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Tumor Recurrence Following Nephron-Sparing Surgery for Renal Cancer: Rate, Patterns, and Predictors

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ABSTRACT

INTRODUCTION: Tumor recurrence following nephron-sparing surgery (NSS) for renal carcinoma is a major concern. The aim of this retrospective study was to assess the rate, patterns, and predictors of tumor recurrence in patients following NSS for renal cancer.

METHODS: Between 1993 and 2008, 229 patients underwent NSS via flank incision for renal cell carcinoma. Patients without metastases at diagnosis (using CT and bone scan) were included in the outcome analysis. Categorical variables were compared with the Fisher-Irwin exact test. Kaplan-Meier was used to determine the probability of overall survival and probability of recurrence curves; significance was tested with the log-rank. The Cox hazard survival model was used to identify whether any of the demographic or clinical variables were predictive of the probability of recurrence.

RESULTS: During a mean (SD) follow-up time of 45 (34) months, tumor recurrence was observed in 13 patients (5.6%). Mean follow-up time for detection of oncological failure was 51 months. All patients with oncological failure were males, with a mean age of 61 years (median 58; range, 51-74 years). The average size of the enucleated lesion was 5 cm (range, 4-7 cm). Intraoperative frozen sections and postoperative pathological examination of the surgical margins were negative in all cases. Predictors of oncological failure included: warm ischemia time > 20 minutes (P = .012), tumor size ≥ 4 cm (P = .001), central tumor location (P = .015), multifocal tumors (P = .001), and male gender (P = .01). The probability of overall disease recurrence at 12 and 60 months was 1.8% and 4.0%, respectively. The overall cancer-specific survival rate was 93.8%. The 12-month and 60-month metastasis-free survival rates were 99.1% and 98.4%, respectively. Recurrence was due to surgeon-related and tumor-related patterns.

CONCLUSIONS: NSS is an effective surgery with satisfactory long-term cancer control. Predictors of recurrence were consistent with previous literature except for warm ischemia time > 20 minutes (noted for the first time). Reasons for cancer relapse include seeding during surgery, residual disease, distant dissemination, and new tumor growth. Careful tumor handling and extensive perirenal fat resection are within the surgeon's control and may reduce failure rates.

KEYWORDS: Renal cell carcinoma; Nephron-sparing surgery; Cancer recurrence

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Abbreviations and Acronyms
NSS = nephron-sparing surgery
RCC = renal cell carcinoma

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Tumor Recurrence Following Nephron-Sparing Surgery for Renal Cancer: Rate, Patterns, and Predictors

INTRODUCTION

Adequate renal function is crucial for normal life expectancy and quality of life. Nephron-sparing surgery (NSS) is considered the preferred treatment for most patients with organ-confined renal cancer, even for patients with 2 normally functioning kidneys. This approach provides cancer control that is comparable to that obtained after radical nephrectomy, with the advantage of renal function preservation. NSS has evolved during the last decades, especially for patients with compromised renal function because of a single kidney, bilateral tumors, or overall reduced renal function. It provides excellent cancer control while preserving as much functional renal tissue as possible [1,2].

The fear that NSS does not provide adequate cancer control has already been ruled out [3]. However, disease recurrence and progression is known to occur following NSS. Some factors that are related to tumor recurrence include large tumor size, multiple tumors, central lesions, and lesions related to genetically inherited disease [4]. However, the causes of tumor recurrence have not been completely investigated in the medical literature. This information is essential for preoperative patient counseling regarding the risk of recurrence. More detail about the patterns of recurrence may also be used to modify and improve surgical technique. Therefore, the aim of the present retrospective study was to assess the rate, patterns, and predictors of oncological failure in patients after NSS.

METHODS

The retrospective study was conducted using the surgical database at the Department of Urology, Bnai Zion Medical Center, Haifa, Israel. The patients were admitted between 1993 and 2008. The protocol was approved by the Institutional Review Board of the Bnai Zion Medical Center.

Patient Population

A total of 235 patients underwent NSS for localized renal cell carcinoma (RCC) during the study period. The variables assessed were age, gender, symptoms at presentation, operative time, warm ischemia time, blood loss, immediate and long-term postoperative serum creatinine, isotope 99m Tc-dimercaptosuccinic acid uptake (QDMSA) preoperative and postoperative renal scans, surgical complications, tumor size, Fuhrman tumor grade, TNM stage, margin status, disease relapse, and patient outcome.

Preoperative evaluation of all patients included detailed history, physical examination, and chest, abdomen, and pelvic computed tomography (CT) scans without and with intravenous contrast. Renal ultrasound, bone scan, or magnetic resonance imaging studies were also performed if needed. A few patients with concomitant or metachronous metastases were not included in the final analyses. The remaining patients had no signs of preoperative extrarenal, nodal, or distant disease.

Operative Technique

The open surgical procedure for NSS in our institute included lateral decubitus positioning of the patient, flank incision, and a retroperitoneal approach. We removed the perirenal fat and sent it separately for pathological examination in formalin. The suspected renal mass was identified and the renal pedicle was isolated. Intravenous mannitol was given before clamping the renal vessels, followed by surface hypothermia with ice slush for 15- 20 minutes. The lesion was removed with a rim of minimal normal renal tissue. Samples from the remaining renal parenchyma at the tumor base were sent for intraoperative frozen section analysis to verify a clear margin. Open blood vessels or collecting system were sutured using monocryl 4/0 continuous sutures. An argon beam coagulator was used to seal the exposed renal parenchyma. In the first 100 cases, large sutures (1/0 vicryl with blunt-end liver needle) were used to approximate the edges of the parenchymal defect. In most of the remaining cases, we used 5-10 mL of tissue adhesive to fill the tumor bed. Pedicle clamping was then removed, warm ischemia time was determined, and the kidney was inspected for bleeding.

Patient Follow-up

The follow-up protocol included physical examination, imaging studies of the chest and abdomen, renal function tests, and urine analysis. For the first 2 years after surgery the patients were seen every 4 months; 2-5 years postoperatively the patients were seen every 6 months and then yearly.

Statistical Analysis

Statistical analysis was done by using SAS/STAT software (SAS Institute Inc; Cary, NC). For categorical variables, frequencies and percentages were calculated. The Fisher-Irwin exact test (a nonparametric test for small numbers of observations) was used to compare categorical variables. For continuous variables, ranges, medians, means and standard deviations were calculated. Probability of overall survival curves and probability of recurrence curves were constructed by the Kaplan-Meier method, and differences between the curves were tested for significance with the log-rank test. The Cox hazard survival model was used to identify whether any of the demographic or clinical variables were predictive of the probability of recurrence. All statistical tests were analyzed to a significance level of .05.

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RESULTS

Patient Population

A total of 235 patients with localized renal cancer underwent NSS during 1993-2008; however, only patients with data from all of the outcome measures were included in the final analysis. A total of 229 patients comprised the study group. Among the patients who were not included in the outcome analysis, no tumor recurrence was diagnosed at the last follow-up.

The mean patient age was 59.5 years (range, 16-85 years). There were 156 males and 73 females. Presenting symptoms that led to the diagnosis of renal mass were noted in 26 (11.3%) patients. These symptoms included flank/abdominal pain (n = 24), elevated liver enzymes (n = 1), and hematuria (n = 1). All other patients were asymptomatic and diagnosis was made incidentally. Of the 229 cases, 26 (11.35%) patients underwent surgery for absolute indications such as solitary kidney (n = 16), bilateral disease (n = 7), significantly impaired renal function (n = 2), or bilateral nephrolithiasis (n = 1).

The mean follow-up time was 45 months (SD 34; median 42; range 6-168 months). All live patients were followed for at least 12 months. One patient had early recurrence and died of metastatic disease 6 months after the surgery; the minimal follow-up time for the study was 6 months because of this single patient.

Tumor Characteristics

The mean tumor size was 3.9 cm (SD 1.4 cm; median 3.5 cm; range 1.5-11 cm). The tumors were located at the upper pole (31%), middle pole (43%) and lower pole (26%) of the kidney. A total of 77 lesions (33%) were in central/hillar locations and the remaining tumors were exophytic.

Pathologic examination revealed that 82.5% of the tumors exhibited clear-cell type and 12.8% were papillary type. The rest were categorized as chromophobe (3.4%) or granular (1.3%). Mean (SD) Fuhrman histological grade was 2 (0.7).

Intraoperative Parameters

Clamping of the renal vessels with surface hypothermia was performed in 224 patients; 5 patients (2.2%) with very small exophytic lesions did not require clamping. The mean operative blood loss was 157 mL (median 40; range 20-3500 mL). Blood transfusion was required in 12 patients (5.2%).

The mean warm ischemia time was 24 minutes (SD 11; median 23.5; range 12-100 minutes). Intraoperative insertion of a double-J stent was required for 3 patients with a concomitant renal tumor and staghorn stone.

Intraoperative frozen section analysis showed a negative surgical margin in all of the patients. However, final pathology showed cancer cells in the examined specimen of 6 cases (2.6%).

Postoperative Complications

Three patients (1.3%) died in the immediate postoperative period: 1 patient died of acute massive myocardial infarction, 1 from acute mesenteric thrombosis, and 1 from pulmonary emboli. Other complications were: pulmonary embolism (n = 1), which was treated by vena cava filter insertion; pseudoaneurysm (n = 2), which was treated by arterial embolization; growing urinoma (n = 2), which was treated with double-J stent insertion; and pleural effusion (n = 2), transient ileus (n = 1), transient urinary retention (n = 1), pulmonary edema (n = 1), and bleeding peptic stress ulcer (n = 1), which were treated conservatively.

Tumor Recurrence and Progression

Tumor recurrence was observed in 13 patients (5.6%). The mean follow-up time for detection of oncological failure was 51 months (median 36; range 6-132 months). All of these patients were males, with a mean age of 61 years (median 58; range 51-74 years).

The average size of the enucleated lesion was 5 cm (median 5 cm; range, 4-7 cm). Eleven tumors (84.6%) were clear-cell type RCC; 1 tumor exhibited predominantly sarcomatoid feature, 1 was papillary RCC, and 1 was a chromophobe tumor. Eight tumors (61.5%) were categorized as Fuhrman grade 3 and 5 tumors were Fuhrman grade 2. Intraoperative frozen sections and postoperative final pathological examination of the surgical margins were negative for all tumors.

The site of tumor recurrence included: distant metastases to the lung or regional lymph nodes (n = 4), surgical scar (n = 2), perirenal fat (n = 2), local renal recurrence at the surgical site (n = 1), and renal recurrence at a different site (n = 4). The probability of overall disease recurrence at 12 months and 60 months was 1.8% and 4.0%, respectively (Figure 1).

Status at Last Follow-up

Among the 13 patients with tumor recurrence, 1 patient died due to RCC metastases and 2 patients died with local recurrence (both had a single kidney) died of end-stage renal disease complications. The remaining 10 patients are currently alive. Two patients with perirenal recurrence underwent surgical exploration and removal of the recurrent mass (one of them is receiving an adjuvant thyrosin kinase inhibitor). Two patients

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Figure 1. Probability of Disease Recurrence (Survival).
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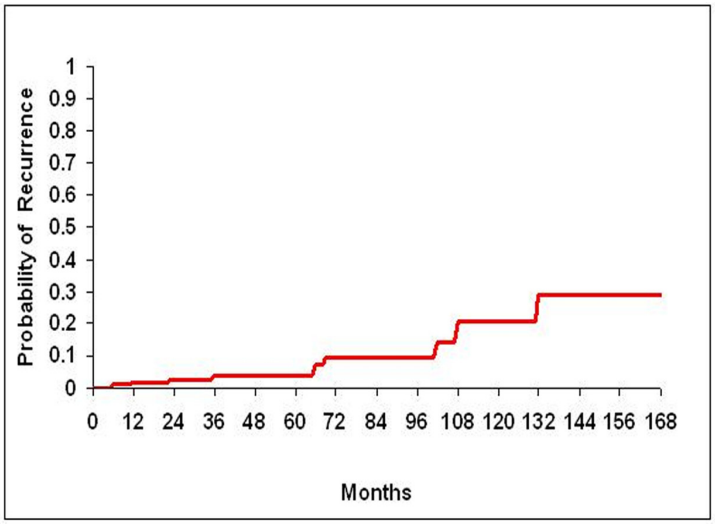

Figure 2. Probability of Cancer-Free (Specific) Survival.
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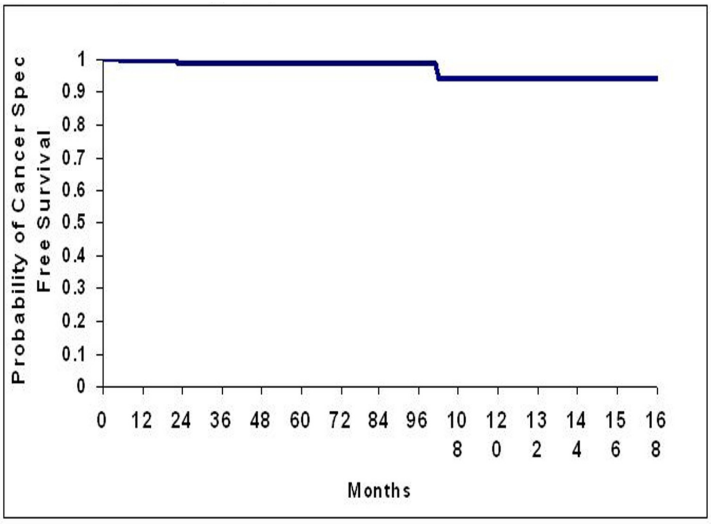

with wound scar recurrence underwent surgical revision of the scar and extensive removal of soft tissue and the recurrent tumor (one of them is receiving a thyrosin kinase inhibitor). One patient with systemic metastases is receiving an adjuvant thyrosin kinase inhibitor with stabilization of the disease. One patient with local failure at the surgical site underwent nephrectomy, and the 4 patients with a new renal lesion that was in a location different from the original surgical site were treated by nephrectomy or NSS.

As shown in Figure 2, the overall cancer-specific survival rate by the end of the study was 93.8%. The 12-month and 60-month metastasis-free survival rates for the entire group were 99.1% and 98.4%, respectively (Figure 3).

Predictors of Oncological Failures

We tried to identify which of the studied variables was predictive of disease recurrence by using the Cox hazard survival model. Table 1 summarizes the variables that were significantly associated with tumor recurrence: warm ischemia time (P = .058), tumor size (P = .001), tumor location (central versus peripheral) (P = .015), and multiple (unilateral or bilateral) lesions (P = .001). In addition, the probability of recurrence at 5 years is 6% for males versus no recurrence for females (P = .011). The variables of age, tumor grade, histological subtype, estimated blood loss, renal function, side, presenting symptoms, and number of kidneys were not predictive of recurrent disease in our study group.

Extended warm ischemic time was associated with increased probability of recurrence. All cases with recurrent disease had warm ischemia time >20 minutes; by contrast, none of those who had ischemia time < 20 minutes had tumor relapse (P = .007). The 5-year probability of recurrence for patients with ischemia > 20 minutes was 5.7% versus no recurrence for those with ischemia < 20 minutes (P = .012).

Tumor size significantly predicted relapse. By the end of the study, recurrence was reported in 11.1% of patients with tumors ≥ 4 cm, compared with no recurrence in patients with tumors <4

Figure 3. Probability of Metastatic-Free Survival.
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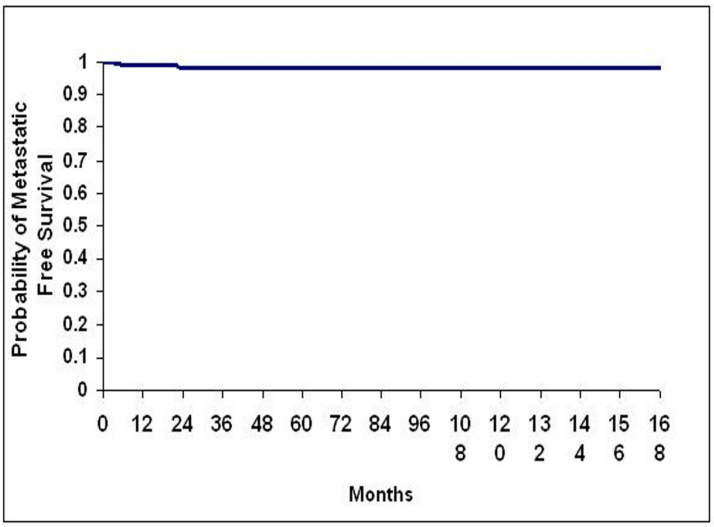

Table 1. Variables Significantly Associated With Tumor Recurrence.
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Variable	*P*
Tumor size > 4 cm	.001
Centrally located lesion	.015
Multiple lesions	.001
Male gender	.011
Warm ischemia time > 20 minutes	.012

cm (*P* = .001). The 5-year probability of oncological failure was 8.2% for patients with tumors ≥ 4 cm, versus no recurrence for those with small tumors (*P* = .001).

A central location was associated with higher failure rate (9.6%) and shorter mean time to progression (23 months) than a peripheral location (2.9% and 69 months, respectively). The probability of disease recurrence for patients with 'central' tumors 5 years after surgery was 8.9%, versus no recurrence for those with peripheral tumors (*P* = .007).

Multifocality (unilateral or bilateral synchronous or metachronous) was a strong predictor of oncological failure. In our study group, patients with multiple tumors had a 40.0% relapse rate; patients with unifocal disease had a 3.3% recurrence rate (*P* = .0001). The 5-year probability of recurrence for patients with multiple lesions was 7-fold higher than for patients with a single lesion (20.5% vs 2.8%) (*P* = .0001).

DISCUSSION

Nephron-sparing surgery has become the standard treatment for renal masses of 4 cm in size [3]. Life expectancy and quality of life for patients with RCC is greatly dependent on the residual renal function after tumor removal [4]. Although renal function is important, NSS should withstand all oncology criteria and provide cancer-control rates similar to radical nephrectomy.

The oncological failure rate in our series was 5.6% (13/229 patients), which is similar to other reports. Hafez et al [5] reported an 11.6% recurrence rate in 327 patients who underwent NSS for sporadic localized RCC, with a mean postoperative follow-up of 55.6 months. Van Poppel et al [6] observed a 3.94% (3/76 patients) systemic failure rate, and Zigeuner et al [7] reported oncology failure in 17 of 114 patients (15%) who underwent NSS, after a mean follow-up time of 80 months. Peycelone et al [8] demonstrated a 5-year and 10-year overall survival of 81% and 78%, respectively, and a 5-year and 10-year tumor-free survival of 92% and 88%, respectively, for patients who underwent NSS due to solid lesions with an average diameter of 5.6 cm.

The oncological failures in the current study can be classified into 2 main patterns: surgically-related relapse and tumor-related relapse. Recurrence at the surgical scar (n=2), perirenal fat (n=2), and local recurrence at the surgical site (n=1) could be attributed to the surgical technique. Renal recurrence at a different site from the original tumor, such as patients who developed a second primary renal neoplasm (n=4) or systemic metastases (n=4), are probably related to the biology of carcinogenesis in the particular patient and tumor.

The patients who presented with perirenal recurrence are an example of local failure due to inadequate peritumoral and perirenal fat removal. In the past, we used the perirenal fat for additional coverage of the operated site. However, the increased use of tissue sealant (mainly BioGlue; CryoLife, Kennesaw, GA, USA) omitted this need completely. In order to keep NSS a radical surgery in terms of cancer control, extensive perirenal fat removal (especially above and adjacent to the tumor) is now routinely performed. Indeed, no further perirenal recurrence was documented later in our series. Yoo et al [9] reported that perinephric fat infiltration was an independent prognostic factor for disease-free survival. In this study, fat infiltration was associated with 14.6% recurrence rate for lesions smaller than 7 cm, and 33% of the patients who had tumor recurrence died of RCC. Jeon HG et al [10] also demonstrated significantly lower survival rates for patients with perirenal fat invasion; however, they concluded that tumor size is the most important prognosticator and fat invasion is directly related to tumor size. Two of the patients in our study underwent reexploration with extensive resection of all fat tissue as well as the recurrent lesions; both patients are currently alive without evidence of disease.

Despite negative surgical margins, 1 patient (0.4%) in this series had local recurrence at the surgical site that was diagnosed 12 months after surgery. The patient underwent radical nephrectomy and is alive without evidence of disease. The rate of positive surgical margins at final pathological examination in our series was 3.4% (8/229 patients); none of the patients with positive margins had local or distant-site recurrence. There is a constant debate about the causes of local recurrence at the surgical site. It was thought that positive surgical margins were among the main determinants of recurrence and poor outcome. However Yossepowitch et al [11] showed that select patients with positive surgical margins may have good long-term disease-free survival. Bensaleh et al [12] assessed 1390

patients with NSS that was performed in several institutions. They documented positive surgical margins in 5.5% of the cases, with no significant difference in outcome between patients with or without positive margins. Involvement of tumor surgical margins in the present study was not associated with an increased risk of local recurrence or metastatic spread. However, it is quite evident that the conservative operation was the cause of local failure for 1 patient in the present study and that this cause could have been eliminated with radical nephrectomy.

Another cause of oncological failure in the present study was tumor seeding, which occurred in 2 cases (0.8%). Predictors for this undesired event among our patients were high tumor grade and relatively large size (4.7 cm and 6.0 cm). Although rare, tumor seeding during partial nephrectomy has been described and (like our cases) was managed with extensive surgery of the recurrent tumor [13,14]. In order to minimize tumor spillage and scar implantation, we carefully protect the operation field during enucleation with a surgical pad and handle the tumor with maximal care to prevent rupture and spillage.

Looking at the patterns of oncological failure in our group, we can conclude that 5 cases (2.18%) occurred as the result of the surgical technique. Four additional cases (1.76%) with a second primary tumor in the operated kidney are failures directly related to the conservative approach and could have been prevented by radical surgery. This undesired outcome rate (3.93%) needs to be balanced against the benefits of functional preservation such as reduced need for renal replacement therapy, risk of cardiovascular death, and influence on the individual patient's quality of life. A close follow-up protocol is employed in patients following NSS and the chance for early recurrent tumor detection is high. Therefore, when making a judgment in the risk-benefit debate, our preference leans toward performing NSS.

Prior to surgery, we excluded patients with distant metastases by using CT and bone scans. Aggressive tumor behavior cannot be assessed prior to surgery because biopsy is not taken at that time. However, we can speculate that in the era of tyrosine kinase inhibitors, patients with adequate renal function will have better quality of life with NSS.

Currently, the choice between NSS and radical nephrectomy is largely based on tumor size [15-17]. The enucleated lesions in the oncological-failure group were significantly larger than in the disease-free group. Most tumors (n=11) were larger than 4.0 cm and their average diameter was 5.0 cm, compared with 3.9 cm for the entire group (P = .001). The 5-year probability of oncological failure was 8.2% for patients with tumors ≥ 4 cm versus no recurrence for those with small tumors (P = .001).

In the past, results of most publications advocated NSS for tumors up to 4.0 cm. However, several recent studies also reported encouraging results in patients with larger tumors. Antonelli et al [18] comparing patients with lesions ≤ 4.0 cm to those with tumors > 4.0 cm in diameter. They showed worse outcome (measured in disease progression and disease-free survival) for the group with the larger tumors. Antonelli et al also reported that patients with larger tumors had no survival benefit if treated by nephrectomy. A recent study by Bernhard et al [19] also found that tumor size > 4 cm was a risk factor for oncology failure. These results are consistent with those of the current study. In contrast, Patard et al [17] analyzed 730 cases following elective NSS and found that the cancer-specific survival was not influenced by tumor size.

All of the patients with oncologic failure in the present study were males. RCC is more prevalent in males (68% in the current study) and our data suggest that males are also more prone to recurrence. The probability of recurrence at 5 years was 6% for males versus no recurrence for females (P =.011). Sunela et al [20] also found better survival rates in female patients.

Multiple synchronous or metachronous tumors were also found to be a significant predictor of recurrence in the present study. Similar results have been reported by others. Pahernik et al [21] reported 5-year and 10-year cancer-specific survival rates of 86% and 75%, respectively, and freedom from local recurrence of 87% and 80%, respectively, in 44 patients with bilateral tumors undergoing NSS. Dimarco et al [22] reported a higher rate of contralateral recurrence for patients with multifocal clear-cell RCC than for patients with solitary tumors (risk ratio 2.91; P = .142). Multiple lesions may represent a genetic predisposition such as in von Hippel-Lindau (VHL) disease or papillary RCC that may be multifocal and require a strict follow-up protocol. Obviously, radical nephrectomy in such cases would eliminate the risk of ipsilateral new tumor growth at the cost of reduced renal function. It should be mentioned that multifocality is not associated with larger tumors, higher tumor stage and grade, or renal cancer death [23].

Our analysis also revealed that warm ischemic time was a statistically significant predictor for tumor recurrence. Patients with warm ischemia longer than 20 minutes had a higher relapse rate when compared with those having warm ischemia shorter than 20 minutes (P = .012). To our knowledge, such an association has not been documented previously in the English medical literature. We can hypothesize that prolonged warm

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ischemia time may represent a more complex procedure that requires a prolonged tumor dissection time. The tumors may be in an unfavorable location (hillar or central); these locations are more frequently observed in patients with tumor recurrence. Alternatively, hypervascular lesions are known to possess more aggressive behavior. Higher microvascular density is related to a higher tumor stage and grade [24-26]. We may speculate that a more aggressive and vascular lesion leads to a more difficult enucleation and a more prolonged warm ischemia time.

The present study has some limitations. These include its retrospective nature, relatively small number of cases, and use of a single institute.

CONCLUSIONS

NSS is an effective surgery with satisfactory long-term cancer control. Predictors of cancer relapse include male gender, tumor size > 4 cm, warm ischemia time > 20 minutes, central tumor location, and tumor multifocality. Seeding during surgery, local extension, incomplete resection, blood and lymphatic spread, and a second primary tumor are the main causes of oncological failure. Careful tumor handling and extensive perirenal fat resection are within the surgeon's control and may reduce failure rates.

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