Elective Nephron Sparing Surgery for Renal Cell Carcinoma Larger Than 4 cm

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Purpose: Elective nephron sparing surgery is established as an alternative to radical nephrectomy for renal cell carcinoma if tumors are small (4 cm or less, stage T1a). We compared outcomes in patients with renal cell carcinoma 4 cm or less (small) vs more than 4 cm (large) who were treated with nephron sparing surgery.

Materials and Methods: Between 1979 and 2006, 618 patients underwent elective nephron sparing surgery at our institution. Of these patients 474 (76.7%) had renal cell carcinoma, which was 4 cm or less in 372 (78.5%) and more than 4 cm in 102 (21.5%). Followup was 4.7 (range 0.1 to 23.9) years for small and 4.7 (range 0.1 to 24.1) years for large tumors. Cancer specific survival and local recurrence free survival were estimated.

Results: The estimated cancer specific survival rate at 5 years was 97.9% and 95.8%, and at 10 years it was 94.9% and 95.8% for small and large tumors, respectively (log rank $p = 0.583$). The survival rate free of local recurrence at 5 years was 98.5% and 98.3%, and at 10 years it was 93.9% and 98.3% for small and large tumors, respectively (log rank $p = 0.282$). In contrast to tumor size, stage 3 was associated with a significant higher risk of tumor related death.

Conclusions: Elective nephron sparing surgery is oncologically safe in select patients with localized renal cell carcinoma more than 4 cm. In our series the selection criterion for choosing elective nephron sparing surgery rather than radical nephrectomy over the years has consistently been safe surgical resectability rather than tumor size. However, there is a correlation between tumor size and unfavorable pathological tumor characteristics, which prompts caution when choosing elective nephron sparing surgery for all large tumors.

Key Words: kidney; carcinoma, renal call; nephrons; nephrectomy; surgical procedures, elective

Nephron sparing surgery is the treatment of choice for surgical excision of solid renal tumors in cases of a solitary kidney, for bilateral renal tumors or if chronic renal failure is present or pending (imperative indication). For 2 decades NSS has also been established as a safe and effective alternative to radical nephrectomy for renal tumors in the presence of a normal contralateral kidney (elective indication).

Currently most investigators advocate limiting elective NSS to tumors up to 4 cm.[1] However, more recently it was suggested that select exophytic renal tumors more than 4 cm may undergo NSS without compromising oncological efficacy.[2–6] We present in a retrospective analysis the outcome in patients who underwent elective NSS for RCC at our institution, which was analyzed for RCC size, including lesions 4 cm or less (small) vs more than 4 cm (large).

METHODS

Between 1979 and 2006, 618 patients underwent elective NSS for cancer suspicious solid renal tumors at our institution. A total of 140 patients (22.7%) with benign tumors and 4 (0.01%) with metastases at presentation were excluded from this retrospective analysis. Of patients with benign tumors 64 (10.4%) had oncocytoma, 36 (5.8%) had angiomyolipoma, 26 (4.2%) had a complicated cyst and 14 (2.3%) had other benign lesions, such as leiomyoma, cystic nephroma and fibrotic tumor. The remaining 474 patients underwent elective NSS for RCC with curative intent, including 372 (78.5%) with RCC 4 cm or less in the pathological specimen and 102 (21.5%) with RCC more than 4 cm. Mean age at surgery was 60.7 (range 23.5 to 86.0) and 60.3 years (range 31.2 to 84.1) in patients with small (4 cm or less) and large (more than 4 cm) tumors, respectively. Followup in patients with small tumors was 4.7 years (range 0.1 to 23.9) and in those with large tumors it was 4.7 years (range 0.1 to 24.1).

With respect to surgery with time we stratified patients undergoing NSS for RCC into 3 periods, including up to 1989, 1990 to 1999 and since 2000. The incidence of RCC more than 4 cm for elective NSS was 27.8% (20 of 72), 18.3% (34 of 186) and 22.2 (48 of 216) for up to 1989, 1990 to 1999 and since 2000, respectively. Mean tumor diameter for elective NSS was 3.57 (range 1.6 to 7.0), 3.22 (range 1.0 to 10.0) and 3.28 cm (range 1.1 to 11.5) for up to 1989, 1990 to 1999 and since 2000, respectively.

In this series the selection criteria for choosing elective NSS rather than radical nephrectomy during the years were consistently safe surgical resectability rather than tumor size. Standard access for kidney exposure was an extraperitoneal flank incision above the 11th or 12th rib. The surgical

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technique was previously described in detail.[7] Intraoperatively the whole tumor specimen and (at surgeon discretion) renal margin biopsies were sent for frozen section to ensure complete tumor excision. In cases of positive margins extended parenchymal resection or conversion to radical nephrectomy was done at surgeon discretion. For our analysis of tumor size the maximum tumor diameter in the surgical specimen was used. Staging was revised according to the 2003 UICC revised TMN staging system, 6th edition. Tumor grading was based on the 1986 classification of Thoenes et al.[8]

Data input and statistical analysis were performed using SPSS®, version 12.0. Patients were grouped into those with small (4 cm or less) and large (more than 4 cm) tumors (see table). For categorical data absolute and relative frequency, and for metrical data the median and range (minimum and maximum) are presented. Differences in patients with small and large tumors concerning the influence of different factors were tested using the Fisher exact and Wilcoxon rank sum tests. Cancer specific survival and local recurrence-free survival were estimated using the Kaplan-Meier method. Multivariate Cox proportional hazard models were used to assess the association of pathological parameters (stage, grade, histology and tumor size) and cancer specific survival. For predictors and outcome parameters the RR and 95% CI were calculated. All statistical tests were 2-sided with significance considered at $p = 0.05$.

RESULTS

Patients were categorized into 2 groups according to pathological tumor size, including small tumors (4 cm or less) in 372 and large tumors (more than 4 cm) in 102. Median small and large tumor size was 3.0 (range 1.0 to 4.0) and 5.0 cm (range 4.2 to 11.0), respectively ($p < 0.05$). Of 506 patients with RCC in whom elective NSS was planned 32 (6.3%) showed positive margins after NSS and they underwent nephrectomy. Thus, 21 of 393 patients (5.3%) with small RCC (4 cm or less) and 11 of 113 (9.7%) with large RCC (more than 4 cm) underwent radical nephrectomy when there were positive margins after NSS. Corresponding median tumor size was 3.0 (range 1.5 to 4.0) and 5.0 cm (range 4.2 to 7.3) for small and large RCC, respectively. In 11 of the 32 nephrectomy specimens (34.4%) RCC was still found, including 8 nephrectomy specimens with tumor at the resection site and 3 specimens showing multifocal RCC.

Univariate analysis of small vs large tumors by patient data and pathological features

	Tumor Size (cm)		
	4 or Less	Greater than 4	p Value
No. pts	372	102	
Mean age (range)	60.7 (23.5–86.0)	60.3 (31.2–84.1)	n.s.
Mean cm tumor size (range)	3.0 (1.0–4.0)	5.0 (4.2–11.0)	<0.05
No. stage (%):			<0.05
pT1a	363 (97.6)	—	
pT1b	—	84 (82.4)	
pT2	—	6 (8.9)	
pT3	9 (2.4)	12 (11.8)	
No. grade (%):			<0.05
1	123 (33.1)	16 (15.7)	
2	223 (59.9)	75 (73.5)	
3	26 (7.0)	11 (10.8)	
No. histological subtype (%):			n.s.
Clear cell	288 (77.4)	73 (71.6)	
Papillary	60 (16.2)	23 (22.5)	
Chromophobe	24 (6.4)	6 (5.5)	
Followup (yrs)	4.7 (0.1–23.9)	4.7 (0.1–24.1)	n.s.

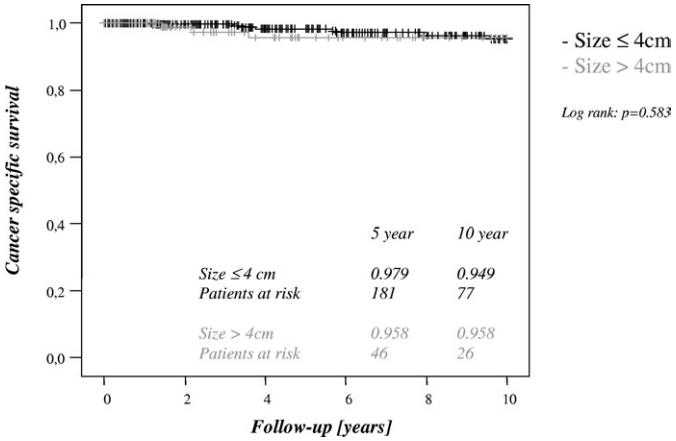

FIG. 1. Tumor specific survival in patients after elective NSS based on 4 cm cutoff tumor size.

The table lists pathological features. Stage distribution was pT1a and pT3 in 363 (97.6%) and 9 (2.4%) patients with small tumors, and pT1b, pT2 and pT3 in 84 (82.4%), 6 (5.9%) and 12 (11.8%) with large tumors (small vs large $p < 0.05$). Grade 1 was found in 123 (33.1%) and 16 (15.7%), grade 2 was found in 223 (59.9%) and 75 (73.5%), and grade 3 was found in 26 (7.0%) and 11 (10.8%) small and large tumors, respectively ($p < 0.05$). Histopathology revealed clear cell carcinoma in 77.4% and 71.6%, papillary carcinoma in 16.2% and 22.5%, and chromophobe carcinoma in 6.4% and 5.5% of small and large tumors, respectively.

In the small RCC group (4 cm or less) 8 of 374 patients (2.1%) died of metastatic RCC, while 3 of 102 (2.9%) with large RCC (more than 4 cm) died of metastatic RCC. Mean time from NSS to death from RCC was 4.72 (range 1.19 to 9.56) and 2.22 years (range 1.36 to 3.59) in patients with small and large tumors, respectively. The estimated cancer specific survival rate at 5 years was 97.9% and 95.8%, and at 10 years it was 94.9% and 95.8% for small and large tumors, respectively (log rank $p = 0.583$, fig. 1). Of the 474 patients 11 (2.3%) had recurrence in the ipsilateral kidney after NSS. Ten of 374 patients (2.7%) underwent primary surgery for small RCC. Mean time from surgery to ipsilateral renal recurrence was 6.26 years (range 3.1 to 15.8) in patients with small RCC. One of 102 patients (1%) with RCC more than 4 cm showed ipsilateral renal recurrence after 3.36 years. The survival rate free of local recurrence at 5 years was 98.5% and 98.3%, and at 10 years it was 93.9% and 98.3% for small and large tumors, respectively (log rank $p = 0.282$, fig. 2).

Multivariate analysis of the associations between the pathological parameters stage, grade, histology and tumor size vs cancer specific survival was done in the whole cohort of 474 patients. Stage 3 vs 2 or less was associated with a significantly higher risk of cancer related death (RR 6.63, 95% CI 1.2–35.8, $p = 0.03$). Due to patient selection (low number of events and low number of patients, that is 21) with stage 3 RCC these results must be interpreted cautiously. Larger series must confirm this issue. In contrast,

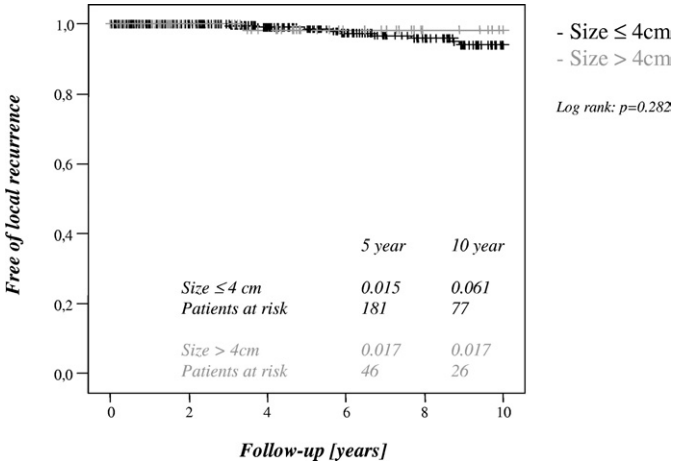

FIG. 2. Local recurrence-free specific survival in patients after elective NSS based on 4 cm cutoff tumor size.

for grade 3 vs 2 or less (RR 1.53, 95% CI 0.52–2.52, p = 0.32), clear cell pathology (RR 0.77, 95% CI 0.28–2.2, p = 0.64) and tumor size more than 4 cm (RR 1.08, 95% CI 0.32–4.39, p = 0.79) no significant associations with cancer specific survival were detected.

DISCUSSION

NSS is increasingly applied as a surgical option for localized RCC. This approach was initially pursued only in patients with an imperative indication for NSS, that is in those with a solitary kidney, bilateral tumors or chronic renal failure.[9] Favorable oncological results of NSS in patients with imperative indications have led to the gradual expansion of this surgical technique to patients with small, peripheral tumors (favorable tumor features) and a normal contralateral kidney (elective indication). The steadily increasing use of imaging has resulted in an increase in the incidence of incidentally discovered, asymptomatic small renal masses, which led to further expansion of elective NSS for RCC.

Elective NSS is now well accepted for tumors that are 4 cm or less. A recent review of the literature including more than 900 patients revealed a local recurrence rate of 2.1% and a cancer specific survival rate in most series of between 95% and 100%.[10] Careful patient selection with small size and peripheral location of tumors accounts for the favorable outcome in these studies.[10] There is also evidence for improved quality of life[11] and decreased renal impairment[12] in patients undergoing NSS compared to radical nephrectomy. However, there are new data about the size limit of tumors amenable to elective NSS. Some investigators have suggested that elective NSS might be a reasonable option in select patients with pT1b RCC (4 to 7 cm).[2–5]

The general recommendation of a tumor size limit of 4 cm is based on a large study of 485 patients investigating the impact of tumor size on oncological outcome and local recurrence after NSS[1] with significantly better cancer specific survival in patients with tumors 4 cm or less. However, the study mostly included patients with imperative indications and, thus, selection bias was toward the preservation of renal function rather than toward oncological safety. In contrast, the newer literature demonstrates that cancer specific survival in select patients with pT1b RCC was better after elective NSS than after radical nephrectomy.[2] However, this was mostly attributed to the careful selection of patients with favorable tumor characteristics. Patients who underwent NSS in this series had smaller tumors, less infiltrative growth patterns, fewer intrarenal tumors and less collecting system involvement.[2] In our series patients treated with elective NSS for tumors more than 4 cm had a median tumor size of 5 cm (range 4.2 to 11.0), so that most tumors were only slightly larger than pT1a stage. Histopathology revealed organ confined disease in 84% of cases and high grade tumors in 11%.

Nevertheless, elective NSS in patients with greater than pT1a RCC remains controversial because high grade RCC, nonorgan confined RCC and systemic disease are directly related to tumor size.[13,14] This was also true in our series on univariate analysis comparing 7% and 11% grade 3 lesions, and 2% and 12% pT3 lesions for small and large tumors, respectively. Moreover, the incidence of multifocality appears to increase with larger tumor size.[14] RCC multifocality was reported to occur in up to 16% of patients.[15] However, ipsilateral renal recurrence rates of up to 6% for elective NSS are much lower, as one would expect,[10,16,17] which might be explained by improved preoperative and intraoperative detection of multifocal tumors, and the low aggressiveness of these preselected tumors. In contrast, local recurrence might be the result of incomplete tumor excision and positive margins. Therefore, the confirmation of tumor-free margins by intraoperative frozen section might decrease local recurrence.

CONCLUSIONS

Elective NSS can be considered in select patients with localized RCC more than 4 cm with careful patient selection. A group of patients with tumors larger than 4 cm can be treated safely with NSS in the elective setting without compromising oncological efficacy. The surgeon decision in regard to organ preservation must consider tumor site and safe surgical resectability rather than tumor size. However, there remains a correlation between tumor size and unfavorable pathological tumor characteristics. This prompts caution for choosing elective NSS for larger tumors since these tumors are associated with decreased cancer specific survival when NSS is performed for imperative indications.

Abbreviations and Acronyms

n.s.	=	not significant
NSS	=	nephron sparing surgery
RCC	=	renal cell carcinoma

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EDITORIAL COMMENT

These authors provide evidence suggesting that traditional criteria for NSS, namely tumor size, may be expanded without compromising oncological outcomes. In a retrospective analysis of a large number of patients undergoing elective partial nephrectomy no differences in cancer specific survival or the rate of local recurrence were observed in those with tumors less vs greater than 4 cm. Combined with data on renal function after radical and partial nephrectomy[1] this observation supports the notion that consideration of nephron sparing techniques should not be limited to smaller tumors. Rather, the ability to safely and effectively excise the tumor along with patient preference[2] are the primary determinants of the surgical approach. Although larger renal tumors are more likely to be of higher stage and multifocal, ultimately cancer specific survival is likely determined by inherent biological behavior, ie metastatic or not, rather than by the local control method, while improved resolution of imaging modalities provides information on whether several lesions are present. It remains to be determined whether there is a size threshold for which elective NSS should be excluded.

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