Predictors and Mechanisms of Oncological Failure Following Nephron-Sparing Surgery for Renal Cancer

Sarel Halachmi MD, Boaz Moskovitz MD, Roi Farfara MD and Ofer Nativ MD

Department of Urology, Bnai Zion Medical Center, affiliated with Faculty of Medicine, Technion-Israel Institute of Technology. Haifa, Israel

ABSTRACT: **Background:** One of the major concerns in performing nephron-sparing surgery (NSS) for renal cell carcinoma (RCC) is the risk of tumor recurrence.

Objectives: To assess the rate, predictors and mechanisms of oncological failure in patients after NSS for renal cancer.

Methods: Between 1993 and 2008 NSS was performed in 229 patients via flank incision. Only patients without metastases at diagnosis and minimal 12 months follow-up were included in the outcome analysis.

Results: During a mean follow-up of 45 ± 34 months (range 6–168 months) tumor recurrence was observed in 13 patients (5.6%). Mean follow-up time for detection of oncological failure was 51 months (range 6–132 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 as well as postoperative final pathological examination of the surgical margins were negative in all recurrent cases. Mechanisms of recurrence were distant metastases (n=4), surgical scar implantation (n=2), perirenal fat recurrence (n=2), local renal recurrence at the surgical site (n=1), and new renal lesions (n=4). Predictors of oncological failure included warm ischemia time ($P = 0.058$), tumor size ($P = 0.001$), tumor location (central versus peripheral) ($P = 0.015$), and multifocality ($P = 0.001$).

Conclusions: Distant dissemination, seeding during surgery, residual disease and new growth are the mechanisms responsible for cancer relapse. Large central lesions, long warm ischemia time and multifocality were significant predictors of oncological failure.

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KEY WORDS: nephron-sparing surgery, oncology, failure, mechanisms, predictors

In the past, radical nephrectomy was considered as the gold standard treatment for localized renal cell carcinoma. As adequate renal function is crucial for normal life expectancy and quality of life, nephron-sparing surgery evolved during the last decades, allowing cancer control with the advantage of preserving functioning renal tissue as much as possible [1,2]. Although NSS has been shown to provide adequate cancer control, recurrence and progression does occur and follow-up should therefore be long term. The aim of this study was to assess the rate, causes and patterns of oncological failure in patients after NSS.

PATIENTS AND METHODS

Between February 1993 and October 2008 a total of 330 patients underwent NSS for localized RCC. In the current analysis we included patients with at least 12 months follow-up post-surgery. We retrospectively collected data including age, gender, symptoms at presentation, operative time, warm ischemia time, blood loss, immediate and long-term postoperative serum creatinine, isotope QDMSA renal scan pre- and postoperatively, surgical complications, tumor size, Fuhrman tumor grade, TNM stage, margin status, disease relapse, and patient outcome.

Preoperative evaluation in all patients included a detailed history, physical examination, and chest, abdomen and pelvic computed tomography scan with and without intravenous contrast. If needed, renal ultrasound, bone scan or magnetic resonance imaging studies were also performed. A few patients with concomitant or metachronous metastases are not included in the final analysis. All the others had no signs of extrarenal, nodal or distant disease preoperatively.

OPERATIVE TECHNIQUE

The open surgical procedure for NSS in our institute comprises lateral decubitus positioning of the patient, flank incision, retroperitoneal approach, removal of the perirenal fat that is sent separately for pathological examination in formalin, identification of the suspected renal mass, and isolation of the renal pedicle. Before clamping the renal vessels, intravenous manitol is given followed by surface hypothermia with ice slush for 15–20 minutes. The lesion is removed with a rim of minimal normal renal tissue. Samples from the remaining renal parenchyma at the tumor base are sent for intraoperative frozen section analysis to verify a clear margin. Open

NSS = nephron-sparing surgery

RCC = renal cell carcinoma

blood vessels or collecting system are sutured using monocryl 4/0 continuous sutures, and an argon beam coagulator is 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, and in most of the remaining cases 5–10 ml of tissue adhesive were used to fill the tumor bed. Pedicle clamping was then removed, warm ischemia time was determined, and the kidney was inspected for bleeding.

FOLLOW-UP

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

STATISTICAL ANALYSIS

Statistical analysis was performed using the STATA software. For categorical variables, frequencies and percentages were calculated. The Fisher-Irwin exact test (a non-parametric test for a small number of observations) was used to compare between categorical variables. For continuous variables, we calculated ranges, medians, means and standard deviation. 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 0.05.

RESULTS

A total of 235 patients with localized renal cancer underwent NSS during the period 1993–2008. The final analysis, however, comprised only patients with at least 12 months follow-up and those for whom all the needed follow-up data were available, i.e., 229 patients. Among patients who were not included in the outcome analysis no tumor recurrence was diagnosed at the last follow-up.

The patients' mean age was 59.5 years (range 16–85 years), 156 were males and 73 were females. Presenting symptoms – such as flank/abdominal pain (n=24), elevated liver enzymes (n=1) and hematuria (n=1) – leading to the diagnosis of renal mass were noted in 26 patients (11.3%). All other patients were asymptomatic and the diagnosis was made incidentally. Of the 229 cases 26 (11.35%) 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).

TUMOR CHARACTERISTICS

Average tumor size was 3.9 ± 1.4 cm (median 3.5 cm, range 1.5–11 cm). Thirty one percent, 43% and 26% of the tumors were located at the upper, mid and lower pole portion of the kidney respectively. Seventy-seven lesions (33%) were in central/hilar locations, and the remaining tumors were exophytic.

Pathological examination revealed that 87.2% of the tumors were clear-cell type and 12.8% were papillary type. The rest were categorized as chromophobe, granular or unclassified. Mean Fuhrman histological grade was 2 ± 0.7.

INTRAOPERATIVE PARAMETERS

Clamping of the renal vessels with surface hypothermia was performed in all patients except for five (~2%) who had very small exophytic lesions. Median operative blood loss was 40 ml (range 20–3500, mean 157 ml); blood transfusion was required in 12 patients (5.2%). Mean warm ischemia time was 24 ± 11 minutes (median 23.5, range 12–100 minutes).

Intraoperative insertion of a double J stent was required in three patients with concomitant renal tumor and staghorn stone. In none of the cases did intraoperative frozen section analysis reveal positive surgical margins. However, final pathology showed cancer cells in the examined specimen of 6 cases (2.6%).

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

TUMOR RECURRENCE AND PROGRESSION

During a mean follow-up time of 45 ± 34 months (median 42, range 6–168 months) tumor recurrence was observed in 13 patients (5.6%). Mean follow-up time for detection of oncological failure was 51 months (median 36, range 6–132 months). All patients were males, with a mean age of 61 years (median 58, range 51–74 years). Average size of the enucleated lesion was 5 cm (median 5, range 4–7 cm). Eleven tumors (84.6%) were clear-cell type RCC, of which one exhibited predominantly sarcomatoid features, one was papillary RCC and one was a chromophobe tumor. Eight cases (61.5%) were categorized as Fuhrman grade 3, and the remaining were grade 2. Intraoperative frozen sections as well as postoperative final pathological examination of the surgical margins were negative in all tumors.

The sites 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 and 60 months is 1.8% and 4.0% respectively [Figure 1].

STATUS AT LAST FOLLOW-UP

In this group of patients with tumor recurrence, one patient died due to RCC metastases and two patients with local recurrence (both had 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 adjuvant tyrosine kinase inhibitor. Two patients 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 tyrosine kinase inhibitor. One patient with systemic metastases is receiving adjuvant tyrosine kinase inhibitor with stabilization of the disease. One patient with local failure at the surgical site underwent nephrectomy, and the four patients with a new renal lesion 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- and 60-month metastases-free survival for the entire group was 99.1% and 98.4% respectively [Figure 3].

PREDICTORS OF ONCOLOGICAL FAILURES

Using the Cox hazard survival model we tried to identify which of the studied variables were predictive of disease recurrence. Table 1 summarizes the variables that were significantly associated with tumor recurrence: warm ischemia time ($P = 0.058$), tumor size ($P = 0.001$), tumor location (central versus peripheral) ($P = 0.015$), and multiple (unilateral or bilateral) lesions ($P = 0.001$).

The probability of recurrence at 5 years by gender was 6% for males versus no recurrence for females ($P = 0.011$).

Extended warm ischemic time was associated with increased probability of recurrence. All cases with recurrent disease had a warm ischemia time of > 20 minutes, whereas none of those who had ischemia time < 20 minutes ($P = 0.007$) had tumor relapse. The 5-year probability of recurrence for patients with ischemia of > 20 minutes was 5.7% versus no recurrence for those with ischemia < 20 minutes ($P = 0.012$).

Tumor size significantly predicted relapse. By the end of the study recurrence was reported in 11.1% of patients with tumor ≥ 4 cm compared to none of those with tumor smaller than 4 cm ($P = 0.001$). The 5-year probability of oncological failure was 8.2% for patients with tumor ≥ 4 cm versus no recurrence for those with small tumors ($P = 0.001$).

Central location was associated with higher failure rate (9.6%) and shorter mean time to progression (23 months) compared with 2.9% and 69 months respectively for peripheral lesions. 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 ($P = 0.007$).

Multifocality (uni- or bilateral synchronous or metachronous) was a strong predictor of oncological failure. In our study patients with multiple tumors had a 40.0% relapse rate while those with unifocal disease had only a 3.3% recurrent event rate ($P = 0.0001$). The 5-year probability of recurrence in patients with multiple lesions was sevenfold higher than in those with a single lesion (20.5% vs. 2.8%) ($P = 0.0001$). Parameters such as age, tumor grade, histological subtype,

Figure 1. Probability of recurrence

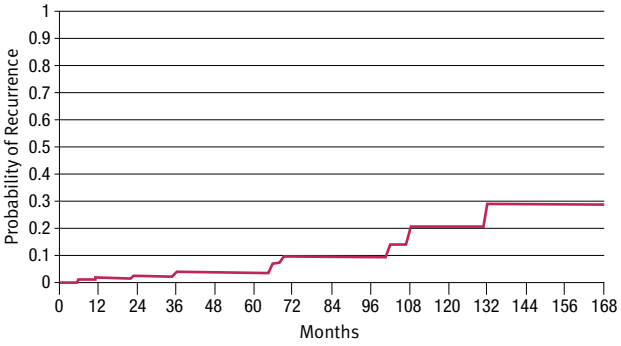


Figure 2. Probability of cancer-specific survival

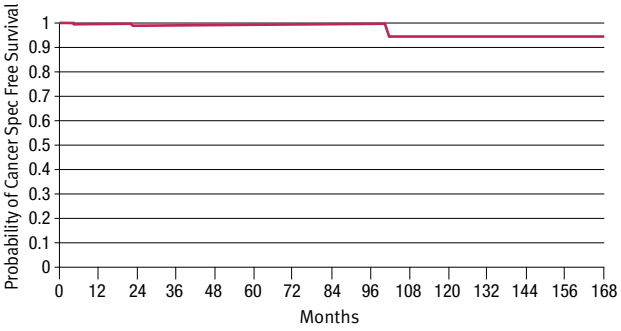
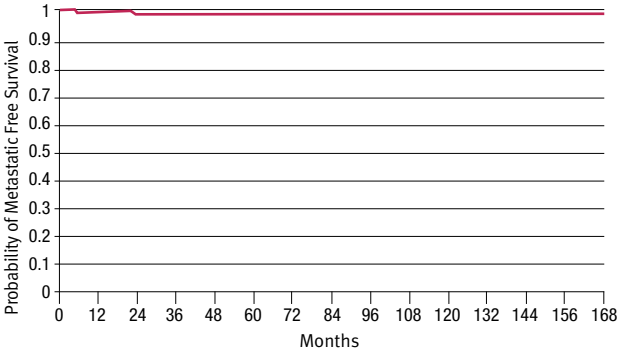


Figure 3. Probability of metastases-free survival



estimated blood loss, renal function, side, presenting symptoms and number of kidneys were not predictive of recurrent disease in our study group.

DISCUSSION

Nephron-sparing surgery has became the standard treatment for renal masses 4 cm in size [3]. It is evident that life expectancy and quality of life for patients with RCC is largely dependent on the residual renal function after tumor removal [4]. Although renal function is important, NSS should meet all oncology criteria and yield cancer control rates similar to those of radical nephrectomy. Recurrence after NSS does occur, hence it is crucial to understand the rate, mechanisms and predictors of oncological failure in order to inform the patients before surgery about the risk of recurrence and to modify and improve the surgical technique.

The oncological failure rate in our series was 5.6% (13/229), 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 in a mean postoperative follow-up of 55.6 months. Van Poppel and collaborators [6] noted a 3.94% systemic failure rate (3/76 patients), and Zigeuner et al. [7] reported oncology failure after a mean follow-up time of 80 months in 17 of 114 patients (15%) who underwent NSS. Peycelon et al. [8] demonstrated 81% and 78% rates for 5- and 10-year overall survival, and 92% and 88% for 5 and 10 years tumor-free survival in patients who underwent NSS due to solid lesions with an average diameter of 5.6 cm.

Looking at the patterns of oncological failures we can subclassify our patients into two main groups: those who had local failure (n=9) and those with systemic relapse (n=4). Patients with local failure could be further classified into two subgroups: a) true local failure including surgical scar (n=2), perirenal fat (n=2) and recurrence at the surgical site (n=1); and b) local renal recurrence at a different site from the original tumor, i.e., patients who developed a second renal primary neoplasm (n=4). For the group of patients with systemic metastases (n=4) the main sites were lymph nodes and lung.

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, Inc., Atlanta, GA, USA) omitted this need completely and in order to continue performing NSS as radical surgery in terms of cancer control, we now routinely perform extensive perirenal fat removal, especially above and adjacent to the tumor. Indeed, no further perirenal recurrence was documented. Yoo and colleagues [9] reported that perinephric fat infiltration was an independent prognostic factor for disease-free survival. In Yoo's study fat infiltration was associated with a 14.6% recurrence rate for lesions smaller than 7 cm, and 33% of the patients who had tumor recurrence died of renal cell carcinoma. Jeon and co-authors [10] also demonstrated significant lower survival rates for patients with perirenal fat invasion; they conclude, however, that tumor size is the most important prognosticator and that fat invasion is directly related to tumor size. Two patients in our study underwent re-exploration with extensive resection of all fat tissue as well as the recurrent lesions; both are currently alive without evidence of disease.

Despite negative surgical margins, one patient (0.4%) in our series had local recurrence at the surgical site diagnosed 12 months after surgery. Radical nephrectomy was undertaken and the patient is alive without evidence of disease. The rate of positive surgical margins at the final pathological examination in our series was 3.4% (8/229); none of the patients with positive margin had a recurrence locally or at a distant site. The causes of local recurrence at the surgical site are under constant debate. It was thought that positive surgical margins are one of the main determinants of recurrence and poor outcome; however, Yossepowitch et al. [11] showed that selected patients with positive surgical margins may have good long-term disease-free survival. Bensalah and team [12] assessed 1390 NSS procedures performed in several institutions and 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 surgical margins by the tumor was not associated with an increased risk of local recurrence or metastatic spread.

Another mechanism of failure is tumor seeding, which we encountered in two cases (0.8%). Predictors for such an undesired event are high grade and relatively large size (4.7 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 operated field with a surgical pad during enucleation 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 five cases (2.18%) occurred as the result of the surgical technique. Four additional cases (1.76%) with second primary tumor in the operated kidney were failures directly related to the conservative approach and could have been prevented by radical surgery. This unfortunate 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.

Today, the decision regarding whether to perform NSS or radical nephrectomy is largely dependent on tumor size [15-17]. The enucleated lesions in the oncological failure group

were significantly larger than the disease-free group. Most tumors (n=11) were larger than 4.0 cm, and their average diameter was 5.0 cm compared to 3.9 cm for the entire group ($P = 0.001$). The 5-year probability of oncological failure was 8.2% for patients with tumor ≥ 4 cm versus no recurrence for those with small tumors ($P = 0.001$).

In the past most publications advocated NSS for tumors up to 4.0 cm. More recently, however, several studies reported encouraging results also in patients with larger tumors. Similar to our findings, Antonelli et al. [17] compared patients with lesions up to 4.0 cm to those with tumors more than 4.0 cm in diameter and found a worse outcome (in terms of progression and disease-free survival) for the group with the larger tumor. Patients with larger tumors had no survival benefit if treated by nephrectomy. In contrast Patard et al. [16] who analyzed 730 cases after elective NSS found that the cancer-specific survival was not influenced by tumor size. A recent study by Bernhard and co-workers [18] also found that tumor size > 4 cm is a risk factor for oncology failure.

All of the patients with oncologic failure were males. RCC is indeed 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 ($P = 0.011$). Similar to our findings, Sunela et al. [19] also found better survival rates in female patients.

Multiple synchronous or metachronous tumors were also found to be a significant predictor of recurrence in our study. Similar results were reported by others. Pahernik et al. [20] reported 86% and 75% cancer-specific survival rates at 5 and 10 years and 87% and 80% freedom from local recurrence rate, respectively, in 44 patients with bilateral tumors undergoing NSS. Dimarco and team [21] reported a higher rate of contralateral recurrence in patients with multifocal clear-cell RCC than in patients with solitary tumors (risk ratio 2.91, $P = 0.142$). Multiple lesions may represent a genetic predisposition such as in Von Hippel-Landau disease or papillary RCC that may be multifocal and require a careful and strict follow-up protocol. Obviously radical nephrectomy in such cases would eliminate the risk of ipsilateral new tumor growth at the cost of reducing renal function. It should be mentioned that multifocality is not associated with larger tumors, higher stage and grade, or renal cancer death [22].

Our analysis also revealed that warm ischemic time was a statistically significant predictor for tumor recurrence. Patients with warm ischemia time of more than 20 minutes had a higher relapse rate compared to those with warm ischemia time of less than 20 minutes ($P = 0.012$). To the best of our knowledge such an association has not been documented in the English medical literature. We can hypothesize that prolonged warm ischemia time may represent a more complex procedure that may be related to an unfavorable location (hilar or central), which is more frequently observed in patients with tumor recurrence. Alternative speculation can be that hypervascular lesions (known to exhibit more aggressive behavior) may demand more meticulous enucleation, and hence may prolong the warm ischemia time.

CONCLUSIONS

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

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Corresponding author:
Dr. O. Nativ
Dept. of Urology, Bnai Zion Medical Center, Haifa 31048, Israel
Phone: (972-4) 835-9523
Fax: (972-4) 835-9709
email: ofer.nativ@b-zion.org.il

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