necrosis, hemorrhage and cystic change [29]. In this study, the subtypes of 3 cases were clear cell with cystic change, papillary and chromophobe respectively. No conclusion can be drawn on the basis of this limited data.

The operator's skill or experience can affect the biopsy results. According to the study by Gellert et al, (2014), the 2 most experienced operators had non-diagnostic rate at 11% and 14% [16]. In the current study, 2 radiologists performed 84 cases and the non-diagnostic rate was 10.7%. Seventy-nine additional biopsies were performed by multiple radiologists and the non-diagnostic rate was 7.6%. These rates do not have statistical difference with a p value of 0.60, as shown in table 14.2. This suggests that high volumes are not required for success in renal core biopsy. These results may be explained by the operators overall experience in performing core biopsies in multiple organs.

6.3. The role of renal core biopsy in surveillance of renal masses

In this study, 54 cases underwent subsequent nephrectomy with 2 cases being urothelial carcinoma and 52 cases being RCC. None of 18 cases of oncocytoma or 5 cases of "suspicious for oncocytic neoplasm" diagnosed on renal core tissue had surgical resection. Neither did 1 case of metanephric adenoma nor 1 case of "benign tissue". Oncocytoma and presumed oncocytoma

constituted 14% of total cases. This percentage is much higher than non-selected incidence of oncocytoma, which is approximately 5% [1,10]. In contrast, this percentage is similar to the studies by Richard et al, (2015) and Schmidbauer et al, (2008), whose results were 16% and 17% respectively [33, 34]. The high percentage of oncocytoma indicates a selection bias towards this benign neoplasm in the renal core biopsy population. Though oncocytoma does not have a completely specific radiological appearance, a stellate scar is commonly observed on the imaging; however this feature is also present on other renal masses [20]. Additionally, oncocytoma lacks imaging features which are commonly seen in clear cell RCC, particularly hemorrhage, cystic change and necrosis [20].

It is important to note that none of the cases diagnosed oncocytoma or "suspicious for oncocytic neoplasm" were resected in our population. Therefore, needle core biopsy provides a significant management role in these cases.

In the past few years, the application of renal biopsy has been increasing [8, 12, 15]. However, published data show that only one fifth of patients on nephrectomy had preoperative renal biopsies [29]. Furthermore, according to one survey conducted in the United Kingdom, approximately one third of the urologists used renal biopsy on a regular basis, one fifth used infrequently, and the remaining never used it [8]. Another recent survey showed similar result that it was the minority of the urologists who used renal biopsy [14]. As the role of renal core biopsy is significant, it is worth educating the urologists and thereafter expanding the usage of renal biopsy.

6.4. The role of subtype of RCC and grade in surveillance of renal masses

We hypothesized that clear cell RCCs and high grade cases would be more likely to undergo nephrectomy than any other subtypes of RCCs and low grade cases. In order to test this hypothesis, the primary tumour group was specifically chosen and the other 3 groups were excluded. The primary tumour group had 127 cases with 74 cases of RCCs having definite subtypes; the details of the subtypes are displayed in Table 3.2.3. Of 74 RCCs subtyped, 58 cases were clear cell RCCs. Furthermore, of 58 clear cell RCCs and 16 other definitely subtyped RCCs, 32 and 9 cases underwent nephrectomy respectively. P value was calculated at 1.0 with no statistically significant difference, as shown in Table 6.1. On the basis of the above results, clear cell RCCs are not more likely to undergo nephrectomy than other subtypes of RCCs. Apart from nephrectomy option, our study does not have additional information regarding clinic management after renal biopsy.

In terms of the role of grading, 47 out of 127 primary tumour cases were graded with 33 cases of low grade, 13 cases of high grade and 1 case undetermined; the details of the grade are shown in Table 4.2. Of above graded cases, 24 cases underwent nephrectomy with 19 cases of low grade, 4 cases of high grade and 1 case undetermined. P value was 0.19 with no statistically significant difference in grade between nephrectomy and non-nephrectomy cases. The details are shown in Table 8.2. Therefore, grading does not seem to have a significant effect in treatment strategy.

6.5. Partial nephrectomy versus radical nephrectomy

Surgery is a treatment option for a potentially malignant renal mass and it includes either radical or nephron sparing partial nephrectomies. Nephrectomy is the ideal and effective procedure to remove the tumour mass in terms of tumour control [26]. However, the concern related to radical

nephrectomy is the loss of significant amounts of nephron with the remaining nephrons undergoing adaption [25, 26]. This adaptive change causes functional and structural hyperfiltration injury in the remaining kidney [25, 26]. With long term adaption, the patients can develop proteinuria, hypertension, decreased glomerular filtration, and eventually renal failure [25, 26]. These adaptive changes are more likely to occur on patients who have a medical history of hypertension or diabetes mellitus [25, 26]. Additionally, hypertension is one of the factors that can increase the incidence of RCC, as mentioned in the Introduction [1]. Therefore, if the patient develops RCC then undergoes nephrectomy; the same patient may have a higher possibility of developing renal function loss due to pre-existing medical conditions [25]. In order to prevent renal function loss, it is important to preserve as much renal parenchyma as possible [28]. In the 1980s and 1990s, partial nephrectomy was introduced to meet the above requirements [28]. Since then, several studies have showed that partial nephrectomy is less likely to result chronical renal failure than radical nephrectomy [25]. In terms of oncological control, partial nephrectomy shows successful results for tumour dimension less than 4 cm or sometimes greater than 7cm [17].

According to the 2009 guidelines of American Urological Association (AUA), partial nephrectomy should be the first option for T1a tumour and could be an option for T1b as well [27]. In the current study, of 52 RCCs undergoing nephrectomy, 24 RCC cases were partial nephrectomy with remaining 28 RCCs undergoing radical nephrectomy. The average tumour dimension for partial nephrectomy cases was 3.4 cm compared to 5.8 cm for the radical nephrectomy cases. Of the partial nephrectomy cases, approximately 90% were staged at T1, with the details in Table 7.2. On the contrary, approximately 57% of the radical nephrectomy cases were staged at T1, with the details in Table 7.2. The urologists involved in this study seem to follow the 2009 AUA guidelines, and consider not only oncological consequence but also

preservation of renal function when surgery options are decided. In case when partial nephrectomy is not feasible, consultation with a nephrologist before surgery or the assessment of non-tumoral renal parenchyma are useful ways to predict renal function after surgery [26, 27] In Winnipeg hospitals, assessment of nonneoplastic renal parenchyma is routinely performed in nephrectomy specimens (personal communication with Dr. H. R. Wightman). If the patient has pre-existing medical conditions, such as hypertension or diabetes, medical treatment should be taken to prevent the progressive renal function insufficiency after surgical procedure [26].

6.6. The role of IHC in renal core biopsy diagnosis

The application of IHC has shown to help with differential diagnosis and be positively related to diagnostic accuracy [15, 16]. In this study, IHC was ordered in 40 out of 92 RCCs subtyped and 8 out of 15 non-diagnostic cases. P value was 0.58 with no statistically significant difference between RCC cases typed and subtyped and non-diagnostic cases, as shown in Table 13.1. The current study also tested if IHC was ordered more frequently by the highest volume pathologist. P value was 1.0 with no statistically significant difference, as shown in Table 13.2. The results from the current study do not establish a correlation between the application of IHC and diagnosis rate.

6.7. The role of FNA

FNA and core biopsy are two methods that are utilized to sample renal mass tissue. Compared to the core biopsy, the diagnostic rate of FNA has been shown to be relatively low with relatively high non-diagnostic results [12, 13]. In the current study, 100 renal biopsy cases had a concurrent FNA. Of 100 cases, 31 cases fell into the diagnostic group with the rest into either unsatisfactory or descriptive groups. The published literatures showed that the diagnostic rate of FNA ranged

from 64% to 97% and was usually 20% lower than that of renal biopsy [12, 30]. From the current study, the diagnostic rate of FNA was 31% versus 84% in renal core biopsy. This result was even lower than the published data, which could be explained by the following reasons. First, the optimal technique may not be used, causing the sampled tissue to be insufficient. However, no detailed information regarding the technique is available for this study. Second, the cytopathologists or cytotechnologists may be hesitant to make a definite diagnosis on FNA material, particularly when superior core material is not available.

When the diagnoses of FNA and core biopsy were compared together, 32 pairs carried same or similar diagnostic information; 59 FNAs had less information and 4 FNAs provided more information. Of these 4 FNAs, 3 concurrent core cases were non-diagnostic and 1 FNA provided subtype of RCC; the details of 4 FNAs are shown in Table 9. With diagnostic rate of FNA being 31% and 2.4% of FNAs adding more information than core biopsy, FNA seems to have limited added value when FNA and core biopsy are combined together. However, continued use of FNA is recommended because FNA is shown to increase the diagnostic rate in the literature [14, 30]. Explanation of the relatively poor performance of FNA in this study would require slide evaluation, which is beyond the scope of the study.

6.8. Biopsy technique: needle size

In the current study, gauge information was provided in 110 out of 163 cases. Of 110 cases, 82% used gauge 20 and 16% used gauge 18. This result is contradictory to the published data, in which the larger size, 18 gauge is the one more commonly used with a better diagnostic rate [8, 14].

Of cases using gauge 20, 70 cases were in the diagnostic group and 12 cases in the non-diagnostic group. In contrast, of cases using gauge 18, all of the 18 cases were in the diagnostic

group and none of case was non-diagnostic. The diagnostic rate was 100% with gauge 18, and decreased to 82% with gauge 20. It seemed that gauge 18 was superior to the diagnostic sensitivity. However, p value was 0.12 with no statistical significance, as shown in Table 14.1. This insignificant p value may be caused by the relatively small number of cases.

6.9. The limitations and future directions of the study

This study has some limitations. First, the number of cases involved in this study is relatively small. For a future study, more cases should be included for better analysis. Second, when the cases were retrieved from the database of DSM, the key words used as per Methods were designed to preferentially identify core biopsy cases performed for renal masses and exclude renal core biopsy performed for medical kidney disease. It is possible that the search criteria eliminated some non-diagnostic biopsies. Third, surgical specimens were used as the gold standard. In this study, only 54 out of 163 cases proceeded to nephrectomy with two thirds of cases having no histological confirmation. This could affect the calculations of histological accuracy and grading accuracy. Fourth, aside from nephrectomy data, this study does not have additional information regarding clinic management after renal biopsy. Without such information, the impact of renal core biopsy in clinical management cannot be fully assessed.

For future direction, the number of cases needs to be increased. Imaging reports and clinical data should be included as well.

7. Conclusions

The main objective of this study is to determine the diagnostic rate and accuracy of renal core biopsy in the diagnosis of carcinoma type, subtype and nuclear grade by using surgical specimens as the gold standard. This retrospective study recruited 163 cases, ranging from 2007 to 2016. The age of the patients spanned from 11 to 90 years old with male to female ratio being 2:13 to 1. The diagnostic rate was 84% and non-diagnostic rate was 9.2%. Histologic type and subtype were 100% concordant, which shows that this study achieves excellent accuracy in the diagnosis of histology subtypes of RCCs.

Additional findings from the study are listed below:

1. None of the oncocytoma or “suspicious oncocytic neoplasms” diagnosed on renal core biopsy tissue had surgical resection. Therefore, needle core biopsy provides a significant management role in these cases.

2. Histology subtype and grade did not affect clinical decision making.

3. FNA had limited added value when FNA and core biopsy were combined together.

4. No difference in diagnostic accuracy was seen between high and low volume radiologists.

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