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Original Contribution

# Low local metastatic rate may widen indication of nephron-sparing surgery for renal cell carcinoma

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**Abstract** To explore the rationale for renal-sparing surgery as an alternative method to radical nephrectomy in the treatment of renal cell carcinoma (RCC), we analyzed clinical data from 94 patients diagnosed as having RCC. They were divided into 3 groups based on the maximum diameter of their tumor specimens. Group A had tumors size ranging from 0 to 4 cm, group B had tumors size ranging from 4 to 7 cm, and group C had tumors size greater than 7 cm. Tissue samples (5 cm) were taken from the upper pole side, lower pole side, and renal pelvic side of the tumor pseudocapsule; if the tumor was located on 1 pole of the kidney, samples were collected from 2 directions. The specimens were then embedded in paraffin and cut serially at segments 0 to 1, 1 to 3, and 3 to 5 cm. Staining with hematoxylin and eosin, anti-pancytokeratin, and vimentin was performed to determine tumor type and tumor infiltration. From the 94 patients analyzed, 2 patients in group A had RCC metastasis within 1 cm of tissue around the pseudocapsule, and 4 patients in groups B and C had lymph node metastasis without metastasis in the tissue 1 cm outside the pseudocapsule in all 3 directions described. There was no statistical significant difference found between the incidence of local metastasis of the various tumor sizes, suggesting that local metastasis of RCC is not associated with the size of the tumor. Based on the observation that incidences of local metastasis were low in early-stage RCC, we came to the conclusion that pseudocapsule of RCC tumor might have growth-limiting effect on the tumor enclosed. It is theoretically a safer and better surgical option for patients with RCC with a smaller size of tumor and indications for radical nephrectomy to undergo renal-sparing surgery with an excision margin of 1 cm of normal tissue around the pseudocapsule of the tumor.


*Keywords:* Renal cell carcinoma; Nephrectomy; Vimentin; Anti-pancytokeratin immunoglobulin

## 1. Introduction

Renal cell carcinoma (RCC) is the most common malignant tumor arising from the kidney and accounts for 2% of all new malignant cancers diagnosed in the world [1]. In 2010, 3% (female) to 4% (male) of the new cases of malignant cancers were diagnosed to be RCC in North America. Out of a total of 58 240 new cancer cases (35 370 in men and 22 870 in women), 8210 deaths in men occurred [2]. In North America, based on statistical data collected from 1992 to 2006, RCC accounted for 85% of all renal neoplasms, whereas other types included 15% of renal pelvic carcinomas and 2% of rare forms of malignant tumors [2].

Early diagnosis and treatment are important in managing RCC, and surgery is the standard method for treating RCC until now. These surgical options include radical nephrectomy (RN) and nephron-sparing surgery (NSS) [3-5]. The NSS has been used to treat RCC in patients with only 1 remaining functional kidney; however, the main controversy remains in weighting options between RN and NSS for treating other patients with RCC. A limited number of past studies have shown that the results of NSS and RN were similar based on the use of hematoxylin and eosin (H&E) staining to determine the extent of local metastasis without further investigations into other histologic changes [6-8].

In the present study, we want to analyze past studies by using immunohistochemistry staining using pancytokeratin

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and vimentin markers to examine the extent of local metastasis of RCC because the double positives of these 2 markers are better distinguished in RCC cells from the surrounding tissues. By combining histologic results and factors influencing tumor growth such as age and sex, we want to provide solid evidence that will eventually lead to better surgical decisions for patients with RCC.

## 2. Materials and methods

### 2.1. Patient's selection and group division

Our study group consisted of 94 patients treated with RN for RCC at our institution from January 2009 to December 2009. Of the 94 patients, 63 were male and 31 were female; the ages ranged from 33 to 86 years. All patients underwent diagnosis and staged preoperatively with computed tomography (CT). The histology of tumor type was redetermined according to the Heildelberg classification [9], grading was assigned according to Fuhrman et al [10], and staging was updated from the American Joint Committee on Cancer (AJCC) TNM 2009 system. Sixty-nine patients in the study group had $cT_1N_0M_0$ tumors, and 25 patients had $cT_2N_0M_0$ tumors. These patients were divided into 3 groups according to the maximum diameter of tumors as 0 to 4 cm (group A; 32 patients), 4 to 7 cm (group B; 37 patients), and greater than 7 cm (group C; 25 patients). The study was approved by local institutional review board, and all patients signed an informed consent form for inclusion of their samples.

### 2.2. Collection and processing of tissue specimen

Tissue samples (5 cm) were taken from the upper pole side, lower pole side, and renal pelvic side of the tumor pseudocapsule; if the tumor was located on 1 pole of the kidney, samples were collected from 2 directions. Each tissue sample was fixed in formalin and embedded in paraffin, and serial sections were cut at segments 0 to 1, 1 to 3, and 3 to 5 cm. If there was not enough tissue outside the pseudocapsule (eg, when the pseudocapsule was only 2 cm from the renal pelvis), then only the tissue segments that were long enough to perform serial sectioning were included in the results. Tissue slices were stained with H&E and processed for immunohistochemical staining using pancytokeratin antibody (Shanghai Long Island Biotech, Shanghai, China) and vimentin antibody (Shanghai Long Island Biotech).

#### 2.2.1. Hematoxylin and eosin staining

Thin tissue sections were prepared and subjected to H&E staining within 5 days postoperation. Before H&E staining, tissue samples were fixed in formalin, dehydrated, embedded in paraffin, and serially sectioned at 4 $\mu$m. Thin sections were then deparaffinized, rehydrated in a gradient of ethanol, and washed in running tap water for 2 minutes. Sections were stained in hematoxylin solution for 5 minutes. Excess stain was rinsed off by washing the sections in running tap water for 1 minute. After 30 seconds of differentiation in acid solution, sections were washed in running water for a few minutes and immersed in 95% ethanol for 1 minute followed by 1 minute of counterstaining in eosin solution. Sections were then dehydrated in serial-graded ethanol washes (70%, 85%, 90%, and 100%), cleared in xylene phenol, and finally mounted with neutral resin.

### 2.3. Immunohistochemical staining for pancytokeratin and vimentin

For immunohistochemical staining with pancytokeratin and vimentin, 4-$\mu$m-thick paraffin-embedded tissue sections were pretreated with 1 mg/mL phosphate-buffered saline (PBS) for 15 minutes at room temperature. For immunohistochemical staining with vimentin, 4-$\mu$m-thick paraffin-embedded tissue sections were pretreated with boiling citrate solution (10 mmol/L, pH 6.0) for 15 minutes followed by a 15-minute incubation at room temperature. Sections were then deparaffinized with xylene and rehydrated in a gradient of ethanol. After antigen retrieval, sections were washed in PBS 3 times for 2 minutes each time. Sections were incubated with primary antibody against pancytokeratin or vimentin (Shanghai Long Island Biotech) for 60 minutes at room temperature. After washes in PBS 3 times for 2 minutes each, sections were incubated for 20 minutes with secondary biotinylated antibody followed by a 20-minute incubation with streptavidin-peroxidase complex (both from Dako Cytomation, Glostrup, Denmark), and then the sections were washed again with PBS 3 times for 2 minutes each. Sections were developed with diaminobenzidine (Dako Cytomation), and the nuclei were counterstained with hematoxylin, followed by dehydration in a gradient of ethanol and mounting with neutral resin medium.

### 2.4. Evaluation of slides

Hematoxylin and eosin–stained tissue sections were observed under the light microscope with ×100 and ×20 magnifications, and the tumor type and range of tumor infiltration were determined. Immunohistochemical-stained sections were observed under the light microscope with ×100, ×20, and ×50 magnifications; the integrity of the tumor pseudocapsule and extent of tumor cells in sections taken from 2 opposite poles of the tumor were determined. Pancytokeratin expression was observed in the cytoplasm of the RCC cells, whereas vimentin was seen on the membrane of the RCC cells. As long as expression was observed, it was considered positive; the strength of expression was not of concern in the current study.

### 2.5. Statistical analysis

Statistical analysis was performed using with SPSS software 11.0 (SPSS Inc, Chicago, Ill). Data were reported in mean ± standard deviation ($x \pm SD$). $t$ Test was used to assess the significance of the difference between the means of 2 samples; $\chi^2$ test and rank sum test (Kruskal-Wallis test)

Table 1
Distribution of age and sex

| Age (y) | Female | Percentage | Male | Percentage | Total | Total percentage |
|---|---|---|---|---|---|---|
| 30-39 | 7 | 23.3 | 3 | 5.0 | 10 | 10.6 |
| 40-49 | 7 | 20.0 | 16 | 25.4 | 23 | 24.5 |
| 50-59 | 6 | 20.0 | 18 | 28.6 | 24 | 25.5 |
| 60-69 | 5 | 16.1 | 15 | 23.8 | 20 | 21.3 |
| 70-79 | 5 | 16.1 | 10 | 15.9 | 15 | 16.0 |
| >80 | 1 | 3.2 | 1 | 1.6 | 2 | 2.1 |
| Total | 31 | 100.0 | 63 | 100.0 | 94 | 100.0 |

were used to compare groups of sample data. $P < .05$ indicated that there was a statistical significant difference, and $P < .01$ indicated that there was a highly statistical significant difference.

## 3. Results

### 3.1. Relationship between age, sex, and tumor size (maximum diameter)

For all of the patients diagnosed as having RCC (94 patients; average age, 56.59 ± 12.347 years), 63 were male (average age, 57.81 ± 10.736 years) and 31 were female (average age, 54.10 ± 14.996 years). Each sex was divided into different age groups (Table 1); there was no statistical significant age difference in both sexes ($P > .05$).

In a total of 47 patients with tumor in the left kidney, 29 were male and 18 were female. In a total of 47 patients of tumor in the right kidney, 34 were male and 13 were female. There were no patients with bilateral RCC tumors. There was no statistical significant difference in the localization of tumor between the 2 sexes ($P > .05$). Also, no significant difference was found between tumor localization, sex, and age according to the results of the rank sum test ($\chi^2 = 1.203$; $P = .273$) (Table 2).

### 3.2. Comparison of preoperative CT imaging with postoperative macroscopic pathology tumor measurements (maximum diameter)

The diameters of tumor specimen measured by macroscopic pathology ranged from 1.2 to 13 cm, with an average of 4.566 ± 2.2783 cm. The maximum diameter of tumors measured by preoperative CT imaging ranged from 1 to 12 cm, with an average of 4.635 ± 2.1262 cm (Table 3).

According to a paired $t$ test, there was no significant difference in the maximum tumor diameters between the 2 groups ($t = 0.853$; $P = .396$). The tumor measurements by CT imaging and macroscopic pathology were further divided in to 3 groups as follows: 0 to 4, 4 to 7, and more than 7 cm. Comparison was made between each size group. No significance difference was found in the tumor size groups measured by these 2 measuring methods ($P > .05$).

Table 2
Distribution of tumor localization and sex

| Tumor localization | Female | Male | Total |
|---|---|---|---|
| Left, n (%) | 17 (58.1) | 28 (46.0) | 45 (50.0) |
| Right, n (%) | 13 (41.9) | 32 (54.0) | 45 (50.0) |
| Total | 31 | 63 | 94 |

Table 3
Maximum diameter of tumors measured by macroscopic pathology and CT imaging

| | Average maximum diameter (cm) | Sample size | SD | SE |
|---|---|---|---|---|
| Pathology | 4.566 | 94 | 2.2783 | 0.2350 |
| CT Imaging | 4.635 | 94 | 2.1262 | 0.2193 |

### 3.3. Comparison of tumor size and sex

Patients were divided into 3 groups according to the maximum diameter of tumor as 0 to 4 cm (group A; 32 patients), 4 to 7 cm (group B; 37 patients), and greater than 7 cm (group C; 25 patients). Group A consisted of 24 men and 11 women; group B consisted of 24 men and 13 women; and group C consisted of 18 men and 7 women (Table 4). The $\chi^2$ test suggested that there was no significant difference in the early-stage RCC tumor size between the 2 sexes ($\chi^2 = 0.386$; $P = .864$). Subdividing tumor size groups into different age groups and comparing the distribution of tumor size and age (Table 5), we found that there was no statistically significant difference in the tumor size between these age groups ($\chi^2 = 7.821$; $P = .451$).

### 3.4. Metastasis of different size tumors around the pseudocapsule

Thin sections of tissue samples prepared by serial sectioning at 0- to 1-, 1- to 3-, and 3- to 5-cm segments of 5-cm tissue samples taken from the different sides of the pseudocapsule were subjected to immunohistochemical staining for pancytokeratin and vimentin. In group A (0-4 cm in tumor diameter), 2 cases showed positive staining for both pancytokeratin and vimentin (Fig. 1, Table 6), which suggested signs of local metastasis within 1 cm outside the tumor pseudocapsule (Table 7). However, there was no significant difference in immunopositivity for both markers between these tumor size groups according to the Kruskal-Wallis test ($\chi2 = 3.917$; $P = .141$). Also, from the H&E staining, 3 cases in group B (4-7 cm in tumor diameter) and 1

Table 4
Distributions of tumor size and sex

| | Female | Male | Total | Total percentage |
|---|---|---|---|---|
| Maximum diameter, 0-4 cm | 11 | 21 | 32 | 34.04 |
| Maximum diameter, 4-7 cm | 13 | 24 | 37 | 39.36 |
| Maximum diameter, >7 cm | 7 | 18 | 25 | 26.60 |
| Total | 31 | 63 | 94 | |

Table 5
Distribution of tumor size and age

| Age (y) | Maximum diameter, 0-4 cm | | Maximum diameter, 4-7 cm | | Maximum diameter, > 7 cm | | Total |
|---|---|---|---|---|---|---|---|
| | Case | % | Case | % | Case | % | |
| 30-39 | 4 | 12.50 | 4 | 10.81 | 2 | 8.00 | 10 |
| 40-49 | 12 | 37.50 | 8 | 21.62 | 3 | 12.00 | 23 |
| 50-59 | 8 | 25.00 | 10 | 27.03 | 6 | 24.00 | 24 |
| 60-69 | 4 | 12.50 | 8 | 21.62 | 8 | 32.00 | 20 |
| >70 | 4 | 12.50 | 7 | 18.92 | 6 | 24.00 | 17 |
| Total | 32 | | 37 | | 25 | | 94 |

case in group C (tumor diameter above 7 cm) had lymphatic metastasis (Table 7).

## 4. Discussion

Renal cell carcinoma is known to metastasize primarily through the venous and lymphatic systems, as was also observed in our study. The classification of RCC cells is conventionally done by histopathologic examination of H&E-stained tissue sections using light microscopy; however, this method may not always reflect the actual pathology of the tissue. In our study, the pathologic diagnosis was further supported by immunohistochemical staining for pancytokeratin and vimentin proteins of the renal tissue surrounding the tumor pseudomembrane.

Pancytokeratin (AE1/AE3) is mainly localized in keratinized epithelium, stratified squamous epithelium, stratified epithelium, simple epithelium, and hyperplastic keratinocytes. Positive staining of pancytokeratin has been observed in a variety of tumors evaluated, such as squamous cell carcinoma (including the spindle cell variant), various types of adenocarcinoma (including adrenal carcinoma and hepatocellular carcinoma), transitional cell carcinoma, small cell carcinoma, malignant mesothelioma, germ cell tumor (except for seminoma), and some cases of synovial sarcoma and leiomyosarcoma. In conjunction with epithelial membrane antigen and carcinoembryonic antigen, pancytokeratin can be used in the differential diagnosis of epithelial tumors and other cancer research.

Vimentin is found in mesenchymal cells and sarcomas; epithelial cells and epithelial tumors generally do not express this protein. The immunostaining of vimentin is used to diagnose malignant tumors of mesenchymal origin, such as mesothelioma, synovial sarcoma, meningioma, and so on. It has an important reference value in the differential diagnosis of cancer and sarcoma, melanoma and cancer, thymoma and lymphoma, and also undifferentiated carcinoma and small cell mesenchymal tumor.

Pancytokeratin and vimentin are immunohistochemical markers widely used clinically for diagnosis and differential diagnosis of normal and abnormal tissues. Because RCC originates from renal tubular lesions, the positive staining of these 2 markers is often found in both clear cell RCC and granular cell RCC tissues. It has been shown that pancytokeratin and vimentin are currently the 2 best immunohistochemical markers for detecting RCC because

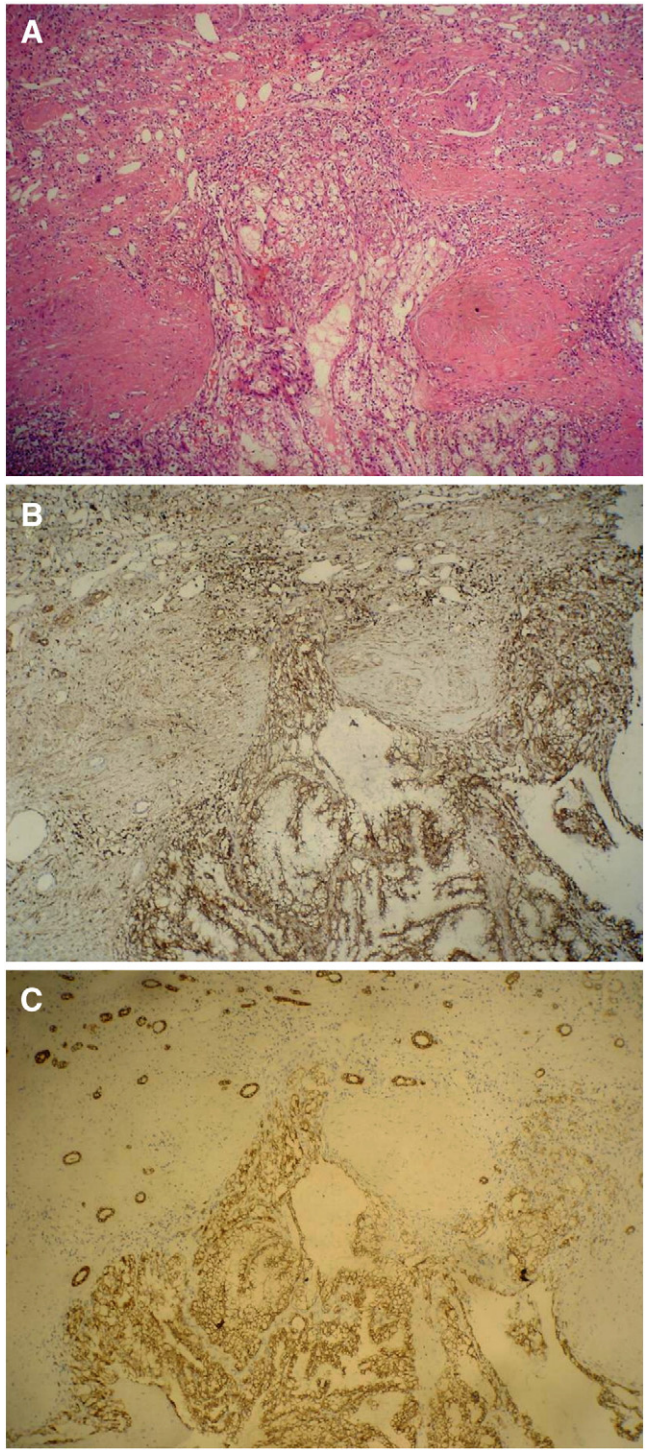


Fig. 1. (A) H&E staining shows local metastasis within 1 cm outside the tumor pseudocapsule. (B) Staining for vimentin shows local metastasis within 1 cm outside the tumor pseudocapsule. (C) Staining for pancytokeratin shows local metastasis within 1 cm outside tumor pseudocapsule (all at ×100).

Table 6
Immunonegativity and immunopositivity for both pancytokeratin and vimentin

| | Immunonegative | Immunopositive | Total |
|---|---|---|---|
| Maximum diameter, 0-4 cm | 30 | 2 | 32 |
| Maximum diameter, 4-7 cm | 37 | 0 | 37 |
| Maximum diameter, >7 cm | 25 | 0 | 25 |
| Total | 92 | 2 | 94 |

coexpression of pancytokeratin and vimentin is seen throughout the cell cycles of RCC cells. These 2 are the ideal combination for assessing the metastasis of RCC compared with other protein marker combinations [11].

In the present investigation, thin tissue sections prepared by serial sectioning at 0 to 1, 1 to 3, and 3 to 5 cm segments of 5-cm tissue samples taken from different sides outside the tumor pseudocapsule were subjected to immunohistochemical staining for pancytokeratin and vimentin. Two double-positive cases were found in the 0- to 4-cm tumor diameter group, but no single-positive case was observed. The nonparametric rank sum test (Kruskal-Wallis test) calculation suggested that there was no significant difference in the number of double-positive cases between the different tumor size groups. This showed that the size of the early-stage RCC was not associated with the local metastasis of tumor cells. In addition, the double-positive cases were found in the smallest tumor size division, and because the signals were within a 5-mm range of the pseudocapsule, it was deemed insignificant.

In our study, we found that the pseudocapsule of RCC tumor has growth-limiting effect on its tumor. Of the 94 cases in the present study, only 2 cases with infiltration outside the pseudocapsule were found, and the extend of infiltration was only within 1 cm from the capsule. From our histopathologic examinations, all of the 4 cases of lymphatic metastasis did not correlate with tumor size. However, local metastasis did not correlate to the maximum diameter of the tumors; furthermore, cases with lymphatic metastasis did not coincide with the occurrence of local metastasis. In the past, it was often thought that disease recurrence after NSS was caused by residual tumor cells in the kidney. However, with immunohistochemical staining of RCC markers pancytokeratin and vimentin in conjunction with other evaluations, it is safe to conclude that the recurrence of RCC after NSS is not merely caused by incomplete tumor resection but also affected by factors such as lymphatic metastasis, location of the tumor, and technical considerations, which restrict the complete resection of the 1-cm tissue surrounding the tumor pseudocapsule.

In summary, the pseudocapsule of NCC tumor can effectively limit the tumor cell metastasis to the surrounding tissue. The tumor size, patient age, and patient sex did not correlate to the aggressiveness or lymphatic metastasis of RCC. No significant difference was found between the tumor size measured by preoperative CT imaging and postoperative macroscopic pathology; therefore, we should have enough confidence to rely on the results of CT imaging for the determination of tumor excision margin. Furthermore, it is wise for patients with indication of RN and no surgical contraindication to undergo elective NSS, which includes the excision of a 1-cm tissue margin surrounding the tumor pseudocapsule, providing the condition allows for proper suturing of the incision. With similar oncologic efficacy and preservation of kidney function provided by NSS, the use of such surgery as first-line therapy in the treatment of early-stage and small-size RCC is justified.

It has been reported that the 5-year cancer-specific survival rate for patients with RCC who chose to undergo NSS was 80% to 100%, and the 5-year local recurrence rate was 1.1% to 3.2%. In recent years, the detection rate of small asymptomatic RCC (diameter, ≤4 cm) had increased significantly. Studies by Cleveland Clinic [12,13] found no difference between the 5-year survival rate of such patients who underwent either RN or NSS. D'Armiento et al [14] retrospectively analyzed the clinical data of patients who underwent NSS and RN, with an average 6-year follow-up; they found that there was no significant difference in survival rate, local recurrence rate, and rate of distant metastasis between the 2 surgical methods. In a previous clinical trial, we conducted a 5-year follow-up of 7 patients who had NSS and 32 patients who had RN from 1998 to 2002 and found that there was no statistical significant difference in the 1- and 5-year survival rates between the 2 approaches. Lundstam et al [15] investigated 87 patients with the indication for RN who had undergone elective NSS and found the 5- and 10-year cancer-specific survival probabilities to be 80% and 75%. However, they concluded that RN is still to be indicated in patients with advanced RCC. Although the choices between open and laparoscopic approaches to RN is less controversial in that laparoscopic surgery allows the reduction of analgesic dosage, smaller incision and scar,

Table 7
Distance of tumor cell metastasis from tumor pseudocapsule for cases with local metastasis or lymph node involvement

| | Distance from pseudocapsule, 0-1 cm | Distance from pseudocapsule, 1–3 cm | Distance from pseudocapsule, 3–5 cm | Lymph node involvement | Total |
|---|---|---|---|---|---|
| Maximum diameter, 0-4 cm | 2 | 0 | 0 | 0 | 2 |
| Maximum diameter, 4-7 cm | 0 | 0 | 0 | 3 | 3 |
| Maximum diameter, >7 cm | 0 | 0 | 0 | 1 | 1 |
| Total | 2 | 0 | 0 | 4 | 6 |

shorter in-hospital stay, and recovery time, it is, however, not well supported by solid follow-up evidence.

In our study, we came to a conclusion that pseudocapsule of RCC has limiting effects on the tumor. From our results, it is shown that there were no cases of local recurrence or infiltration outside the capsule as suggested by H&E, pancytokeratin, and vimentin stains. Nevertheless, there were 4 cases of lymph node metastasis observed in the pathologic diagnosis. These cases, however, had larger sized tumors (3 cases with a tumor size of 4-7 cm and 1 case with a tumor size of >7 cm), and the age of the patients were generally older(56, 64, 67, and 71 years). In the past, it was concluded that patients with tumors of less than 4 cm had better survival than those with tumors of more than 4 cm [16,17]. However, from a recent report, Joniau et al [18] studied all the clinical progression-free survival rate (84%), overall survival rate(72%), and cancer-specific survival rate (99%) of 67 patients with tumors of 4 to 7 cm in a median (range) during a follow-up of 40.1 (1-98.3) months. Their results with T1b tumors showed excellent cancer-specific survival and recurrence-free survival rates after NSS, which appear to be comparable with those quoted in contemporary RN series. Correlated with our result of the study on the patients with T1b tumor that there were no suggested signs of local metastasis within 1 cm outside the tumor pseudocapsule, the feasibility of NSS for T1 RCC should depend more on tumor location and surgeon experience with NSS than on tumor size in isolation.

## 5. Conclusion

From clinical application point of view, for patients with smaller-sized tumors (T1a) who have indications for RN, perhaps NSS is a better surgical option. The lack of a long-term follow-up was one of the major shortcomings of the present study. In the future, by increasing sample size, extending the range of TNM staging in patient selection, and by long-term follow-up, we hope to gain insights into better treatment options for RCC.

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