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# Pathologic Concordance of Sporadic Synchronous Bilateral Renal Masses

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## Abstract

**Objective—**Bilateral synchronous sporadic enhancing renal masses account for as many as 6% of newly diagnosed cases of renal cell carcinoma (RCC). The data regarding concordance rates of malignant and benign phenotypes, histologic subtypes, nuclear grade, and pathologic stage are limited.

**Methods—**We reviewed the Surveillance Epidemiology and End Results (SEER) database, the published English language literature and our own institutional tumor registry to identify all cases of sporadic, synchronous localized (cT1-3NoMo) bilateral renal masses. Malignant and benign concordance rates were defined as agreement of any benign or malignant tumor type bilaterally. Histologic concordance was defined as bilateral histologic agreement. Tumors with mixed histologies were discordant unless all patterns were identical bilaterally. Nuclear grades were concordant if bilateral tumors were either “high” grade or “low” grade.

**Results—**The malignant concordance rate in the SEER data was 99% (273/274), and benign concordance was 0% (0/1). In the published literature and FCCC series, malignant concordance rates ranged from 84% to 95%, while benign concordance ranged from 39% to 67%. The SEER data revealed a histologic concordance rate of 93% (256/274) and nuclear grade concordance was 85% (88/103).

**Conclusions—**These data demonstrate that in cases of bilateral sporadic localized synchronous renal masses, a diagnosis of ipsilateral RCC is associated with contralateral RCC in the vast majority of patients, while ipsilateral benign pathology is associated with contralateral benign disease at a substantially lower rate. Histologic concordance is similarly high, meaning most cases of clear cell or papillary tumors ipsilaterally are concordant in the contralateral kidney. Concordance rates of nuclear grade were slightly lower. These data are important when counseling and managing patients with bilateral synchronous sporadic renal tumors.

## Introduction

Patients presenting with bilateral synchronous renal tumors (BSRT) represent a unique population accounting for approximately 1-6% of all patients with sporadic enhancing renal masses.[1-4] BSRT pose multiple prognostic and therapeutic challenges, similar to those of

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patients with hereditary RCC. Recent reports demonstrate cancer free survival rates are comparable among patients with sporadic unilateral and bilateral renal cell carcinoma (RCC) following surgical intervention.[2,5] Although surgery remains the mainstay of treatment, several institutional series demonstrate an increased risk of chronic renal insufficiency following radical nephrectomy for sporadic RCC.[6-8] Patients treated surgically for bilateral disease often require staged procedures and complex nephron sparing approaches with associated reconstruction of the renal remnant.[9] Therefore, the risk of progressive renal insufficiency, hyperfiltration injury and the need for future renal replacement therapy is likely to be even higher in this select population.

When planning surgical strategies in patients with BSRT the incidence of benign disease, either unilateral or bilateral, needs to be carefully considered in light of the risks of operative intervention. While percutaneous fine needle aspiration and/or core biopsy have been utilized in selective cases, the ability of the evaluating pathologist to delineate malignant and benign pathology is limited, particularly with low grade lesions with oncocytic features.[10-18] Thus a negative aspiration or biopsy rarely obviates the need for surgical extirpation. The ability to predict benign or malignant concordance reliably may help select patients for ablative therapies or alternatively active surveillance of their enhancing renal masses.[19] Here, we reviewed the collective experience evaluating pathological concordance rates of sporadic BSRT reported in SEER, the published English literature, and treated at Fox Chase Cancer Center. Specifically, we analyze the concordance rates of malignant versus benign disease, histological type, tumor stage, and nuclear grade.

## Materials and Methods

The Surveillance Epidemiology and End Results 9 Registries Database (SEER) was utilized to identify a cohort of patients diagnosed with BSRT between the years 1988 to 2002. BSRT was assigned to patients presenting with bilateral renal tumors within six months of each other.[20] SEER is maintained by the National Cancer Institute and collects information on incident cancers diagnosed in approximately 14% of the United States population. Analyses were performed using STATA 8.0. Patients less than 30 years old and those with inadequate histologic classification were excluded from analysis. We used the International Classification of Diseases 03 (ICD03) to determine histology. Codes used were: 8310, 8270, 8317, 8050, 8130, 8260, 8290, 8320, 8140. Additional histologies we classified as “other.” SEER describes tumor grade as well, moderately, poorly differentiated, undifferentiated and unknown. Well and moderately differentiated tumors were categorized as “low grade”, and poorly differentiated and undifferentiated as “high grade.”

All published reports reviewing BSRT in the English literature in a MEDLINE review (1966 to the present; key words: bilateral renal masses, renal neoplasm). Series lacking sufficient histologic evaluation of the BSRT were excluded from further analysis. The Fox Chase Cancer Center renal tumor registry was queried for all cases of sporadic BSRT presenting to and treated at our institution between 2000 and 2007. Synchronous localized disease was defined as any patient with radiographic evidence of cT1-2N0M0 bilateral non-hereditary disease on initial presentation. In all analyses, multifocal disease was defined as any one kidney with more than one tumor present on initial presentation.

The term “concordance” was used to compare characteristics between bilateral renal tumors. Malignant concordance was defined as RCC of any histologic subtype identified bilaterally. Benign concordance was defined as bilateral benign disease without evidence of malignancy on both sides. Histologic concordance was used to compare differing histologic subtypes of RCC (according to Heidelberg classification) or benign disease.[21] For example, clear cell RCC and papillary RCC would be characterized as having malignant concordance, but would

be histologically discordant. Tumors with mixed histology were considered histologically discordant unless all patterns were identified bilaterally. Tumor grade was determined according to the Fuhrman nuclear grading classification in cases of clear cell carcinoma. “Low grade” lesions were considered to be Fuhrman grade 1 or 2 clear cell RCC and/or any designation by the interpreting pathologist as “low grade”. “High grade” lesions were considered to be Fuhrman grade 3 or 4 and/or any designation by the pathologist as “high grade”. Nuclear grade concordance was determined using these “low” and “high” designations.

## Results

Review of the SEER database identified 308 patients with BSRT treated within 6 months of each other (synchronous). Adequate pathologic information was available to evaluate malignant concordance in 274 patients, histologic concordance in 274, and nuclear grade concordance in 103 patients. Of these patients, 99% (273/274) had bilateral RCC. The only patient noted to be discordant possessed a RCC in one renal unit and a contralateral oncocytoma. Histologic concordance in patients with bilateral RCC was 93% (256/274). Nuclear grade was concordant in 85% (88/103) patients such that the majority had either bilateral high or bilateral low grade disease. (Table 1)

A MEDLINE search of the English literature identified two series evaluating the pathology of sporadic BSRT.[1-2] Both series report on the management and outcomes of this group of patients and do not specifically address pathologic concordance rates. These combined studies include 148 cases of RCC of which pathological concordance data were available in 135 cases (Table 2). These studies reported information on bilateral pathology, and Patel et al additionally reported on specific RCC histologic subtype. However, both series did not evaluate concordance in terms of pathologic stage or grade. Additionally, the series by Patel et al contained 13 patients with asynchronous disease.

Review of the Fox Chase Cancer Center tumor registry identified 731 cases of sporadic kidney cancer presenting to and treated at our center between 2000 and 2007. Of these 4% (28/731) of patients presented with and were treated for BSRT. Four patients were excluded from analysis due to inadequate pathologic data, leaving 24 patients for analysis. The sample population consisted of 75% (18/24) males with a median patient age of 68 years (mean 66, range 35-83). In total, 72 tumors were identified with a median size of 3.0 cm (mean 4.7cm, range 0.3cm- 30cm). Multifocal disease was present in 46% (11/24) of patients with BSRT. 33% (8/24) had unilateral multifocal tumors and 13% (3/24) possessed bilateral multifocal tumors in the absence of other manifestations or family history of hereditary RCC. 35% (25/72) of all lesions were≥cT1b. Malignant disease was present in 83% (20/24) of all patients presenting with bilateral synchronous renal tumors. Of these patients 95% (19/20) had bilateral malignant disease. Only 4% (1/24) of patients demonstrated discordance in regard to benign and malignant disease. The lone patient with discordant pathology had an oncocytoma in one renal unit and a chromophobe RCC on the contralateral side. Histologic subtypes of RCC identified included clear cell, chromophobe, and papillary. Patients with bilateral RCC demonstrated 89% (17/19) concordance in respect to histologic subtype. Nuclear grade was concordant in 79% (15/19) of patients and pathologic stage was concordant in 58% (11/19) of patients overall. The majority of patients presented with bilateral T1a and/or T1b tumors, 74% (14/19). Bilateral benign disease (benign concordance) accounted for 17% (4/24) of patients. Three patients had bilateral oncocytomas and one patient had bilateral angiomyolipoma without evidence of tuberous sclerosis. Of the patients with benign disease in one renal unit the concordance rate of having benign disease in the contralateral renal unit was 67% (4/6) (Table 2).

## Comment

The management of BSRT presents several challenges. Radiographic imaging modalities cannot differentiate between benign and malignant renal pathology. Additionally, pathologic assessment of renal tumors via percutaneous biopsy or fine needle aspiration is often limited by insufficient sampling, false negatives, the inability to establish pathologic data regarding perirenal fat and vascular invasion, and difficulty differentiating oncocytic type neoplasms.[10-18] As a result, surgical intervention remains the primary treatment for enhancing renal masses. However, in patients presenting with BSRT, other issues must be addressed including the need for complex nephron sparing surgery, staged procedures, prognosis, decline in renal function, the prospect of progressive renal insufficiency, hyperfiltration injury, and the need for future renal replacement therapy. With these issues in mind, concordance of malignancy, histologic subtype, nuclear grade, and pathologic stage may have a significant impact on treatment algorithms and disease specific prognosis.

Prior single institutional retrospective series have demonstrated high concordance rates of malignant disease in patients presenting with bilateral sporadic renal tumors. Patel et al, reviewed their experience with 46 patients with bilateral sporadic renal tumors.[2] The observed incidence of bilateral tumors in their dataset was 4.25%. Of the patients with a pathologically confirmed renal malignancy, a 95% concordance rate of contralateral malignant disease was noted. While those patients with benign disease in one renal unit exhibited a 60% benign concordance rate in the contralateral kidney. However, this series did include 13 patients with asynchronous tumors. The largest series to date by Blute et al included 94 patients with BSRT. The observed concordance rate of malignant disease was 84% if RCC. While the concordance rate of bilateral benign disease was 39%. When data from these series are analyzed with FCCC and SEER data demonstrating a malignant concordance rate >95%, it suggests that the finding of malignant pathology in one kidney strongly predicts the occurrence of malignancy in the contralateral kidney. Additionally, the finding of benign disease is a poor predictor of benign disease in the contralateral kidney.

Concordance rates for histologic subtype were 89% in our institutional series, which is consistent with the 93% histologic concordance rate noted in the SEER database. These rates are slightly greater compared to the 76% histologic concordance rate noted by Patel et al. The most common histologic subtype identified bilaterally in all series was conventional clear cell RCC. Discordant histology can impact prognosis and is important when discussing pathology with patients with synchronous disease.[22] This high rate of histologic subtype concordance seems logical as we learn more about the molecular pathways involved in the transformation of renal epithelia.[23] Prior reports have failed to document concordance rates of nuclear grade which is an important pathologic prognostic variable in RCC. The concordance rates for nuclear grade and pathologic stage were 79% and 58% respectively in our institutional series and nuclear grade concordance was 85% in the SEER data. A recent retrospective review of 629 patients with RCC revealed 5 year disease free survival for nuclear grade as 87%, 71%, 46%, and 15% for nuclear grades G1-G4.[24] Similar findings were seen in several other published series concluding nuclear grade impacts prognosis and patient outcome.[25-27] Furthermore, these studies also revealed that pathologic stage asserts itself as an independent predictor of disease specific survival. Ficarra et al. report a dramatic difference in five and ten year disease specific survival based on TNM stage: 94% and 92% in stage I, 90% and 78% in stage II, 63% and 46% in stage III, and 28% and 16% in stage IV. [28] Discordant pathologic stage and grade can have significant effects on prognosis and 10 year cancer specific survival, since outcomes are likely determined by tumor with the worst prognostic features. Several studies have reported on the survival outcomes of unilateral versus bilateral tumors. A recent study demonstrated that the cancer specific survival outcome in patients with BSRT was similar to survival outcomes in patients with unilateral disease.[5,29] Of note, the investigators found a small

increase in local tumor recurrence and demonstrated that selected bilateral tumors can be safely approached at a single surgical procedure. However, Novick et al report a statistically significantly decreased five-year survival rate in patients with bilateral disease compared to patients with unilateral disease.[30] Of interest in that series, a significant difference in survival between synchronous and metachronous tumors was not noted.

Although series have evaluated the clinical and histologic similarities of BSRT, limited information is available on the genetic clonality of BSRT. Genetic clonality refers to two or more tumors derived from the same origin, suggesting metastatic disease. In contrast, tumors that are genetically dissimilar are considered to represent separate and genetically distinct primary tumors. Thus, genetic clonality is an important consideration when approaching patients with BSRT, as the implications of a metastatic and a distinct primary tumor differ drastically. In the available series investigating the genetic clonality of BSRT sample size is relatively small, ranging from 3-10 patients.[31-33] Genetic clonality was evaluated by different methods in each series and ranged from 0-60%. Because of the limited sample size in each series and the lack of adequate follow up, it is difficult to assess the impact of genetic clonality on clinical outcomes. Future investigations involving more patients with extended follow up are needed in order to determine the true clinical importance of genetic clonality when treating patients with BSRT.

Multifocal tumors were identified in 46% of patients with bilateral sporadic tumors inour series. Multifocality was present 14% of patients bilaterally and in 32% of patients unilaterally. This represents a slightly higher overall percentage than the 22% of patients with multifocal tumors reported in the series by Patel et al. A series by Richstone et al reported the occurrence of multifocal renal tumors in 5% of all patients with RCC, and 11% of patients with synchronous BSRT.[3] Additional studies have also supported the notion that the incidence of multifocal tumors appears to be greater in patients with bilateral synchronous disease than unilateral disease.[3] This finding becomes important when considering nephron sparing surgery for patients with bilateral disease. Ultimately the surgeon must be cognizant of this higher incidence of multifocality when determining operative plans on these complex patients with BSRT.

There are several limitations to these current data. One important factor remains that only patients with sufficient pathologic data could be included in the study. This exclusion factor eliminates data from several important subgroups of patients with BSRT, specifically patients in active surveillance protocols and those undergoing ablative therapies with insufficient tissue for pathologic diagnosis on biopsy. Masses treated by these modalities typically represent small lesions that could possibly impact concordance data. A second limitation in this series is illustrated by a significantly lower number of patients, 29%, with available data on nuclear grade. Additionally, interobserver variability can impact nuclear grade assignment. This is definitely a limitation on data obtained from SEER, as there is not a central pathology review of these patients. Furthermore, comparisons of concordance rates between individual series must be made with caution because of the differences of populations examined and lack of centralized pathology review. Finally, further data regarding survival differences of patients with synchronous versus metachronous bilateral versus unilateral renal masses are needed.

## Conclusions

A high rate of malignant and histologic concordance is observed in patients with sporadic BSRT. The data suggests that when RCC of any type in present on one side RCC will be present on the contralateral side in a vast majority of patients; however, when benign disease is present there is a lower chance of only benign disease on the contralateral side. Nuclear grade

concordance was relatively high at 79%-85%. These data are important when counseling patients, especially in patients with benign disease noted in the first operative specimen.

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## Table 1

SEER histology and grade

| Ipsilateral Renal Unit | | | | |
|---|---|---|---|---|
| Contralateral Renal Unit | *Histology* | | | |
| | | Clear cell | Papillary | Chromophobe |
| | Clear cell | 245 | 6 | 1 |
| | Papillary | 5 | 8 | 3 |
| | Chromophobe | 1 | 1 | 3 |
| | Oncocytoma | 1 | 0 | 0 |
| | *Nuclear Grade* | | | |
| | | Low Grade (I/II) | | High Grade (III/IV) |
| | Low grade (I/II) | 72 | | 9 |
| | High Grade (III/IV) | 6 | | 16 |

**Table 2**

Reported concordance of malignant and benign disease

| Study | N | % bilateral malignant histology | % bilateral benign histology | % High Grade concordance | % low grade concordance |
|---|---|---|---|---|---|
| SEER | 274 | 99% (273/274) | 0% (0/1) | 52% (16/31) | 83% (72/87) |
| FCCC | 24 | 95% (19/20) | 67% (4/6) | 44% (4/9) | 75% (10/15) |
| Blute et al | 94 | 84% (71/85) | 39% (9/23) | N/A | N/A |
| Patel et al | 41 | 95% (36/38) | 60% (3/5) | N/A | N/A |