

**Predictive factors for ipsilateral recurrence  
after Nephron Sparing Surgery in Renal Cell Carcinoma.**

Jean-Christophe Bernhard<sup>a</sup>, Allan J Pantuck<sup>b</sup>, Hervé Wallerand<sup>a</sup>, Maxime Crepel<sup>c</sup>, Jean-Marie Ferrière<sup>a</sup>, Laurent Bellec<sup>d</sup>, Sylvie Maurice-Tison<sup>e</sup>, Grégoire Robert<sup>a</sup>, Baptiste Albouy<sup>f</sup>, Gilles Pasticier<sup>a</sup>, Michel Soulie<sup>d</sup>, David Lopes<sup>g</sup>, Bertrand Lacroix<sup>h</sup>, Karim Bensalah<sup>c</sup>, Christian Pfister<sup>f</sup>, Rodolphe Thuret<sup>i</sup>, Jacques Tostain<sup>h</sup>, Alexandre De La Taille<sup>g</sup>, Laurent Salomon<sup>g</sup>, Clément Abbou<sup>g</sup>, Marc Colombel<sup>j</sup>, Arie S Beldegrun<sup>b</sup>, Jean-Jacques Patard<sup>c</sup>

<sup>a</sup> Department of Urology, University Hospital, Bordeaux, France,

<sup>b</sup> Department of Urology, University of California Los Angeles, Los Angeles, Ca, USA,

<sup>c</sup> Department of Urology, University Hospital, Rennes, France,

<sup>d</sup> Department of Urology, University Hospital, Toulouse, France,

<sup>e</sup> Department of Medical Information, University Hospital, Bordeaux, France,

<sup>f</sup> Department of Urology, University Hospital, Rouen, France,

<sup>g</sup> Department of Urology, University Hospital, Creteil, France,

<sup>h</sup> Department of Urology, University Hospital, Saint-Etienne, France,

<sup>i</sup> Department of Urology, University Hospital, Montpellier, France,

<sup>j</sup> Department of Urology, University Hospital, Lyon, France

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Corresponding author : Jean-Christophe BERNHARD – Department of Urology, University Hospital, Place Amélie Raba Léon 33076 Bordeaux, France – Tel. +33 5 56 79 55 35 – Fax +33 5 56 79 56 51 – E mail : jcb31000@hotmail.com

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## ABSTRACT

**Background:** Ipsilateral recurrence after Nephron Sparing Surgery (NSS) is rare and little is known about its specific determinants.

**Objective:** To determine clinical or pathologic features associated with ipsilateral recurrence after NSS performed for renal cell carcinoma (RCC).

**Design, Settings and Participants:** 809 NSS procedures for sporadic RCCs, performed at 8 academic institutions, were retrospectively analyzed.

**Measurements:** Age, gender, indication, tumour bilaterality, tumour size, tumour location, TNM stage, Fuhrman grade, histological subtype and presence of positive surgical margins (SM) were assessed as predictors for recurrence in univariate and in multivariate analysis by using a Cox proportional hazards regression model.

**Results and limitations:** Among 809 NSS procedures with a median follow-up of 27 (1-252) months, 26 ipsilateral recurrences (3.2%) occurred at a median time of 27 (14.5-38.2) months. In univariate analysis, the following variables were significantly associated with recurrence: pT3a stage ( $p = 0.0489$ ), imperative indication ( $p < 0.01$ ), tumour bilaterality ( $p < 0.01$ ), tumour size  $>4\text{cm}$  ( $p < 0.01$ ), Fuhrman grade 3 or 4 ( $p=0.0185$ ) and positive SM ( $p < 0.01$ ). In multivariate analysis, tumour bilaterality, tumour size  $>4\text{cm}$  and presence of positive SM remained independent predictive factors for RCC ipsilateral recurrence. Hazard ratios were 6.31, 4.57 and 11.5 for tumour bilaterality, tumour size  $>4\text{cm}$  and positive SM status, respectively. Main limitations of this study included its retrospective nature and a short follow-up.

**Conclusion:** RCC ipsilateral recurrence risk after NSS is significantly associated with tumour size  $> 4\text{cm}$ , tumour bilaterality (synchronous or asynchronous) and positive SM. Careful follow-up should be advised in patients presenting such characteristics.

## Introduction

Renal cell carcinoma (RCC) accounts for 3.1% of all cancers in Europe [1]. While the incidence of all RCC stages is increasing, organ confined RCC incidence has increased more rapidly than its advanced counterpart [2]. Therefore, the use of partial nephrectomy has been adopted preferentially for the treatment of small renal masses. Even though fear of incomplete resection leading to local recurrence has limited the widespread implementation of nephron-sparing surgery (NSS) in the elective setting [3], it has been demonstrated that when applied to tumours  $\leq 4$  cm, Radical Nephrectomy (RN) and Partial Nephrectomy (PN) offer similar cancer control [4-6].

More recently, it has been proposed to perform elective NSS in selected patients with tumours  $>4$  cm [7]. However, there is a concern that such aggressive NSS strategies, in addition to increased morbidity [8], could potentially increase positive surgical margins (SM), recurrence rates, and ultimately the risk of dying from cancer.

The frequency of ipsilateral recurrence after NSS, varies from 0 to 10,6% in the literature [6,9,10]. Among previous studies that have addressed the issue of local recurrence after NSS, none have designed a multivariate model for identifying independent predictive factors [8,11,12]. Indeed, their identification could allow a better definition of NSS limits, intensified follow-up in high risk patients and early salvage therapy in case of recurrence. Therefore, the primary objective of our study was to analyse ipsilateral recurrence events in relation to clinical and pathological features in order to identify valuable risk factors.

## Material and Methods

### Data collection

The study included patients from eight academic centres: Rennes, Bordeaux, Toulouse, Saint Etienne, Créteil, Lyon, and Rouen in France, and the University of California at Los Angeles (UCLA) in the United States. Sixty variables of interest were extracted from each institutional database regarding pre-, per-, and post-operative data for implementing a unique NSS database. Years of treatment ranged from 1984 to 2006. Specific data which were collected for the purpose of this study included age, sex, NSS indication (imperative vs elective), tumour size, TNM stage, Fuhrman grade, tumour location, history of a bilateral tumour, multifocality, tumour histology and SM status.

Ipsilateral recurrence was defined as a new imaging evidence of tumour within the operated kidney. The delay of recurrence was also recorded.

Tumour stage was determined according to the 2002 TNM classification [13].

Histological subtype was recorded according to the 2004 WHO classification [14].

Tumours were graded according to the Fuhrman grading scheme by pathologists at each institution [15].

### Statistical analysis

The end point of interest was ipsilateral recurrence. Patients' characteristics in both ipsilateral and no recurrence groups were compared by using  $X^2$  (or Fisher) and t-tests for qualitative and quantitative variables respectively. The Cox proportional hazards model was used for investigating time to the event occurrence. In the univariate analysis, a p-value of 0.05 was requested to select explanatory variables

for the multivariate analysis. A backwards elimination was used to select clinical or pathologic features independently associated with ipsilateral recurrence. Results were given as hazard ratios (HRs) and 95% Confidence Intervals (CIs). A p value < 0.05 was considered as significant. The model validity was verified by testing the risk proportionality hypothesis for the variables present in the final model.

## Results

### Patients and tumours

A total of 809 NSS procedures performed for sporadic kidney cancer were included in this retrospective study. The number of procedures per centre and per year of surgery is reported in Table 1.

There were 570 men (70.5%) and 239 women (29.5%). Mean age at diagnosis was  $59.3 \pm 12.1$  years and mean tumour size was  $3.4 \pm 1.9$  cm. NSS was performed for an imperative indication in 284 cases (35.1%). Solitary kidneys accounted for 131 cases (16.2%), including 65 with history of RCC related nephrectomy (metachronous bilateral RCC). Synchronous bilateral tumours were present at the time of NSS in 120 patients and chronic renal failure justified an imperative PN for 33 patients. Sixty four (8.1%) procedures were conducted laparoscopically.

Mean and median follow-up were  $39 \pm 37.7$  and 27 (1-252) months, respectively.

Twenty six local recurrences (3.2%) occurred in a median time (interquartile range) of 27 (14.5-38.2) months. Main tumour characteristics such as TNM stage, nuclear grade, histological subtype and resection status are described in Table 2.

### Univariate analysis

We first carried out a univariate analysis for determining the relationship between patient or tumour characteristics and the occurrence of ipsilateral recurrence (Table 3). When splitting pT stages in organ and non organ confined tumours (pT1-T2 vs. pT3a) it appeared that pT3a tumours were associated with significantly increased recurrence rate (7.8% vs. 2.8%,  $p=0.04$ ). Similarly, high Fuhrman grade tumours (G3-4), were associated with a significantly increased recurrence risk (6% vs. 2.4%,

$p=0.01$ ). When comparing tumours  $\leq 4$  cm ( $n=623$ , 77%) with tumours  $>4$  cm ( $n=186$ , 23%), risk of ipsilateral recurrence was again significantly increased in larger tumours (8% vs. 1.8%,  $p=0.0001$ ). Eighty one % of patients experiencing an ipsilateral recurrence underwent a PN for an imperative indication whereas imperative indications accounted for 35.1% of the 809 NSS procedures in this study. Ipsilateral recurrence rate in case of imperative indication was 7.4% as compared to 1% for elective indications ( $p=0.0001$ ).

Tumour bilaterality was noticed in 65.4% ( $n=17$ ) of local recurrence cases and ipsilateral recurrence rate in case of bilateral tumour was 9.2% as compared to 1.5% for unilateral tumours ( $p=0.0001$ ). No difference was noted between synchronous ( $n=8$ ) and asynchronous ( $n=9$ ) bilateral tumours regarding local recurrence.

Positive SMs were observed in 1.5% of the cases. Among these cases, which were subsequently managed by careful follow-up (median (interquartile range) follow-up = 32 (20.5-64.0) months) one third developed a local recurrence (median time to detection (interquartile range) = 23.2 (5-57) months) , compared to 2.9% when surgical resection margins were negative ( $p=0.0001$ ).

None of the 26 patients with ipsilateral recurrence presented nodal invasion at diagnosis. Conversely, none of the 12 node positive patients of the series experienced ipsilateral recurrence after a median follow-up of 11.5 (1-67) months.

#### Multivariate analysis

Based on univariate analysis results, we performed a multivariate analysis. We therefore demonstrated that tumour size  $> 4$ cm, tumour bilaterality and positive SM were independent predictive factors for local recurrence (Table 4).

### Outcome after ipsilateral recurrence

Mean and median follow-ups for patients who experienced a local recurrence were  $77.5 \pm 58$  and 58.5 (7-252) months respectively.

Twenty patients had pure local recurrence whereas 6 had concurrent metastases.

Patients' outcome after local recurrence whether it was associated or not with distant metastasis is presented in figure 1.

At the end of follow up, 18 patients (69%) were still alive, 6 (23%) had died from cancer and 2 (8%) had died from another cause. Half of surviving patients (9) had undergone salvage surgery and were subsequently rendered cancer free. All patients who died from cancer and 5 out of 6 patients who had local + distant recurrences, belonged in the imperative indication group.



## Discussion

NSS is current standard of care for renal tumours measuring 4 cm or less [4-6].

Recently, several investigators suggested that a poorer outcome associated with larger tumours was independent from surgical technique [16-18]. Even though local recurrence following PN does not necessarily translate into increased risk of death thanks to appropriate follow-up and salvage therapy, we judged useful to determine risk factors that could potentially impact NSS therapeutic efficacy.

Robust data regarding risk of recurrence after NSS is missing from the current literature. In most studies, oncological results are reported in terms of cancer free survival (CFS) mixing local recurrence and progression events. Mitchell et al compared NSS and RN performed for tumours > 4 cm and concluded that only tumour diameter had an impact on recurrence free survival in uni and multivariate analysis [18]. However, in the same study, no difference was reported regarding cancer specific survival according to the type of surgery and to tumour size. Finally, all recent studies addressing the issue of cancer control after PN in tumours > 4 cm have confirmed the excellent outcome achieved by a conservative strategy [7]. Our study indeed identified the 4 cm cut-off as an independent risk factor for ipsilateral recurrence with a hazard ratio of more than 4. However, as we previously demonstrate, it is likely that an increased tumour size is also associated with increased risk of new oncological events following RN [17]. Tumour size is obviously a continuous variable and an arbitrary cut-off should not be used for delineating surgical options in the treatment of RCC [7,19]. Therefore, even though increased tumour size might be associated with higher risks of ipsilateral recurrence, it does not

mean that NSS is detrimental in that setting. The ratio between risk and benefit is still in favour of NSS thanks to a better preservation of renal function potentially influencing overall survival [20]. However, the identification of tumour size > 4 cm as a potential risk factor prompts us to recommend an intensification of imaging schedule after NSS in T1b-T2 tumours. This is consistent with the general belief that post operative follow-up should be driven by the aggressiveness of the primary renal tumour [21]. Therefore, provided that primary tumour biology does not carry out other adverse risk factors it is likely that when local recurrence occur local salvage surgery allows comparable outcome to what would have been achieved with RN.

In the present study, we also indentified tumour bilaterality as an independent risk factor for ipsilateral recurrence following NSS. This is consistent with the results of many other studies on synchronous bilateral RCC reporting an increased risk of local recurrence in that setting [22, 23]. Interestingly, Blute et al clearly linked multifocality with tumour bilaterality independently of tumour histology. Thus, multifocality was found in 28% of bilateral synchronous ccRCCs and 33% of bilateral synchronous papillary RCCs compared to 2% and 7% in unilateral clear cell and papillary RCCs respectively [23]. Tumour multifocality has also been related to metachronous bilateral renal cancers and multifocal primary RCC was reported as being an independent risk factor for contralateral recurrence [24-25]. Despite recent progress of preoperative imaging, multifocality remains indeed unknown in a substantial number of cases [26]. Unfortunately, information about multifocality was not available from our study. To what extend tumour multifocality would have emerged as an independent predictive factor compared to tumour bilaterality remains to be determined. Even though neither multifocality nor tumour bilaterality seem to impact

cancer specific survival [27] our results together with the current literature plead for careful follow up when one or both conditions are met.

In our study, although positive SM occurred in only 1.5% of the cases, it was identified as the most important independent risk factor for ipsilateral recurrence. The current literature provides us important information regarding SMs in the specific case of RCC. First, the depth of free SM does not matter [28]. Secondly, the impact of positive SM on local recurrence has to be put into perspective. Kwon et al with a median follow-up of 22 months reported a 4% local recurrence rate in patients with positive SMs. In the meantime, 0.5% of patients with a negative SM also had a local recurrence [29]. By comparison, our 33% local recurrence rate in positive SM patient cases is high. That could be explained by a longer follow-up in our series or by selection bias in the aggressiveness of the tumour population that was included. Additionally, evidence is accumulating suggesting that positive SM do have little impact on disease free survival following NSS [12]. We recently analysed through a large multicenter study the outcome of 111 patients with positive SMs following NSS. It appeared that survival was not significantly different between positive and negative SM cases and that no patients died from cancer in elective NSS cases [30]. These data taken together suggest that predictive factors for local recurrence after NSS perhaps they are not associated with other tumour aggressiveness factors do not necessarily impact survival and should not prohibit conservative surgery in that setting.

Finally our study also highlighted 2 important characteristics of local recurrence following NSS. First, it is a rare event, which frequency ranges from 0 to 10% in the literature, and reached only 3.2% in our series [6-9-10]. Secondly, ipsilateral recurrences following NSS can appear late (up to 209 months in our series).

Importantly, the mean follow-up of patients who finally experienced a local recurrence was of 77.5 months. Based on these findings, we strongly recommend a prolonged follow-up in patients meeting with one or more of the 3 predictive factors we identified.

Our study is not exempt from significant limitations. First of all, due to its retrospective character we can't exclude a certain degree of inaccuracy in the way variables were recorded. Different surgical techniques were used and different pathologists in each institution contributed to that report. Finally, although our definition of ipsilateral recurrence included both recurrences at the site of surgery and recurrences within the same kidney, we were not able to differentiate in our final analysis between the 2 situations. Therefore we were not able to truly identify what factors may be attributable to surgical strategy rather than biology of the primary tumour.

## **Conclusion**

We identified 3 independent factors driving an increased risk of ipsilateral recurrence following NSS: tumour size > 4cm, tumour bilaterality and positive SM status.

Patients presenting with any of these risk factors should be considered for a prolonged and careful follow-up. Indeed, early diagnosis and appropriate salvage therapy are likely to minimise the potential impact of an isolated local recurrence on cancer specific survival.

**FIGURE LEGENDS**

Figure 1 – Outcome at last follow-up after ipsilateral recurrence.  
NED=No Evidence of Disease.

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