THE EVOLUTION OF PARTIAL NEPHRECTOMY FOR KIDNEY TUMORS – ARE WE ABANDONING THE BASIC PRINCIPLES OF ROBSON'S RADICAL NEPHRECTOMY?

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SUMMARY – Fifty years ago, Robson introduced radical nephrectomy (RN) setting the gold standard for treating kidney tumors. Experience has shown that partial nephrectomy (PN) can be equally effective with the advantages of preserving kidney function and avoiding unnecessary nephrectomies for benign tumors. The purpose of this report is to demonstrate the evolution of clinical presentation and choice of treatment for patients with kidney tumors at our department, emphasizing changes in the PN utilization trends. Clinical data were abstracted for the years 2002, 2007 and 2012. We assessed annual trends for changes in the choice of operative treatment related to tumor size, pathologic stage and diagnosis. During the study, there was an increase in the share of T1 tumors, from 46.6% in 2002 to 69.8% in 2012. The rate of PN increased more than ten-fold, from 2.7% in 2002 to 31.7% in 2012. The annual rates of PN for T1 tumors increased even more, from 6.6% in 2002 to 46.7% in 2012. Opposite to RN group, there was an increase in the mean tumor size in PN group (from 1.8 cm in 2002 to 3.9 cm in 2012). The rate of RN for benign tumors was reduced impressively from 85.7% in 2002 to 23.1% in 2012. Our data argue strongly that PN should be expanded and not restricted. Robson's principles have been partially deserted over the last decade; however, proving that PN is superior to RN still remains to be elucidated.

Key words: *Kidney neoplasms – surgery; Carcinoma, renal cell – surgery; Nephrectomy – methods; Organ sparing treatment; Outcome assessment*

Introduction

Renal cell carcinoma (RCC) is most lethal of all urologic cancers and surgery is still the only curative therapeutic approach. Historically, surgery has been mostly responsible for improvement in survival of patients with localized RCC. In 1963, Robson described radical nephrectomy (RN) as a method to treat RCC, which remained the procedure of choice for treating solid kidney tumors for the remainder of the century[1]. However, in the late 1970s, nephron sparing surgery (NSS) was introduced as a method that preserved healthy kidney tissue and as such broke all the principles of radical surgery set by Robson. Partial nephrectomy (PN) allowed for healthy kidney tissue to be salvaged but concern about a higher incidence of relapse was a valid argument for those who preferred RN. Subsequent research has shown that, for tumors up to a certain stage, PN can be performed with the same survival rate as RN. In 2002, the upper limit for resectable tumors was set at 4 cm in diameter (stage T1a). However, recent studies have shown that the acceptable limit is 7 cm (stage T1) and in some cases even 10 cm (stage T2)[2]. During the last decade, PN has emerged as a standard treatment for small renal masses offering oncologic control equivalent to RN with preservation of renal function and evidence for improved survival. The size of resectable tumors has increased over years, showing that the boundaries of NSS are constantly being pushed forward.

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Received December 3, 2013, accepted August 6, 2014

The purpose of this report is to evaluate our experience in surgical management of solid kidney tumors. We retrospectively evaluated postoperative data of patients having undergone PN or RN for kidney tumors in our institution. Changes and advances in patient selection criteria and type of surgical management are evaluated and discussed emphasizing the significance of changes in PN utilization trends during the observation period. Recent literature on the topic is reviewed and discussed.

Material and Methods

We retrospectively analyzed preoperative and early postoperative clinical data of patients treated surgically for solid kidney tumors at our institution (Department of Urology, Sestre milosrdnice University Hospital Center, Zagreb, Croatia). A computerized database was created and data abstracted directly from the records at our department for the years 2002, 2007 and 2012. From our database, we identified patients that had undergone surgery for solid kidney tumors by PN or RN and simple nephrectomy. For study purposes, patients undergoing simple nephrectomy were included in the RN group. Patients with nonfunctional kidneys, infections and trauma where excluded from analysis even though nephrectomy was performed. The information abstracted and entered included the date of surgery, type of surgery, patient age, tumor size, final pathologic diagnosis and stage. Patients were staged according to the 2010 TNM staging criteria[3]. Clinical and pathologic data were analyzed and compared for annual changes over the observation period. Descriptive statistics and time-flow charts were used to analyze trends over time.

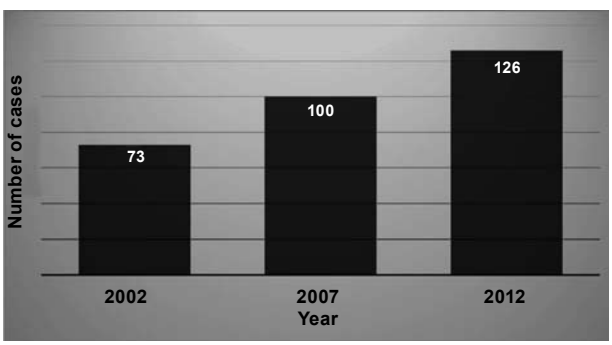

Fig. 1. Number of patients undergoing surgery for all kidney tumors in 5-year intervals.

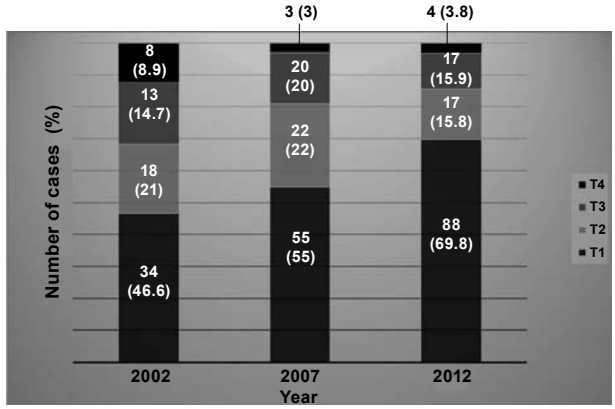

Fig. 2. Postoperative stage migration: increase in the share of T1 disease.

Results

The mean patient age at diagnosis was 61.2 years in 2002. It gradually increased yearly to reach 61.9 (overall range 27 to 97) years in 2012. The mean age of patients undergoing PN and RN was 72.6 (range 35 to 86) years and 60.1 (range 27 to 87) years, respectively.

The annual frequency of surgical interventions increased markedly at our department, from 73 to 126 during the observation period (Fig. 1).

The distribution of postoperative tumor stages with time is shown in Figure 2. Annual distributions of postoperative stages demonstrate stage migration towards T1 disease. Annual rates of postoperative pT1 stages were 46.6%, 55% and 69.8% in the observation period. The rates of pT2 disease decreased from 21% in 2002 to 15.8% in 2012. As expected, the con-

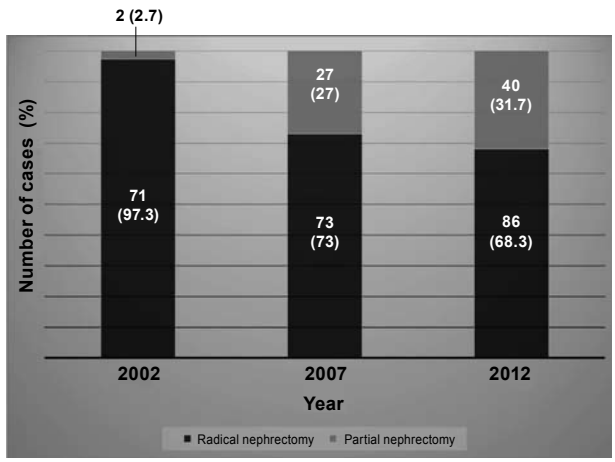

Fig. 3. Annual rates of patients undergoing radical nephrectomy and partial nephrectomy for all kidney tumors.

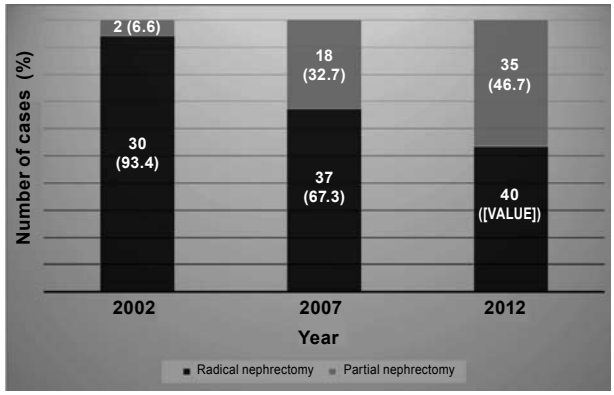

Fig. 4. Annual rates of patients undergoing radical nephrectomy and partial nephrectomy for T1 kidney tumors.

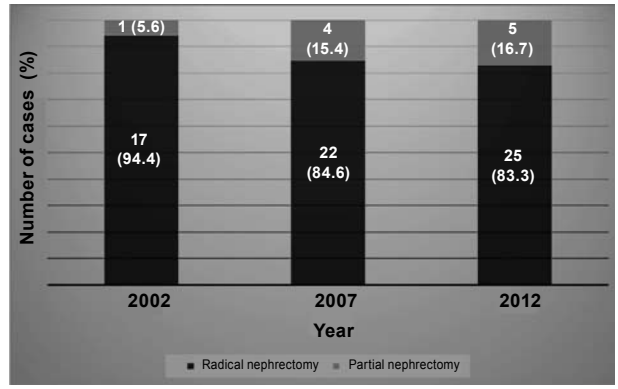

Fig. 6. Annual rates of patients undergoing radical nephrectomy and partial nephrectomy for T1b kidney tumors.

tributions of pT3 and pT4 disease decreased steadily over years.

The annual rates of RN and PN utilization are illustrated in Figure 3. The proportion of patients with kidney tumors treated with PN increased markedly throughout the study and ranged from 2.7% in 2002 to 31.7% in 2012.

The annual rates of patients undergoing PN for T1 tumors only increased even more, from 6.6% in 2002 to 46.7% in 2012 (Fig. 4). The annual utilization trends of PN and RN for T1a and T1b subgroups of tumors are illustrated in Figures 5 and 6. For T1a (<4 cm) tumors, PN was performed in 7.7%, 20.7% and 55.6% of patients in the observation period. On the other hand, the rates of PN for larger T1b (4-7 cm) tumors were only 5.6%, 15.4% and 16.7%, respectively.

For patients treated with RN, the mean tumor size was 6.8 cm, 6.1 cm and 6.6 cm in the observation period (range from 1.4 to 19 cm) (Fig. 7). As expected, the mean tumor size for patients treated with PN increased gradually from 1.8 cm in 2002 to 3.9 cm in 2012 (range from 1.1 to 9.5 cm) (Fig. 7), indicating improvement in preoperative imaging assessment and surgical technique.

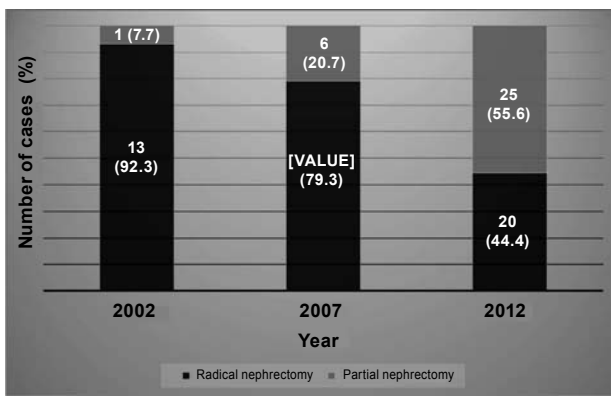

Fig. 5. Annual rates of patients undergoing radical nephrectomy and partial nephrectomy for T1a kidney tumors.

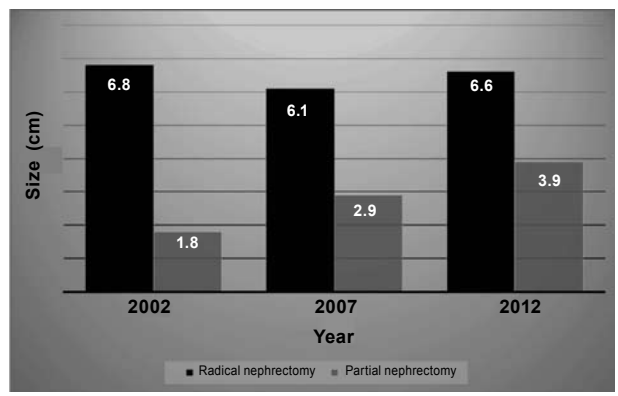

Fig. 7. Mean tumor size in patients undergoing radical nephrectomy and partial nephrectomy for all kidney tumors.

Figure 8 illustrates annual rates of patients undergoing RN and PN for benign tumors. The rate of patients undergoing unnecessary RN for benign tumors was reduced impressively from 85.7% in 2002 to 23.1% in 2012. In 2002, seven (9.5%) patients underwent surgery for benign tumors, whereas in 2007 and in 2012 there were 13 such cases each year (13% and 10.3%, respectively). The histopathologic diagnosis showed only two types of solid tumors (excluding simple cysts) with an almost equal distribution, i.e. 17 (51.5%) patients with angiomyolipomas and 16 (48.5%) patients with oncocytomas.

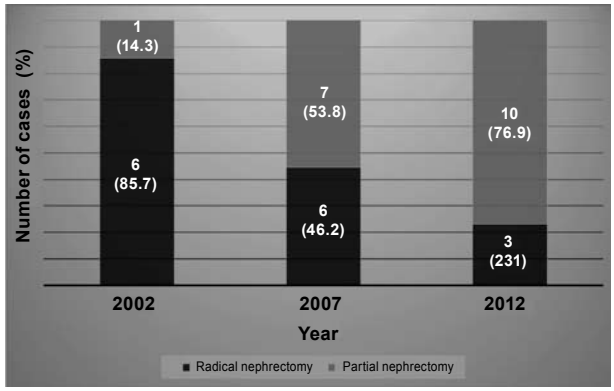

Fig. 8. Annual rates of patients undergoing radical nephrectomy and partial nephrectomy for benign tumors only.

Discussion

Renal cell carcinoma is the third most frequent urologic cancer that accounts for 2%-3% of all adult malignancies[4]. Adenocarcinoma is the most prevalent histologic subtype, responsible for approximately 85% of renal tumors[5]. Currently, up to 40% of kidney neoplasms are detected incidentally because of the widespread use of imaging technologies[5]. Today, we are looking at the downward migration toward the diagnoses of asymptomatic, incidental, smaller and lower-stage lesions.

Since the publication of Robson's landmark article in 1969, and due to concerns about incomplete tumor excision, local recurrence, microscopic satellite tumors and multifocality, RN had remained the gold standard for the treatment of localized RCCs for almost three decades[6]. This procedure was questioned in the 1980s by several reports demonstrating favorable results with NSS for imperative indications[7]. Initial applications of NSS in the modern era were limited to absolute indications such as bilateral renal masses or tumor in a functionally or anatomically solitary kidney. During the last decade, elective PN has supplanted RN as the treatment of choice for small renal masses with comparable oncologic outcomes and benefits of renal preservation. Until recently, 4 cm (T1a tumor) was considered as a cut-off size for PN. Two landmark studies established 4 cm as the upper limit below which PN could be indicated; for elective indications, NSS for T1a tumors provided recurrence free and long-term survival rates similar to those observed after radical surgery[8]. Based on these data, the cut-off limit of 4 cm was arbitrarily set to delineate the indications for PN. Those figures were the scientific background for the 2002 TNM staging system update and this observation has, in part, led to substratification of the stage T1 classification into T1a and T1b. The advantages of NSS over RN for tumors up to 4 cm in diameter, such as lower mortality and lesser risk of developing renal insufficiency and cardiovascular disease have been reported [9-11].

Novel developments and improvements in radiologic imaging, such as ultrasonography, computed tomography (CT), and magnetic resonance imaging have succeeded in diagnosing small renal masses found incidentally during investigation of unrelated complaints, which have allowed for a shift towards a more organ-preserving approach[12,13]. Our findings show an increased number of diagnosed patients with a migration towards lower stages during the study period, with the majority of diagnosed tumors today being discovered at T1b stage or less, which allowed for greater application of PN at our institution.

The utilization rates of PN at tertiary care centers among patients with localized RCC ranged from 33% to 52%[14]. Similarly, the proportion of patients treated with PN in our institution increased markedly throughout the study and ranged from 2.7% in 2002 to 32.0% in 2012. At our institution, a ten-fold increase was recorded from 2002 to 2012 in choosing PN as the method of treatment, showing only partial abandonment of Robson's principles of radical surgery in selected patients. Among patients with tumors less than 4 cm (T1a), 7.1% underwent PN in 2002 compared with 55.6% in 2012. This relative increase is mirroring the increase in the incidence of the more organ-confined disease described during a similar interval and highlighting the growing acceptance of PN as a viable therapeutic option. Interestingly, the rates of PN for larger T1b (4-7 cm) tumors at our institution were not so high (from 5.6% in 2002 to 17% in 2012). Therefore, when confronted with larger and more complex tumors, RN is still the preferred treatment in our institution. Collectively, these data provide a compelling case for possible underuse. Nevertheless, the mean size of resected tumors in our study increased from 1.8 cm in 2002 to 3.9 cm in 2012, indicating that positive outcomes of prior operations and accumulated surgical experience allowed us to resect larger tumors rather than perform radical surgery.

Despite vast improvements in modern imaging, between 16.4% and 23% of patients following surgical resection of a suspect renal mass will have a benign lesion such as angiomyolipoma, oncocytoma, metanephric adenoma or hemorrhagic cyst[15,16], and in these cases radical surgery is not justified. Although percutaneous renal biopsy can be performed using CT guidance with ease, differentiation between benign and malignant tumor or determination of tumor histologic subtypes by current radiologic and biopsy techniques alone or in combination has only 60%-70% accuracy[17]. In 2012, we succeeded in reducing the number of patients undergoing RN for benign tumors to less than one quarter compared to 2002. The rate of unnecessary RN for benign tumors was reduced impressively from 85.7% to 23.1%. It is as important to note that 26% of patients with RCC have a clinically unsuspected chronic kidney disease. For this group of patients, overaggressive surgery could result in the need of dialysis and/or kidney transplantation, which, of course, is associated with complications as well as resulting in the quality of life loss and substantial economic cost[18].

In addition, just when the issue of elective PN appeared to be settled in 2002, it is now controversial again, with some centers proposing expansion of indications to include larger tumor size. Partial nephrectomy has been shown in multiple studies to be safe and feasible in selected patients with T1b (4-7 cm) renal tumors with oncologic outcomes comparable to RN[2].

Thus, NSS is an overriding theme in the management of clinical T1 renal masses when it is considered technically feasible. We have accepted elective PN as the standard of care for small renal masses and even selected patients with T1b tumors, but what about even larger tumors >7 cm? Recent studies add to a growing literature suggesting that elective PN may also be a reasonable option even for selected patients with T2 (7-10 cm) tumors[19]. Many of these studies actually report better cancer-specific survival in patients with T1b and larger tumors managed with elective PN when compared with RN. However, herein lays the problem: the expanding indications are without substantive supportive evidence. In most of these series, patients managed with elective PN had more favorable tumor characteristics (tumors were peripherally located with no apparent involvement of the collecting system, perinephric fat, or venous structures on preoperative imaging), indicating significant selection bias. Most series were single center, retrospective and nonrandomized; cohorts were small and often unmatched. Nowadays, as a standard elective method of treatment, PN is recommended only for T1 tumors[20]. According to the recent European Association of Urology guidelines, PN for larger tumors (T2) remains a method the implementation of which should be considered but is not a standard treatment of choice[20].

So, what are the reasons not to abandon the basic principles of Robson's radical surgery? Elective PN for patients with T1b and larger tumors remains controversial for a variety of reasons. The risk of malignancy is higher and larger tumors are more likely to have negative prognostic indicators such as higher tumor grade, necrosis, and T stage. Therefore, the number of cases for which PN is beneficial due to benign pathology will naturally be lower[21]. The risk of systemic metastasis is also directly related to tumor size, and many patients have micro metastases at the time of surgery[21]. Obviously, the management of local tumor will not affect outcome in this case. The incidence of multicentricity appears to increase with larger tumor size and accounts for most local recurrences after PN[22]. Local recurrence rates after PN ranged from 4% to 6%, except when restricted to smaller tumor size, and this is a potential benefit of RN for larger tumors[14]. Another concern regarding elective PN in patients with T1b and larger tumors relates to the increased perioperative morbidity reported in all recent series[23]. Taking all of these considerations into account, we have to be very prudent when recommending elective PN for large and technically demanding tumors. Our current perspective is that only highly selected and well-counseled patients should be considered for elective PN for tumors sized >7 cm[23].

The ultimate solution to this form of dilemma is analysis of a properly powered randomized prospective clinical trial. In 2011, the European Organization for Research and Treatment of Cancer (EORTC) reported results from a prospective phase 3 trial randomizing patients with solitary renal lesions 5 cm and a normal contralateral kidney to PN or RN[24]. Surprisingly, the results clearly showed that PN was not

superior to RN in terms of cancer specific and overall survival. We have Level 1 evidence that PN is not superior to RN for tumors <5 cm. The choice of treatment for the patient with localized RCC needs to be individualized. Preservation of renal function without compromising the oncologic outcome should be the most important goal in the decision-making process.

Conclusions

Surgery still remains the only curative approach for localized RCC. During the study period, kidney tumors shifted significantly to more organ-confined stages due to a widespread use of imaging techniques. Our data also argue strongly that indications for PN related to tumor size should be expanded and not restricted. With a time delay, our findings are consistent with trends observed at several well-known academic institutions. When choosing between RN and PN, one should consider the location, radiologic characteristics, individual patient attributes and technical abilities available, not only tumor size. The maximum size of tumors treatable with RN remains controversial. We have to be very cautious in recommending elective PN for larger tumors. The expanding indications are still without substantive supportive evidence and we have Level 1 evidence that PN is not superior to RN in terms of overall and cancer specific survival[24]. Robson's principles have been partially deserted over the last decade, however, proving that PN is superior to RN in terms of cancer specific and overall survival for larger tumors remains to be seen.

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Sažetak

RAZVOJ PARCIJALNE NEFREKTOMIJE ZBOG TUMORA BUBREGA – NAPUŠTAMO LI OSNOVNA NAČELA ROBSONOVE RADIKALNE NEFREKTOMIJE?

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Prije 50 godina Robson je izveo prvu radikalnu nefrektomiju (RN) te time postavio zlatni standard za kirurško liječenje tumora bubrega. Iskustvo je pokazalo da je parcijalna nefrektomija (PN) jednako učinkovita s prednostima očuvanja bubrežne funkcije i izbjegavanjem nepotrebne nefrektomije zbog dobroćudnih tumora. U radu se prikazuju promjene kliničke slike i napredak u izboru operativnog liječenja tumora bubrega na našoj klinici, naglašavajući razvoj indikacija za primjenu PN. Studija je obuhvatila sve bolesnike koji su operativno liječeni zbog tumora bubrega na našoj klinici u 2002., 2007. i 2012. godini. Analizirali smo izbor operativne metode u danim razdobljima prema veličini tumora, stadiju bolesti i dijagnozi.U promatranom razdoblju porastao je udio tumora T1, s 46,6% u 2002. na 69,8% u 2012. godini. Od ukupnog broja operiranih bolesnika u 2002. godini 2,7% ih je operirano metodom PN, dok je u 2012. taj udio bio 32%, što predstavlja porast veći od 10 puta. Porast godišnjeg udjela PN za stadij bolesti T1 bio je još veći, sa 6,6% u 2002. na 46,7% u 2012. godini. Za razliku od skupine RN, u skupini PN zabilježen je porast prosječne veličine tumora s 1,8 cm u 2002. na 3,9 cm u 2012. godini. Impresivno je smanjenje RN kod bolesnika s dobroćudnom patologijom koja je u 2002. godini iznosila 85,7%, a u 2012. samo 23,1%. Rezultati našega istraživanja pokazuju da indikacije za PN treba proširivati, a ne ograničavati. U zadnjih 10 godina Robsonova načela su djelomice napuštena, ali superiornost PN nad RN tek treba dokazati.

Ključne riječi: *Bubrežni tumori – kirurgija; Karcinom, bubrežne stanice – kirurgija; Nefrektomija – metode; Organi, poštedno liječenje; Ishod zdravstvene skrbi – ocjena*