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Adult Sporadic Multifocal Renal Cell Carcinoma: Helical CT and Pathology Correlations in a Recent and Consecutive Set of Patients Assessed with a Multidisciplinary Approach

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Abstract

Background and Aims: To assess helical CT sensitivity in detecting preoperatively Multifocal Renal Cell carcinoma (MFRCC) and clinical occult multifocality in a contemporary and consecutive set of patients according to a multidisciplinary approach.

Methods: The renal masses were assessed preoperatively by volumetric multislice helical CT with the objective to detect multifocality. Renal cells carcinoma (RCCs) were classified as unifocal (UF) or multifocal (MF). MFRCCs were selected in 2 groups including CT detected (CT+) and CT undetected (CT-). RCCs were classified in UF and MF. MFRCCs were selected in 2 groups including CT+ and CT-. CT and pathologic findings of MFRCCs were correlated and CT sensitivity was assessed. Statistical methods were performed in order to compare the CT sensitivity with the overall mean sensitivity calculated from the reported literature, to assess statistical inference between UF and MF – RCCs; and to detect statistical significance between CT(+) and CT(-) MFRCCs .

Results: Over a period of 24 months, 116 kidney units (KU) of 111 patients were surgically treated for RCC. Multifocality was assessed in 13/116 KU of 12 patients (10.8%). Helical CT detected preoperative multifocality in 8/111 patients (7.2%) and preoperative occult multifocality was assessed in 4 (3.6%), as well. Helical CT sensitivity difference between our (66.7%) and the reported literature experience (22.9%) was significant ($p < 0.0001$). Significant predictors for multifocality were tumor size ($p = 0.007$), laterality ($p = 0.002$), pT ($p = 0.008$) and surgery ($p = 0.0002$). Primary tumor size ($p = 0.05$) and satellite tumor size ($p = 0.01$) were significantly correlated to CT-undetected (CT-) multifocal tumors.

Conclusions: In our experience, helical CT was effective in improving preoperative detection of sporadic primary MRCC as well as in lowering clinical occult multifocality. Clinical predictors of multifocality including bilaterality and primary tumor size as well as technical and methodological improvements in performing Helical CT will improve its sensibility in detecting renal masses less than 0.5 cm. CT preoperative detection of clinical multifocality may help in planning effective preoperative surgical treatment as well as lowering local recurrence after nephron sparing surgery.

Keywords: Renal Cell Carcinoma, Multifocal Renal Cell Carcinoma, Helical CT

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Introduction

Renal cell carcinoma (RCC) accounts for approximately 3.5% of all malignancies and it is the third most common as well as the most lethal of all genitourinary tumors (1). RCC has the biological potential for multifocality (MFRCC) which includes both hereditary and sporadic forms, the latter having more clinical impact. The clinical incidence of sporadic MFRCC has been reported since 1988 and Mukamel was the first investigator who focused on this topic (2). Successive literature reports (3-15) have shown that there was a difference between preoperative and postoperative detection of MRRCC and, as a result, the clinical incidence of sporadic MFRCC was undetected preoperatively and clinical occult multifocality was the evident consequence when assessing postoperative findings (6, 7, 10, 12, 14, 16). It has also been shown that clinical occult multifocality was related to the low CT sensitivity, (6, 7, 10, 12, 14-16). But the reported literature is not always easy to understand when investigating and focusing specifically on this topic. Thus, with a multidisciplinary approach, the objective of this study was to focus on helical CT sensitivity in detecting preoperatively MFRCC and assessing clinical occult multifocality in a contemporary and consecutive set of patients.

Table 1. Clinical incidence of sporadic MFRCC in large literature series

Authors	Year	n/total	(%)
Mukamel et al.	1988	13/66	19.7
Chang et al.	1991	7/100	7
Steinbach et al.	1994	13/490	2
Nissenkorn et al.	1995	3/27	11.1
Oya et al.	1996	7/108	6.5
Kletscher et al.	1995	16/100	16
Whang et al.	1995	11/44	25
Rabbani et al.	1997	9/83	11
Gohji et al.	1998	10/64	15.6
Kinouchi et al.	1999	8/124	6.5
Baltaci et al.	2000	22/103	21.4
Lang et al.	2004	37/155	14.5
Richstone et al.	2004	57/1071	5.3
Klatte et al.	2007	216/938	23
Porcaro	2008	12/111	10.8

Materials and Methods

Kidney tumors were assessed according to a multidisciplinary approach in order to detect multifocality which was defined as the existence of at least 2 RCCs in the same kidney unit (KU). The renal masses were assessed preoperatively by volumetric multislice helical CT with the objective to detect multifocality. CT examinations were performed on Somatom plus 4 scanners. For each study, 120 ml of iohexol was injected IV at 3 ml/sec. CT scans were detected before and after the administration of 120 ml (velocity 3 ml/sec) of contrast media according to the multiphasic technique including the vascular, cortical nephrographic, diffuse nephrographic and excretory phases. Images were obtained during the different phases and the CT scanning protocol included 0.75-sec scans with 3.5 mm collimation. For patients undergoing nephron sparing surgery (NSS), multifocality in the kidney unit (KU) was assessed through both accurate intraoperative observation and ultrasound investigation.

The surgical specimens were assessed by the uropathologist. In nephrectomy specimens, the parenchyma was sectioned serially at approximately 3 – 5 mm of thickness and all subcapsular and intraparenchymal satellite lesions were counted and studied

Table 2. Clinical incidence of multifocality (OCI-MF), preoperative detection of multifocality (PD-MF), occult preoperative multifocality (POMF) and CT sensitivity (CTS) in detecting sporadic MF-RCC as reported from the literature and compared with our experience

		OCI-MF		PD-MF		PO-MF		CTS	
Authors	**Year**	**n/total**	**(%)**	**n/total**	**(%)**	**n/tot**	**%**	**n/tot**	**%**
Oya	1996	7/108	6.5	1/108	0.9	6/108	5.6	1/7	14.0
Kletscher	1995	16/100	16	7/100	7.0	9/100	9.0	7/16	44.0
Gohji	1998	10/64	15.6	1/64	1.5	9/64	14.0	1/10	10.0
Schlichter	2000	48/281	17.1	11/281	13.5	37/281	13.0	11/48	22.9
Baltaci	2000	22/103	21.4	3/103	2.9	19/103	18.4	3/22	14.0
Richstone	2004	57/1071	5.3	19/1071	1.8	38/1071	3.5	19/57	33.0
Porcaro	2008	12/111	10.8	8/111	7.2	4/111	3.6	8/12	66.7

macroscopically. Primary and satellite RCCs were sampled and studied according to routine pathology standards. Tumors were diagnosed histologically according to the Heidelberg classification (17), staged according to the TNM classification (18) and graded according to the four grade system of Fuhrman (19).

RCCs were classified in unifocal (UF) and multifocal (MF). MFRCCs were selected in 2 groups including CT detected (CT+) and CT undetected (CT-). CT and pathologic findings of MFRCCs were correlated and CT sensitivity was assessed. Approximate inference for a single proportion with the normal distribution was used to compare the CT sensitivity with the overall mean sensitivity calculated from the reported literature. In order to assess statistical inference between UF and MF – RCCs, the chi squared test was performed for noncontinuous variables (sex, KU, surgery, bilaterality, histology, stage and grade) and the two-sample ANOVA F-test for the continuous ones (age and tumor size). For assessing statistical significance between CT(+) and CT(-) MFRCCs the Fisher's exact test was performed for noncontinuous variables (sex, KU, surgery, number of primary and satellite tumors, histology, stage and grade) and the two-sample ANOVA F-test was performed for the continuous variables (age, size of primary and satellite tumors).

Results

Over a period of 24 months, 116 kidney units (KU) of 111 patients were surgically treated for RCC. Bilaterality was detected in 8/111 patients. Multifocality was assessed in 13/116 KU of 12 patients (10.8%). The literature reported clinical incidence of MF RCC including our experience is summarized in Table 1. The overall mean incidence of MFRCC from the reported literature was calculated as 13.02% (SD = 7.02). Helical CT detected preoperative multifocality in 8/111 patients (7.2%) and preoperative occult multifocality was assessed in 4 (3.6%), as well. Table 2 shows our CT findings and those from the reported literature where the mean overall preoperative CT-detected multifocality was 4.6% (SD = 4.87), the mean overall occult multifocality 10.58% (SD = 5.58%) and the mean overall imaging sensitivity 22.9% (SD = 13.2%). As

Table 3. Clinical and Pathologic Features of patients with UF (N=99) and MF (N=12) RCC

Variables	UF	MF	P value
Patients	99	12	<
Age			
mean	61	56	0.3029
range	27 - 87	33 - 85	
Sex			
male	66	9	0.5603
female	33	3	
KU			
dx	43	7	0.7618
sx	60	6	
Surgery			
NXT	90	6	0.0002
NSS	13	7	
Tumors			
number	103	29	
mean size	5.39	2.61	0.0007
range	1.4 - 14	0.3 - 10	
Laterality			
unilateral	95	8	0.0002
bilateral	4	4	
Hystology			
clear cell	82	23	0.351
papillary	13	6	
chromoph	5	0	
bellini	3	0	
Stage T			
1a	44	16	0.0088
1b	15	0	
2	14	1	
3a	21	12	
3b	9	0	
Grade			
G1	8	2	
G2	58	14	0.2643
G3	30	13	
G4	7	0	

UF, Unifocal; **MF**, Multifocal; **RCC**, Renal cells carcinoma; **KU**, kidney units.

a result, helical CT sensitivity difference between our (66.7%) and the reported literature experience (22.9%) was significant (p <0.0001). Clinical-pathologic characteristics of unifocal (UF) and multifocal (MF) RCCs of our set of patients are depicted in table 3. As shown, significant predictors for multifocality were tumor size (p = 0.007), laterality (p = 0.002), pT (p = 0.008) and surgery (p = 0.0002). Clinical and pathologic findings of CT-detected (CT+) and -undetected (CT-) multifocal tumors are reported in table 4. Primary tumor size (p = 0.05) and satellite tumor size (p = 0.01) were significantly correlated to CT-undetected (CT-) multifocal tumors.

Discussion

RCC has the biological potential for multifocality which has also been confirmed by our experience where the detection rate of multifocality (10.8%) was close to the calculated overall mean incidence of the reported literature in clinical series (13.02%) (2-15) as well as autopsy series (13.85%) (20).

As confirmed by our experience, MFRCCs have the propensity to escape detection (7, 8, 10, 12, 14, 16). The calculated risk of the mean occult preoperative multifocality from the literature is quite high (10.58%) and the results of our experience (3.6%) were located to the lowest values (3.5%). The low incidence of occult MFRCC and the significant CT sensitivity in detecting MFRC could be explained both by the context of the study which was planned in a multidisciplinary approach as well as to the sharp evaluation of unenhanced CT scans together with the enhanced corticomedullary and nephrogenic phases. As a result, MFRRC is under-reported preoperatively and for patients with MFRC undergoing NSS there is a risk of missing satellite tumors which has been calculated to be 40% (10). The risk for unknown multifocality could explain the incidence of locally recurrent disease after NSS (21, 22). Thus the local recurrence rate after NSS may reflect undetected preoperative multifocality or occult multifocal RCC.

Table 4. Clinical and pathologic features of patients CT (+) (N=8) and CT (-) (N=4) for MFRCC

Variables	CT+	CT-	P value
Patients	8	4	<
Age			
mean	58	52	0.411
range	44-85	33-65	
sex			
male	4	5	0.508
female	3	0	
KU			
dx	4	3	0.727
sx	4	2	
Surgery			
NXT	2	3	0.652
NSS	6	2	
Tumors (number)			
pr	8	5	0.565
sat	11	5	
Primary tumor size			
mean	3,8	4,34	0.055
range	3.0-7.0	2.2-10	
Satellite tumor size			
mean	1,8	0,5	0.010
range	0.5-3.5	0.3-0.9	
Primary histology			
clear cell	7	4	0.580
papillary	1	1	
Satellite histology			
clear cell	9	3	0.442
papillary	2	2	
Primary tumor stage			
1A+2	3	5	0.123
3A	5	0	
Satellite tumor stage			
1A	5	4	0.603
3A	6	1	
Primary tumor grade			
primary			
G1+2	3	5	0.123
G3	5	0	
Satellite tumor grade			
G1+2	4	4	0.538
G3	7	1	

Factors significantly associated with MFRCCs were bilaterality (p = 0,002), primary tumor size (p = 0,007), pathologic stage (p = 0,008) and NSS (p = 0.0002). Investigators have already shown that bilaterality, primary tumor size and tumor stage are significant predictors of MRCC (15, 23-25). In this set of patients NSS was significantly performed more frequently in MFRCCs than UFRCC and this could be explained because of the difference of the primary tumor size between the 2 groups.

The mean primary tumor size was significantly larger in CT-undetected (CT-) than CT-detected (CT+) MFRCCs. This result could be explained by findings reported from the literature which showed that significantly more MFRCCs are seen in tumors between 21 and 40 mm in diameter (23). The mean tumor size was significantly lower in CT-undetected (CT-) (0.5 cm) than CT-detected (CT+) (1.8 cm) cases. This finding could be explained by both the significantly different satellite mean tumor size and the technical limits of CT in assessing set of small renal masses that ranged from 0.3 to 0.9 cm in the CT-undetected (CT-) group compared to the other ones where satellite masses ranged from 0.5 to 3.5 cm.

Conclusions

RCC has the biological potential for multifocality and bilaterality as well as the propensity to escape detection when NSS is planned with the consequent risk of local recurrence. In our experience, helical CT was effective in improving preoperative detection of sporadic primary MRCC as well as in lowering clinical occult multifocality. Clinical predictors of multifocality including bilaterality and primary tumor size as well as technical and methodological improvements in performing Helical CT will improve its sensitivity in detecting renal masses less than 0.5 cm. CT preoperative detection of clinical multifocality may help in planning effective preoperative surgical treatment as well as lowering the local recurrence after nephron sparing surgery.

Conflict of Interest

None declared.

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