How long can patients with renal cell carcinoma wait for surgery without compromising pathological outcomes?

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Abstract

Introduction: Surgical wait times have been shown to be of significance in other malignancies, but limited studies exist in renal cell cancer (RCC). We analyzed surgical waiting time for RCC patients to see if there was an adverse impact on pathological characteristics.

Methods: Our centre triages RCC patients on the basis of perceived tumour risk. The waiting time for surgery is adjusted stage for stage: clinical T1 at 90 days, T2 at 40 days, T3 and T4 at 30 days. We retrospectively reviewed the charts of 354 patients who underwent surgery for RCC. Patients were assessed for pathological upstaging, positive lymph nodes, tumour recurrence and tumour size within each stage. Analysis was performed, using surgical waiting time as a categorical variable, to test for associations with disease recurrence or adverse pathological characteristics.

Results: The median time from the first consultation to surgery was 41 days and the mean follow-up was 26.6 months. Waiting time stage for stage was: clinical T1 at 57.12 days, clinical T2 at 36.8 days, clinical T3 and T4 at 30.32 days. On multivariate analysis, pathological tumour size was associated with progression, whereas no significant association was found between waiting time and upstaging. Higher stage tumours, sarcomatoid pathology and clinical evidence of progression were associated with shorter waiting times for early interventions.

Conclusions: There was no statistically significant evidence for upstaging or progression during the waiting period for our group of patients. The data reinforce previous studies reporting a "safe" period of active surveillance in T1 RCC without affecting their final pathological outcome.

Résumé

Introduction : Il a été montré que les temps d'attente en chirurgie ont de l'importance avec d'autres tumeurs malignes, mais il existe peu d'études concernant l'hypernéphrome. Nous avons analysé le temps d'attente avant une intervention chirurgicale des patients atteints d'hypernéphrome pour voir si ce temps d'attente avait un effet négatif sur les caractéristiques pathologiques.

Méthodes : Notre centre trie les patients atteints d'hypernéphrome sur la base du risque perçu lié à la tumeur. Le temps d'attente pour la chirurgie est ajusté en fonction du stade : stade clinique T1, 90 jours, stade T2, 40 jours, stades T3 et T4, 30 jours. Nous avons examiné de façon rétrospective les dossiers de 354 patients ayant subi une chirurgie pour traiter un hypernéphrome. Les patients ont été évalués pour cerner la présence d'une progression du stade pathologique ou de ganglions lymphatiques positifs, et la récidive et la taille de la tumeur pour chaque stade. L'analyse a été effectuée en utilisant le temps d'attente avant l'intervention comme variable catégorique, afin de vérifier son lien avec la récurrence de la maladie ou des caractéristiques pathologiques néfastes.

Résultats : Le délai médian entre la première consultation et l'intervention était de 41 jours, et le suivi moyen était de 26,6 mois. Le temps d'attente en fonction du stade allait comme suit : stade clinique T1, 57,12 jours, stade clinique T2, 36,8 jours, stades cliniques T3 et T4, 30,32 jours. Lors de l'analyse multivariée, une corrélation a été établie entre la taille de la tumeur et la progression, alors qu'aucun lien significatif n'a été observé entre les temps d'attente et la progression du stade pathologique. Un stade tumoral supérieur, des caractéristiques sarcomatoïdes à l'examen pathologique et des preuves cliniques de progression ont été associés à des temps d'attente plus courts pour les interventions précoces.

Conclusions : Il n'y avait aucune donnée statistiquement significative montrant une progression du stade pathologique au cours de la période d'attente pour notre groupe de patients. Les données confirment les résultats d'études antérieures signalant une période « sans danger » de surveillance active dans les cas d'hypernéphrome de stade T1 sans que cela n'affecte le résultat pathologique final.

Introduction

It is estimated that in Canada 4600 patients will be diagnosed with renal cell carcinoma (RCC) and 1600 patients will die of this disease in 2009.[1] The incidence rates of RCC in Canada have been increasing by 0.8% to 1.3% per year between 1996 and 2005[1] in all stages, but especially in tumours <4 cm.[2] The mortality rate has remained stable,[1] which suggests the necessity of a different therapeutic approach.

Studies addressing active surveillance in RCC are retrospective, mainly in elderly patients with significant comorbidities, and focus on growth kinetics and survival as endpoints. These studies suggest that small renal masses are less aggressive and might be observed safely with appropriate follow-up. Methods to identify which patients are going to develop aggressive disease are based only on clinical and radiological criteria and no pathological variables or nomograms have been developed for this purpose. Only 1 ongoing, prospective multicentre trial with a highly selected population has demonstrated that active surveillance is a reasonable option for patients with small renal masses.[3]

Surgical wait times for cancer have become an issue for health systems under stress by limited resources and an increasing population. Information derived from conservative treatment in different malignancies might be used to guide health policies with respect to safe waiting times. Surgical wait times have shown to be of significance in other malignancies, such as bladder cancer,[4] but limited studies exist in RCC.

Government agencies, such as the Ontario Provincial Ministry of Health in Canada,[5] have recommended different levels of waiting time, triaging by symptoms and possibility of progression (24 hours, 2 weeks, 4 weeks, 12 weeks). The National Health Service (NHS) in the United Kingdom has recommended no more than 4 weeks waiting time for surgery in RCC patients.[6] However, there is no definitive data to support either of these recommendations.

Pathological analysis of how renal masses change after surgical waiting time has not been well-studied and the literature on this issue is limited.[7,8] In this study, we optimized the surgical waiting times by stage in our institution, taking into consideration the slow growth rates of small renal masses, and analyzed how this approach affected pathological and clinical outcomes.

Methods

Our centre triages patients with renal masses on the basis of perceived tumour risk. The maximal target waiting time established for surgery is stage for stage: clinical T1 at 90 days, T2 at 40 days, T3 and T4 at 30 days. These waiting times were decided by consensus of the urologists at our institution.

After institutional ethics board approval (UWO REB #12549E), we retrospectively reviewed the charts of 354 patients who underwent surgical resection for RCC. Patient characteristics and the date of the patient referral to the urologist and when the surgical decision was made were collected. Surgical waiting time was defined as the period from the date when the urologist and patient decided to proceed with surgery to the date when the procedure was performed. Delays due to other patient comorbidities, patient requested delays and delays for imaging tests were excluded as the final decision to operate had not been made. Patients with benign pathology on final analysis were excluded from the analysis. All the histological subtypes of RCC were included and preoperative biopsy was not typically performed. Evaluable patients were assessed for pathological upstaging, positive lymph nodes, evidence of recurrence and pathological tumour size within each stage.

Univariate and multivariate analyses were performed, using surgical waiting time as a categorical variable, to test for associations with disease recurrence or adverse pathological characteristics. Data was summarized using appropriate descriptive statistics. Missing data was excluded from analysis. The p values <0.05 were considered statistically significant. Data was analyzed using SAS/STAT (SAS Inc., Cary, NC).

Results

We reviewed 365 patients who underwent surgical resection from 1996 to 2007 for RCC. Eleven patients were excluded due to incomplete records, which left us with 354 patients with a mean age of 59.7 years ± 13.4 standard deviation (SD). Eighty-six patients underwent partial nephrectomy (24.3%) and 268 underwent radical nephrectomy (75.7%). The mean follow-up time was 27.17 months ± 26.9 SD and the median time from consultation to surgery was 41 days (range 1-409) (Table 1).

The mean tumour size was 5.5 cm ± 3.45 SD; the group was mainly integrated by T1 60.11% and clear cell carcinomas 75.98% (Table 2).

The waiting time for the entire group was 49.47 days ± 44.3 SD and when analyzed stage for stage the waiting time was as follows: clinical T1 at 57.12 days ± 49.4 SD, clinical T2 at 36.8 days ± 28.62 SD and clinical T3 and T4 at 30.32 days ± 22.1 SD.

On multivariate analysis, the pathological tumour size, clinical stage, pathological upstaging, sarcomatoid features, tumour size and tumour grade were associated with disease recurrence (Table 3); no significant association was found

Table 1. Patient characteristics of entire cohort

No. patients	354
Men (%)	221 (62.4)
Women (%)	133 (37.57)
Mean age at diagnosis (SD)	59.68 years (± 13.4)
Nephrectomies (%)	
Partial laparoscopic	37 (10.42)
Partial open	49 (13.8)
Radical laparoscopic	152 (42.82)
Radical open	117 (32.96)
Mean follow-up, months (SD)	27.17 (± 26.9)

SD: standard deviation.

Table 2. Pathological characteristics of entire cohort	
Mean cm tumour size (SD)	5.5 (± 3.45)
T stage (%)	
T1	211 (60.11)
T2	52 (14.81)
T3	85 (24.22)
T4	3 (0.85)
Fuhrman grade (%)	
1	13 (3.8)
2	173 (51.8)
3	125 (37.4)
4	23 (6.9)
Histology	
Conventional clear cell	269 (75.98)
Papillary	47 (13.27)
Chromophobe	29 (8.19)
Mixed	7 (1.97)
Unclassified RCC	2 (0.56)
Sarcomatoid features	7 (2)
Positive nodes	9 (2.7)
Positive margins	10 (2.8)

SD: standard deviation.

between surgical waiting time (as currently defined) and tumour size, pathological upstaging, margin status, tumour grade or positive lymph nodes. Additionally, higher stage tumours ($p = 0.0005$), sarcomatoid pathology ($p = 0.0273$) and recurrences ($p = 0.0435$) were associated with shorter waiting times and more clinical progression; this finding likely reflects a combination of an increased priority given to higher stage lesions, as well the association of more aggressive tumours with symptomatic disease (Table 3).

Most patients undergoing surgery in the first 30 days have clinical T3 or T4 disease and most patients with clinical T1 disease are waiting longer and undergo surgical resection between 30 and 90 days (Fig. 1). Despite triaging patients, about 40% of our T3 and T4 patients waited more than 30 days which may contribute to the null hypothesis.

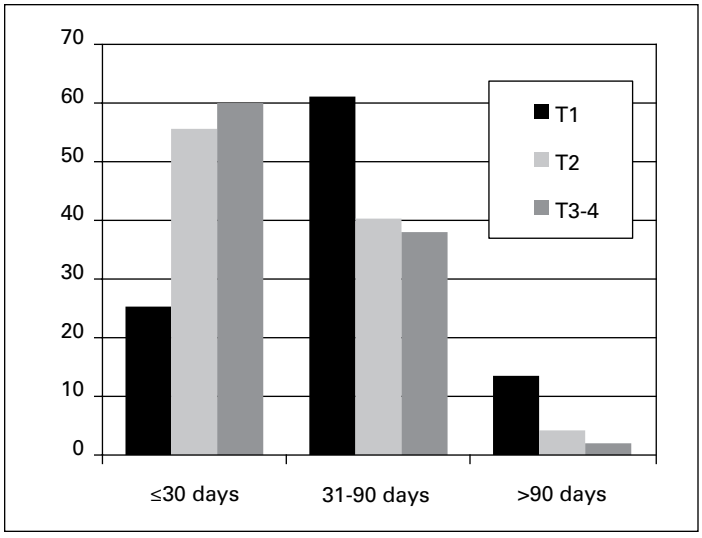

Fig. 1. Surgical waiting time by clinical stage.

Discussion

In our study, we observed that patients with sarcomatoid features, higher Fuhrman grade, larger tumours and higher clinical stage had increased risk of recurrence. The multivariate analysis evaluating the impact of waiting time on the different pathological outcomes showed no association with disease progression. These findings follow the same pattern as other studies with regards to treating small renal masses conservatively.

Jewett and colleagues, in a multicentre, prospective phase II trial, recruited 131 patients with 151 small renal masses (mean diameter 2.2 cm); they authors included patients who were elderly, had significant comorbidity and/or refused surgical treatment. The mean follow-up was 15 months and the average growth rate was not statistically different than 0. A total of 72 biopsies were performed; 13% of these were benign, 26% were non-diagnostic and 61% were consistent with RCC. Two patients developed metastatic disease at 5 and 12 months. Seven patients met the criteria for tumour progression, although 3 of them did not receive treatment due to medical comorbidities.[3]

Alternatively, small RCC masses may have metastatic potential, albeit rare. Hsu and colleagues reported 50 small renal masses of <3 cm; 38% of these masses presented extension beyond renal capsule and 28% had high nuclear grade (Furhman 3 and 4).[9] Small renal masses causing lung metastasis have also been reported.[10] How one determines which small renal masses are going to progress is an unanswered question, but pathological findings may play a role since no biomarkers are available that can accurately predict the natural untreated biology for all RCC tumours.

In the present study, the statistically significant correlation of waiting time with sarcomatoid features, high clinical stage and recurrence rate was associated with early surgical interventions derived from our triage strategy; this finding reinforces the necessity of early interventions in the clinical T3 and T4 RCC tumours, as this patient population is clearly associated with more recurrences.

It should be acknowledged that the surgical waiting times as currently defined (from time of decision to operate to the surgery date) constitutes only a portion of the delay in therapy. Our study was limited by its retrospective design and inherent selection bias, such as the triaging of patients by each surgeon (leading to additional logistic delays deriving in longer waiting times especially affecting the group of T3/T4 patients) or the earlier surgeries in symptomatic T1 patients. Additional limitations include our target waiting

Table 3. Multivariate analysis results of recurrence by stage and associated with wait time

Recurrence by stage	*p* values
Clinical T	< 0.0001
Pathological upstaging	< 0.0001
Sarcomatoid features	0.03
Tumour size	< 0.0001
Tumour grade	< 0.0001
Associated with wait time	
Tumour size	0.40
Margins status	0.21
Upstaging	0.73
Positive nodes	0.43
Tumour grade	0.25
Clinical T	< 0.0001
T1	0.42
T2	0.20
T3-T4	0.50
Sarcomatoid features	0.0273
Recurrence	0.0435

times, which made it difficult to demonstrate differences between T2 and T3/T4 groups with a 10-day difference; the absence of a comparison cohort, which did not allow us to demonstrate the impact of longer or shorter waiting times in this population, is another limitation.

Prospective studies, with particular attention to the triage bias, to validate our results are required. The current patient population studied did not include patients who were treated with cryotherapy, radiofrequency ablation or active surveillance, all of which would contribute to a selection bias. To determine tumour size, we used the tumour measurement from preoperative imaging rather than a calculated tumour volume, which may be more clinically meaningful. Our results are based on final pathology and should not be extrapolated for tumour biopsies.

Conclusions

Patients with sarcomatoid features, higher Fuhrman grade, larger tumours and higher clinical stage had increased risk of recurrence. There was no statistically significant evidence for RCC upstaging or progression or adverse pathological changes during the waiting period for our group of patients. The data reinforce previous studies reporting a "safe" period of active surveillance in T1 RCC without affecting their final pathological outcome. Whether or not other patients with higher clinical stage can be triaged within the same time frame will require further study.

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