Clinical Urology

International Braz J Urol Vol. 36 (6): 670-677, November - December, 2010
doi: 10.1590/S1677-55382010000600004

The Beginning of the 21st Century: A Paradigm Shift in the Surgical Management of Renal Cell Carcinoma in South America

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ABSTRACT

Purpose: The incidence of renal cell carcinoma (RCC) has been rising by 2.3 to 4.3% every year over the past three decades. Previously, RCC has been known as the internist's tumor; however, it is now being called the radiologist's tumor because 2/3 are now detected incidentally on abdominal imaging. We compared patients who were treated toward the end of the 20th century to those treated during the beginning of the 21st century with regard to RCC size and type of surgical treatment.
Materials and Methods: The study included 226 patients. For analysis of tumor size, we considered a cut point of < 4 cm and > 4 cm. For analysis of type of surgery performed, we considered radical and partial nephrectomy.
Results: After the turn of the century, there was a reduction of 1.57 ± 0.48 cm in the size of the RCC that was operated on. Nephron sparing surgeries were performed in 17% of the cases until the year 2000, and 39% of the tumors were < 4 cm. From 2001, 64% of the tumors measured < 4 cm and 42% of the surgeries were performed using nephron sparing techniques. Mean tumor size was 5.95 cm (± 3.58) for the cases diagnosed before year 2000, and cases treated after the beginning of 21st century had a mean tumor size of 4.38 cm (± 3.27).
Conclusions: Compared with the end of the 20th century, at the beginning of the 21st century due to a reduction in tumor size it was possible to increase the number of nephron sparing surgeries.

Key words: *carcinoma; renal cell; incidence; diagnostic imaging; urological surgical procedures*
Int Braz J Urol. 2010; 36: 670-7

INTRODUCTION

The incidence of the renal cell carcinoma (RCC) has been increasing by 2.3 to 4.3% per year over the last three decades in the United States (1). Unfortunately, approximately 1/3 of the patients who have been diagnosed with RCC will die due to progression to metastatic disease (1).

Since Bell's classic study (2), the first to relate RCC size to prognosis, there has been a variety of stage modifications in the TNM system related to tumor size variations. This information suggests that tumor growth significantly influences the prognosis of this lethal disease. The majority of studies that have reported a large number of patients indicate that the stratification size related to RCC prognosis is between 4 and 5 cm (3,4).

Fortunately, most RCC cases diagnosed today are incidental tumors with smaller sizes, and identified after ultrasonography (US) or computed tomography (CT) examinations performed for other reasons (5). There has been a reduction in size of recently diagnosed tumors from 7.8 to 5.3 cm, and an increase in organ confined disease, 47 to 78%, from 1989 to 1998 respectively (6). Due to the demonstration that nephron-sparing surgery is effective in RCC, the number of nephron-sparing surgeries (NSS) has also grown (7). At the turn of the century, the management of RCC underwent a paradigm shift favoring nephron-sparing surgery in a large part due to the identification of smaller-sized lesions, and similar oncologic outcomes. The Mayo Clinic study showed that patients who underwent radical nephrectomy presented a higher possibility to have elevated serum creatinine levels and proteinuria higher than 2.0 ng/mL (8).

The goal of this study was to compare RCC size between cases treated during the end of the 20th century to those treated during the beginning of the 21st century. We also analyzed the type of surgeries that were performed during both periods.

MATERIALS AND METHODS

During the period between January 1995 and December 2005, 226 patients with RCC who underwent surgery at our institution had their clinical data retrospectively analyzed. Preoperative evaluation included blood and imaging exams such as US, CT, and/or magnetic nuclear resonance, chest x-ray, bone scintillography, and occasionally, urography.

Initially, we analyzed whether the clinical presentation at the time of diagnosis was incidental or symptomatic. Then, a single pathologist analyzed the anatomic and pathological variables as follows: histology type, Fuhrman nuclear grade, presence of intra-tumoral microvascular invasion, and tumor size. The study included calculation of disease-free survival and specific cancer-survival curves with respect to all the above variables. The study compared the tumor size over these 11 years and the surgical treatment, nephron sparing or radical surgeries. The study also included an analysis of the individuals who underwent NSS. The features of RCC treated during the last six years of the 20th century were compared to the first five years of the 21st century.

The post-surgical follow-up of the individuals was performed in a clinic, and afterward, there was a 3 months period of confirmation by telephone of the current health status of the patient. The clinical follow-up included a chest x-ray, abdominal CT scan and/or US, and blood tests every 4 months during the first year, every half-year from the second to the fifth year, then annually after this period.

The statistical analysis was based on Kaplan-Meier curves and the differences in survival between the groups used the Log rank test. Results were considered significant when the p-value was below 5% ($p < 0.05$).

RESULTS

Up to the year 2000, the majority of tumors had a size greater than > 4 cm (61%). However, after the turn of the century, there was a change in tumor size that underwent resection. After 2001, 64% of the tumors were < 4 cm, and the nephron-sparing surgery was duplicated as shown in Table-1.

Table-2 shows the average, median, and standard deviations of the tumor size from patients who underwent surgery from 1995 to 2005.

The types of surgeries performed during the study period are shown in Table-3. It is important to emphasize that during the period of 1995-2000 the NSS and radical nephrectomy were 17% and 83%, while during 2001-2005 it was 42% and 58%, respectively.

Figure-1 shows the profile of tumor sizes over the years, allowing for the perception of a gradual reduction in the tumor size over this period.

Table-4 shows RCC sizes in four subgroups noting the increase in the incidence of tumors with sizes < 3 cm and between 3-4 cm, as well as the reduction in the incidence of the tumor sizes in subgroups from 4.1 - 7 cm, and > 7 cm after the year 2000.

The demographic and anatomic/pathological data of patients who underwent NSS is described in Table-5.

Table 1 – *Distribution of kidney tumors before and after the year 2000, regarding tumor sizes and the type of surgery performed.*

Year	≤ 2000	> 2000	p Value
Tumor Size			0.001
< 4 cm	56 (39%)	53 (64%)	
≥ 4 cm	87 (61%)	30 (36%)	
Surgery			0.001
Nephron sparing	24 (17%)	35 (42%)	
Radical	119 (83%)	48 (58%)	

The main finding is that majority of tumors were T1 (95%), 78% incidental and low degree. The creatinine serum and urea pre and postoperative are demonstrated in Table-6.

COMMENTS

Our study shows that there has been a paradigm shift in the surgical treatment of RCC in Brazil. A significant reduction in the average tumor size has taken place, 5.1 cm from the end of the past century, to 3.9 cm after the year 2001. This has increased (25%) the indication for nephron sparing surgery by 17% until 2000 and 42% after 2001.

For a long time, tumor size has been considered one of the most important independent prognostic factors for RCC. This has resulted in a number of frequent publications addressing this issue (9,10), as well as, encouraging continuous proposals for changes in the staging of the disease (5). These frequent changes in the RCC staging, always related to the tumor size, certainly assure that this is the major prognostic factor, and that it most faithfully defines the disease's behavior.

The survival outcome for tumors < 7 cm that were re-resected by radical nephrectomy is similar; however, the possibility of RCC recurrence varies from 2.6% to 9% in T1a and T1b tumors, respectively (11). In this study, we found that the average survival

Table 2 – *Size of tumors.*

Year	Mean	Standard Deviation	Median	Minimum	Maximum	N
1995	5,222	2,6746	4,500	1.5	12.0	18
1996	5,813	2,8823	5,100	2.0	12.0	16
1997	5,075	3,1266	4,350	1.5	13.0	20
1998	6,633	3,2462	6,250	3.0	13.5	18
1999	5,279	2,9221	5,000	1.5	13.0	19
2000	6,443	5,0735	5,000	1.2	19.5	23
Subtotal	4,924	3,7036	5,1714	1.2	19.5	114
2001	5,800	5,9024	3,700	1.2	24.0	15
2002	4,533	2,8359	3,800	1.5	10.5	15
2003	4,569	2,5674	4,150	1.2	11.0	16
2004	3,674	2,1509	3,000	1.5	10.0	19
2005	3,440	1,5688	3,000	1.2	8.0	15
Subtotal	4,6693	3,5042	3,9416	1.2	24.0	80

Table 3 – *Percentage distribution of surgeries performed during the period of 1995 - 2000 and 2001 - 2005.*

Year	Partial (%)	Radical (%)	p Value
20th Century			
1995	6 (33)	12 (67)	0.04
1996	2 (12.5)	14 (87.5)	> 0.9
1997	5 (25)	15 (75)	0.1
1998	0 (0)	18 (100)	-
1999	4 (21)	15 (79)	0.009
2000	4 (17)	19 (83)	0.003
Total	24 (17)	119 (83)	
21st Century			
2001	6 (40)	9 (60)	0.002
2002	5 (33)	10 (67)	0.5
2003	6 (40)	9 (60)	0.001
2004	10 (53)	9 (47)	0.01
2005	7 (47)	8 (53)	0.2
Total	35 (42)	48 (58)	

of patients with T1a tumors was 91%, while in T1b tumors, 79% were free from the disease in 5 years. The size of the tumor is so relevant in RCC that the growth of 1 cm in the RCC size increases the possibilities of cancer progression by 17%, according to the important editorial by Marshall (12). Patients with RCC greater than 5 cm have a five-fold greater chance of dying due to the disease when compared to those with tumors with less than 5 cm (risk ratio = 4.93) (12).

Although RCC used to be referred to as the internist's tumor, it may now be more appropriate to refer to it as the radiologist's tumor, because 60% of renal tumors are detected incidentally during abdominal imaging obtained for other reasons. In this context, laparoscopic NSS proved to be effective and safe in the treatment of renal tumors (13). Currently, robotic NSS is already a reality, with one important series performing surgeries for tumors from 1.4 to 3.6 cm (14). Despite the development of alternative ablative techniques for solid kidney lesions, surgical excision remains the cornerstone in treating RCC.

In our study, we found that after the turn of the century, there was a significant difference between the size of the tumors and the type of surgery performed. It was only after 2001 that the median tumor size decreased below 4 cm, 39% of cases before 2001 compared to 64% after. On the other hand, the

Table 4 – *Distribution of tumor sizes between the end of the 20th century and the beginning of the 21st century.*

	20th Century (%)	21st Century (%)	Total
Size			
< 3 cm	14 (12)	26 (32)	40 (21)
3 - 4 cm	28 (25)	22 (28)	50 (27)
4.1 - 7 cm	41 (36)	18 (23)	59 (30)
> 7 cm	31 (27)	14 (17)	45 (22)
Total	114	80	194

Table 5 *– Demographic data and pathology results of 59 excised tumors in nephron sparing surgery.*

	N = 59
Age (min - max)	57 (23 - 81)
Male / Female (%)	49 (83%) / 10 (17%)
Pathological data	
High-grade	12 (22%)
Low-grade	46 (78%)
Microvascular invasion	4 (6.8%)
Necrosis	10 (17%)
Fat invasion	1 (1.7%)
Pathologic stage	
T1	56 (95%)
T2	1 (2.5%)
T3a	1 (2.5%)
Incidental	46 (78%)
Symptomatic	12 (22%)
Median follow-up (months)	60 (4 -168)
Survival free of local recurrence	59 (100%)
Cancer-specific survival	58 (98%)

percentage of nephron sparing surgeries increased significantly from 17% to 42%.

The size of renal tumors at the time of diagnosis has been decreasing over the years, with a reduction in the average size resected lesions from 7.8 to 5.3 cm, from 1989 to 1998 (7). For this reason, a migration of the RCC stage has taken place according to Kane et al. (15). This migration has occurred particularly in the pT1 stage where the median RCC size decreased from 4.1 in the year 1993, to 3.6 cm in 2003. The survival gain for patients treated in 1993 to 1998 rose by 3.3%. It is worth pointing out that between the years 1993 and 2004, the proportion of patients with RCC in Stage I grew from 43% to 57%; on the other hand, the proportion of patients with pT4 stage decreased during the same period from 27.4% to 18.7% (16).

With a normal contralateral kidney, the cumulative incidence of renal insufficiency (defined as a serum creatinine level of > 2.0 mg/dL) at 10 years has been reported to be significantly higher after radical nephrectomy than after partial nephrectomy (22% vs. 12% (17). Proteinuria was also more common after radical nephrectomy (55% vs. 35%) (17). Also, metachronous renal tumors in the contralateral kidney can occur in up to 10% of patients (18), underscoring the importance of avoiding unnecessary nephron loss. Recent findings suggest that NSS is greatly underused in the USA because, in a large nationwide hospital database, only 9.6% of patients with surgically treated renal tumors underwent partial nephrectomy (19). At many academic centers, partial nephrectomy comprises 60-70% of the operations for RCC (20). However, when using the nationwide inpatients sample, these authors reported that only 7.5% of kidney tumor operations in the USA from 1988 to 2002 were partial nephrectomies (19). In England, a similar underuse of partial nephrectomy was reported in 2002 with only 4% out of 2671 nephrectomies performed (21).

One of the limitations of this study is that it is a retrospective analysis; however, the fact that we have a reliable database of individuals treated by a same group of surgeons from a single institution is a positive point. We believe that with the increasing diagnosis rate of solid renal lesions with progressively smaller sizes, the indications for nephron sparing therapies will increase significantly, favoring the preservation of the renal function and improving RCC outcomes.

Table 6 *– Hematological analysis pre and postoperative.*

Nephrectomy	**Creatinine** (ng/mL)		**Urea** (ng/mL)	
	Preoperative	**Postoperative**	**Preoperative**	**Postoperative**
Partial	1.23	1.21	40.19	48.74
Radical	1.44	1.83	40.56	47.34

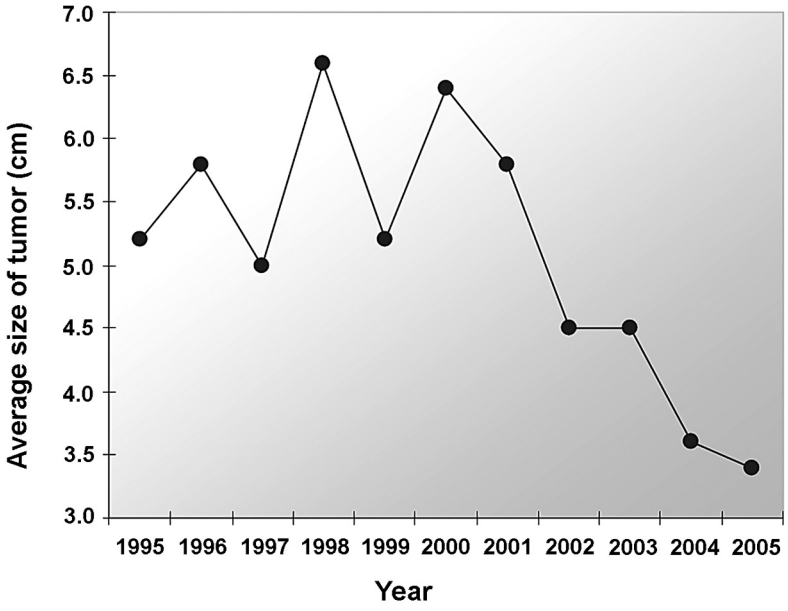

Figure 1 *– Reduction of the tumor size during the transition from the 20th to the 21st century.*

CONCLUSIONS

Comparing patients diagnosed with RCC after the beginning of the 21st century to those diagnosed before, the patients diagnosed later were more likely to undergo nephron-sparing surgery increasing the probability of avoiding later chronic renal insufficiency.

ACKNOWLEDGEMENT

Adriana Sañudo performed the statistical analysis.

CONFLICT OF INTEREST

None declared.

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Accepted after revision:
January 14, 2010

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EDITORIAL COMMENT

The paper by Dall'Oglio et al. nicely depicts that a paradigm shift has occurred in the surgical management of localized renal masses in Brazil paralleling similar changes worldwide particularly for lesions ≤ 4 cm. At the present time, nephron-sparing surgery remains the "gold standard" for the management of small renal masses (SRM), with clear benefits in terms of cardiovascular toxicity while minimizing the risk of post-operative dialysis requirement. There is an unquestionable change in our underlying surgical

approach to SRM in that the clinical question often asked is: when should a partial nephrectomy not be performed? In my clinical practice, over 70% of patients with renal masses less than 7 cm are treated by partial nephrectomy (in the absence of absolute indications for partial nephrectomy i.e. solitary kidney, underlying renal insufficiency, or bilateral renal masses). Whether the partial nephrectomy is performed using an open, pure laparoscopic, or robotic assisted laparoscopic approach is simply a technical consideration taking size, location, and surgical expertise into account. We cannot get away from the simple fact that for SRM, a partial nephrectomy (irrespective of its approach) is a better treatment choice for patients than radical nephrectomy. Recently, percutaneous (and laparoscopic) ablative techniques (i.e. radiofrequency ablation and cryoablation) have been proposed as a treatment alternative for SRM in well selected cases (typically lesions less than 2.5 cm and away from the renal hilum) understanding such treatment alternatives do not have long-term data (beyond 10 years) and require routine serial imaging following the ablative procedure. With these clear limitations, I feel percutaneous (and laparoscopic) ablative procedures should only be offered to a select subset of patients (1). With evolving technology and imaging modalities, newer treatment alternatives will become readily available to patients with SRM however partial nephrectomy has set the bar and we must never loose sight of the clear benefits it offers to our patient population. The impetus lies on the scientific community to develop imaging modalities or validate percutaneous renal biopsy strategies able to distinguish benign from malignant renal neoplasms such that treatment can be geared to those requiring definitive intervention.

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