*Original Article*

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# *What is the Optimal Time Period for Postponing Nephrectomy in Patients with Renal Cell Carcinoma of Various Stages?*

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## Abstract

**Objective:** The coronavirus disease-2019 pandemic has shown us that postponing elective surgeries that include nephrectomy due to renal cell carcinomas (RCC) was undertaken by the physicians to use hospital facilities in a balanced way. However, both urologists and patients were concerned about postponements that may increase the risk of progression. To determine the optimal threshold of postponement time-period for surgery (PTP) and according to the clinical T stages in patients who underwent nephrectomy due to RCC, we used the Urologic Cancer Database-Kidney.

**Materials and Methods:** Patients who underwent detailed clinical T stage analysis with admission and surgery dates were included in the study. PTP was calculated using the dates of definitive preoperative diagnosis and surgery date. Recurrence, overall mortality (OM), recurrence-free survival, and overall survival (OS) were evaluated. The effects of PTP on oncological outcome according to tumor diameter and clinical T stages were also evaluated. We also analyzed the optimal cut-offs of PTP based on clinical T stages.

**Results:** Among 3.258 patients, in the evaluation of 2.946 clinically localized patients, PTP and tumor diameter were found to be important predictors of recurrence ($p=0.037$ and $p<0.001$). The optimal PTP of 30 days was found to be an important significant threshold time for the T1 stage and 20 days for T2-4 stage tumors. Patients with longer PTP according to the thresholds shown in this study had higher upstaging for clinical T1a, T2a, and T3 stages; higher recurrence rates for T1b and T2b stages; and higher OM for T2a and T3 tumors. The survival have also shown that more than 20 days of PTP affected OSs for clinical-stage T1 ($p=0.019$), T2 ($p=0.021$) and T3 ($p=0.007$) tumors.

**Conclusions:** All patients with tumors, including clinical T1 tumors, had worsening oncological results as the PTP increased (>20-30 days).

**Keywords:** Mortality, nephrectomy, overall survival, postponement time-period for surgery (PTP), recurrence free survival, renal cell carcinoma (RCC)

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## Introduction

The coronavirus disease-2019 (COVID-19) pandemic has shown us that postponing elective surgeries that include nephrectomy due to renal cell carcinomas (RCC) was undertaken by most of the physicians to use hospital facilities in a balanced way and to minimize the risk of contact. In this context, many recommendation guidelines on postponing elective surgeries have been published (1,2,3). Although some of these recommendations are related to the postponement of oncological surgeries such as RCC, which are tumors with a high risk of progression, it is predicted that the postponement of RCCs may lead to differences in survival over time. Therefore, determining the optimal postponement time-period for surgery (PTP) in kidney tumors is crucial in terms of putting the recommendations of treatment postponements on a scientific basis and minimizing patient victimization.

We revealed the optimal PTP and its thresholds according to the clinical T stages in patients who underwent radical nephrectomy (RN) or partial nephrectomy due to kidney tumors in the current study.

## Materials and Methods

Completely anonymize kidney tumor data from the Urologic Cancer Database-Kidney (UroCaD-K), Turkish Urooncology Association (TUOA), were retrospectively reviewed in compliance with local regulations. Study data were collected and managed using research electronic data capture (REDCap) tools hosted at the TUOA (4,5).

REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

From the database, patients who were diagnosed with RCC after partial or RN between 2007 and 2019 were evaluated. Among the evaluated patients, those with complete data of radiological tumor diameter, clinical T stage, first admission (or first imaging) date, and operation date were included in the study. Clinical T stages of the patients were determined according to the maximum tumor diameter, which was measured on the images (computed tomography or magnetic resonance imaging) and noted in the database.

PTP was defined and calculated from the first clinical diagnosis of renal tumor to the operation date. From the follow-up data, the recurrence time (operation date to recurrence date), survival time (operation date to death date), and follow-up time (operation date to last follow-up date) were determined. Upstaging status (concordance between clinical and pathological stages), recurrence (detecting locally or metastatic new lesion on the images of patients in follow-up), local recurrence, metastasis, overall mortality (OM), and cancer-specific mortality (CSM) were evaluated. Survival data were also investigated as recurrence-free survival (RFS), overall survival (OS), and cancer-specific survival (CSS). The effects of PTP on oncological outcomes according to tumor diameter and clinical T stages and the cut-off values of PTP based on clinical T stages were aimed to determine.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Completely anonymized kidney tumors data of the UroCaD-K, TUOA was retrospectively reviewed in compliance with local regulations. Study data were collected and managed using REDCap tools hosted at TUOA. The project approval number of Turkish Urooncology Association: TUO-RE-20-01.

### Statistical Analysis

For all statistical analyses, the Statistical Package for the Social Sciences (SPSS) version 22.0 was used. To determine the cut-off values of PTP affecting oncological outcomes such as upstaging, recurrence, and mortalities, receiver operating characteristic curve analysis was used. To detect the effects of PTP on oncological outcomes, the chi-square test was used based on detected cut-off values according to the clinical T stages. Kaplan-Meier survival analysis was used for RFS, OS, and CSS of PTP according to the clinical T stages. Statistical significance was set as a p-value less than 0.05 level.

## Results

A total of 3258 patients were evaluated in this study. The clinical, pathological, and oncological data of all patients are given in Table 1. From the clinical data, 2.946 of the patients had clinically localized (clinical T1-2 stage) RCC, whereas locally invasive (clinical T3-4 stage) disease was observed in 312 of the patients.

In the evaluation of clinically localized patients, PTP and tumor diameter were found to be important predictors of recurrence. PTP was 56.1 days and 49.8 days in patients with no recurrence and recurrence, respectively ($p=0.037$). Similarly, tumor diameters were 7.3 cm and 5.1 cm, respectively ($p<0.001$).

There were 2.324 patients in the clinical T1 stage 622, 220, and 92 patients evaluated in the clinical T2, T3, and T4 stages, respectively. When we look at the oncological outcomes, upstaging was found in 10.7% (n=248) and 26.7% (n=166) of patients in clinical T1 and T2 stages ($p<0.001$). Recurrence was observed in 2.8% (n=64), 10.9% (n=68), 20% (n=44) and 23.9% (n=22) of patients with clinical T1, T2, T3, and T4 stages, respectively ($p<0.001$). Similarly, OM was observed in 2%, 5%, 6.8%, and 10.9% of T1, T2, T3 and T4 tumors, respectively ($p<0.001$).

Cut-off values of PTP according to the clinical T stages were determined based on the status of upstaging (to T3 or T4), recurrence, and OM. The cut-off values, sensitivities, and specificities of the PTP values that affect oncological outcomes according to the T stages are given in Table 2. In this context, PTP was found to be associated with upstaging (especially in T1a), recurrence (especially in T1b), and OM for the clinical T1 stage and with upstaging (especially in T2a) and OM (especially in T2a) for the T2 stage (Table 2). When we look at the cut-offs, 30 days was an important significant threshold for T1 stage

and it was detected to be as 20 days for T2-4 stage tumors. In addition, the oncological outcomes of the determined cut-offs based on T stages are given in Table 3. Upstaging was significantly higher above the PTP thresholds of T1a (8.9% vs. 5.5%, p=0.021), T2a (30% vs. 20.7%, p=0.026) and T3 (15.7% vs. 7.1%, p=0.044) than below the values. Recurrence was higher in T1b and T2b with above the PTP thresholds compared with below values (for T1b 5% vs. 2.6%, p=0.037 and for T2b 14.9% vs. 4.8%, p=0.021). OM was found to be higher in T2a and T3 tumors with above the PTP thresholds compared with below values (for T2a 7% vs. 2.3%, p=0.015 and for T3 9.7% vs. 2.4%, p=0.030) (Table 3).

When we look at the survivals, defined PTP of 20 days affected OSs for clinical stage T1 (p=0.019), T2 (p=0.021) and T3 (p=0.007) tumors (Figure 1). RFSs for clinical stage T1 (p=0.205), T2 (p=0.160) and T3 (p=0.003) tumors according to the cut-off 20 days of PTP are given in Figure 2. Among these, only the RFS of the clinical T3 stage was found to be significantly different according to the cut-off 20 days of PTP. However, in the subgroup of clinical T2a and T3a stage tumors, treatment in

**Table 1. Clinical, pathological, and oncological data of the patients**

| | | **n=3258** |
|---|---|---|
| Age (year) | | 57.2±12.2 (14-99) |
| Gender, n (%) | Female | 1093 (33.5) |
| | Male | 2148 (65.9) |
| BMI (kg/m$^2$) | | 27.7±4.7 (15.2-53.2) |
| Time to surgery (day) | | 49±96.7 (1-1830) |
| Mean radiological tumor diameter (cm) | | 5.5±3.3 (1-49) |
| Clinical T stage, n (%) | T1a | 1265 (38.8) |
| | T1b | 1059 (32.5) |
| | T2a | 444 (13.6) |
| | T2b | 178 (5.5) |
| | T3a | 180 (5.5) |
| | T3b | 39 (1.2) |
| | T3c | 1 (0.03) |
| | T4 | 92 (2.8) |
| Mean pathological tumor diameter (cm) | | 5.9±3.5 (1-37) |
| Operation type, n (%) | Partial nephrectomy | 1328 (40.8) |
| | Radical nephrectomy | 1894 (58.1) |
| Operation method, n (%) | Open | 2341 (71.9) |
| | Laparoscopic | 840 (25.8) |
| Histopathology of the tumor, n (%) | Clear cell RCC | 2225 (68.3) |
| | Papillary RCC | 509 (15.6) |
| | Chromophobe RCC | 335 (10.3) |
| | Unclassified RCC | 80 (2.5) |
| | Other subtypes | 109 (3.3) |
| Upstage to T3 or T4, n (%) | | 441 (13.5) |
| Fuhrman grade (n=2327) | 1 | 263 (8.1) |
| | 2 | 1193 (36.6) |
| | 3 | 646 (19.8) |
| | 4 | 225 (6.9) |
| Recurrence, n (%) | | 198 (6.1) |
| Local recurrence, n (%) | | 75 (2.3) |
| Metastasis, n (%) | | 214 (6.6) |
| Overall mortality, n (%) | | 103 (3.2) |
| Cancer-specific mortality, n (%) | | 33 (1) |
| Mean follow-up time (month) | | 25.4±31 (1-165) |

BMI: Body mass index, RCC: Renal cell carcinomas

<20 days affected RFS compared to more than 20 days (for T2a tumors 49±13.5 months vs 16.2±5.1 months, p=0.042, and for T3a tumors 20.4±8.1 months vs 2±1.4, p=0.013).

## Discussion

In summary we evaluated 3.258 patients and found that PTP and tumor diameter were the most important predictive factors for recurrence in 2.946 clinically localized patients. PTP was also found to be associated with pathological upstage for clinical T1a and T2a stage kidney tumors. It was also associated with recurrence for the clinical substage of T1b tumors and OM for T2a stage tumors.

These two factors (stage and PTP) that we identified in our study are also emphasized in previous studies (6,7,8,9). In some of these studies, the optimal PTP stated that surgery should be considered within 1 month for kidney tumors (6,7). In one of these cases, the necessity of performing surgery has been defined and stated within 2 and 4 weeks after the diagnosis of kidney tumors in radiological imaging (7). However, with the postponement of RCCs during the COVID-19 pandemic, PTP and its possible oncological effects have come to the fore again. In parallel to the postponements within the last year, another previous study stated that median PTPs were 84 and 386 days for early and delayed times for surgery of small renal masses (≤4 cm tumors). In that study, 401 (81%) and 94 (19%) patients

**Table 2. Cut-off days of PTP affecting oncological outcomes in clinically localized kidney tumors (clinical stage T1-2 tumors)**

| Clinical T stage | Oncological outcomes | n (%) | Cut-off time (day) | Sensitivity | Specificity | AUC | p-value |
|---|---|---|---|---|---|---|---|
| T1 (n=2323) | Upstage to T3 | 248 (10.7) | 30 | 56% | 51% | 0.541 | 0.037 |
| | Recurrence | 64 (2.8) | 28 | 69% | 53% | 0.605 | 0.004 |
| | Overall mortality | 47 (2) | 29 | 66% | 51% | 0.595 | 0.026 |
| T1a (n=1264) | Upstage to T3 | 92 (7.3) | 37 | 59.8% | 57% | 0.590 | 0.004 |
| T1b (n=1059) | Recurrence | 39 (3.7) | 30 | 64% | 54% | 0.625 | 0.008 |
| T2 (n=622) | Upstage to T3 | 166 (26.7) | 20 | 57% | 50% | 0.560 | 0.022 |
| | Overall mortality | 31 (5) | 20 | 71% | 51% | 0.629 | 0.015 |
| T2a (n=444) | Upstage to T3 | 113 (25.4) | 20 | 60.2% | 52% | 0.568 | 0.032 |
| | Overall mortality | 21 (4.7) | 20 | 76.2% | 50.1% | 0.660 | 0.013 |
| T2b (n=178) | Recurrence | 18 (10.1) | 24 | 77.8% | 56.2% | 0.688 | 0.009 |

ROC curve analysis was performed for all predictions of PTP (day) and the determination of cut-off times. PTP: Postponement time-period for surgery, ROC: Receiver operating characteristic, AUC: Area under the curve

**Table 3. Oncological outcomes (upstage to T3, recurrence and overall mortality) of clinical T stages according to 30 and 20 PTP cutoff days**

| Clinical T stage | Cut-off time (day) | n | Upstage to T3 or T4 | | Recurrence | | Overall mortality | |
|---|---|---|---|---|---|---|---|---|
| | | | n (%) | p-value | n (%) | p-value | n (%) | p-value |
| T1 (n=2323) | ≤30 | 1193 | 113 (9.5) | 0.054 | 24 (2) | 0.025 | 22 (1.8) | 0.531 |
| | >30 | 1130 | 135 (11.9) | | 40 (3.5) | | 25 (2.2) | |
| T1a (n=1264) | ≤30 | 613 | 34 (5.5) | 0.021 | 9 (1.5) | 0.208 | 9 (1.5) | 0.755 |
| | >30 | 651 | 58 (8.9) | | 16 (2.5) | | 11 (1.7) | |
| T1b (n=1059) | ≤30 | 580 | 79 (13.6) | 0.262 | 15 (2.6) | 0.037 | 15 (2.2) | 0.484 |
| | >30 | 479 | 77 (16.1) | | 24 (5) | | 14 (2.9) | |
| T2 (n=622) | ≤20 | 301 | 71 (23.6) | 0.091 | 28 (9.3) | 0.207 | 9 (3) | 0.027 |
| | >20 | 321 | 95 (29.6) | | 40 (12.5) | | 22 (6.9) | |
| T2a (n=444) | ≤20 | 217 | 45 (20.7) | 0.026 | 24 (11.1) | 0.896 | 5 (2,3) | 0.015 |
| | >20 | 227 | 68 (30) | | 26 (11.5) | | 16 (7) | |
| T2b (n=178) | ≤20 | 84 | 26 (31) | 0.745 | 4 (4.8) | 0.021 | 4 (4.8) | 0.639 |
| | >20 | 94 | 27 (28.7) | | 14 (14.9) | | 6 (6.4) | |
| T3 (n=220) | ≤20 | 85 | 6 (7.1) | 0.044 | 18 (21.2) | 0.729 | 2 (2.4) | 0.030 |
| | >20 | 134 | 21 (15.7) | | 26 (19.4) | | 13 (9.7) | |
| T4 (n=92) | ≤20 | 31 | - | - | 4 (12.9) | 0.063 | 2 (6.5) | 0.277 |
| | >20 | 61 | - | | 18 (29.5) | | 8 (13.1) | |

The chi-square test was performed for the comparison of PTP levels according to the PTP cut-off times in all clinical T stages. PTP: Postponement time-period for surgery

underwent early and delayed surgery (p<0.001) and it was stated that delayed surgery was not associated with adverse pathology (p=0.8) (8). In a recent study, delayed (>6 months) nephrectomy was compared with the immediate (<1 month) approach for small renal masses (clinical T1a tumors) in 14.677 patients, and comparable long-term OS was detected between immediate nephrectomy and the delayed approach for clinical T1a renal cell carcinoma (9). On the other hand, in the analysis of 6.237 pathological stage T1a tumors, delayed nephrectomy (>3 months) was associated with a higher risk of CSM in univariate analysis [hazard ratio (HR): 2.07, confidence interval: 1.58-2.72; p<0.001], but it has not been detected in multivariate analysis (10). In another study, after determining the threshold of PTP as 3 months, a longer PTP was found to be associated with worse OS compared with a shorter PTP (HR:1.17, p=0.0002). Gender, tumor size, and tumor histology were also determined as factors that possibly affect disease upstaging, recurrence and CSS. The most common causes have been defined for delaying more than 3 months as treatments of comorbidities and clinical evaluation of patients (11). In a recent systematic review and meta-analysis for the COVID-19 pandemic, in the evaluation of delayed surgery for localized renal cell carcinoma, there has not been indicated any sufficient evidence to support the approach that delayed surgery is safe for localized RCCs (12).

However, these studies show that there are unclear findings between recent results and previous studies. Therefore, we investigated PTP and its possible oncological effects. It was also aimed to determine the thresholds of PTP according to the clinical T stages in the study. In this context, we detected thresholds of 20 and 30 days for clinical T1 and T2-4 tumors, respectively. When we look at the thresholds, pathological upstaging rates were detected to be associated with more than 30 days PTP for clinical T1a stage tumors (8.9% vs. 5.5%, p=0.021) and also more than 20 days PTP for clinical T2a and T3a stage tumors (30% vs. 20.7%, p=0.026 and 15.7% vs. 7.1%, p=0.044; respectively). On the other hand, disease recurrences were found to be higher in clinical T1b and T2b stage tumors with longer PTP (5% vs. 2.6%, p=0.037 and 14.9% vs. 4.8%, p=0.021; respectively). In addition, we also detected that OM was associated with longer PTP in each clinical T2a and T3 stage tumor (7% vs. 2.3%, p=0.015 and 9.7% vs. 2.4%, p=0.030; respectively).

In the evaluation of the threshold of 20 days PTP in all stages, we found that OS was affected more than 20 days PTP in all T1, T2, and T3 stage tumors. On the other hand, among the RFS findings, we found that only the clinical T3 stage was significantly higher in <20 days PTP. However, when we look at the subgroups, especially in the subgroup of the clinical T2a and

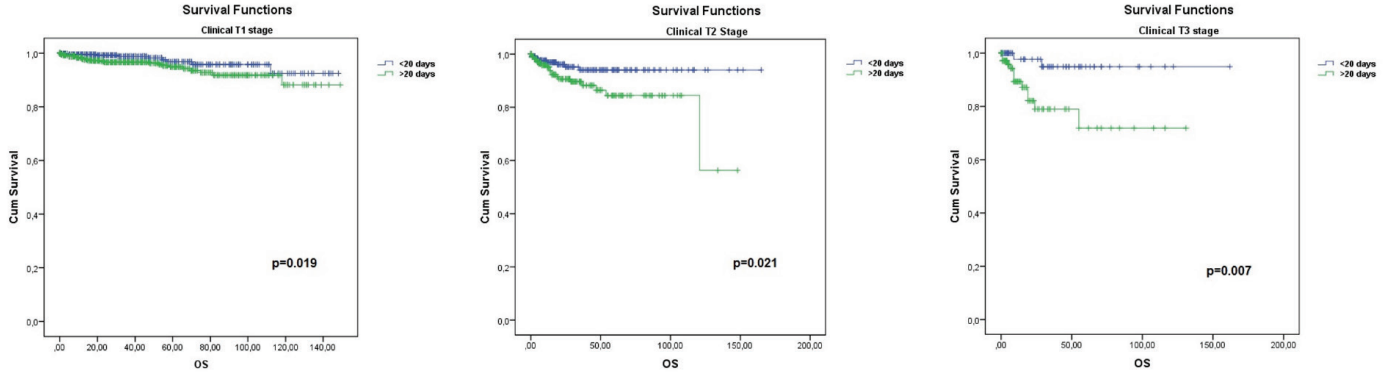


**Figure 1.** Overall survival plots for clinical stage T1, T2, and T3 tumors according to the cut-off 20 days of PTP

PTP: Postponement time-period for surgery

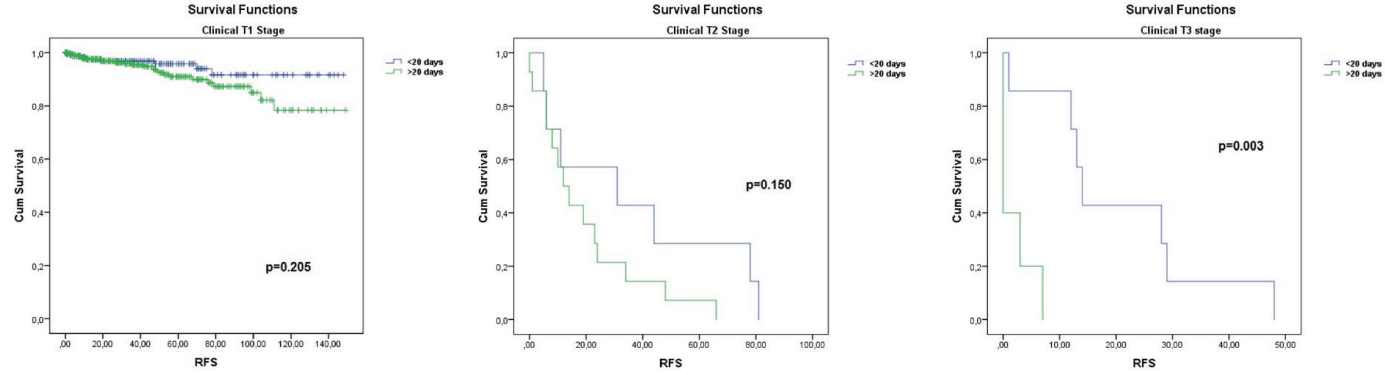


**Figure 2.** Recurrence-free survival plots for clinical stage T1, T2, and T3 tumors according to a cut-off 20 days of PTP

PTP: Postponement time-period for surgery

T3a stages, <20 days PTP affected RFS compared to more than 20 days PTP (49±13.5 months vs. 16.2±5.1 months, p=0.042, and 20.4±8.1 months vs 2±1.4, p=0.013; respectively).

### Study Limitations

The major limitations of our study are its retrospective design and nature. Another important limitation is that it excludes any patients from the period of the COVID-19 pandemic. Although there were no centralized radiological and pathological examinations, the use of a multicentric database from the nationwide respective centers and long-term data acquisition reflect the real-life data for the current study.

## Conclusion

All patients with tumors, including clinical T1 tumors, had worsening oncological results as the PTP increased (>20-30 days). These worsening were reflected as only upstaging in clinical T1a tumors, whereas, as increasing of recurrence in clinical T1b tumors, upstaging and increasing OM in clinical T2a tumors and increasing recurrence in clinical T2b tumors. For clinically local invasive tumors, the worsening has been reflected as upstaging, increasing OM, and decreasing OS and RFS, especially in clinical T3 tumors. In conclusion, postponing surgery even for a relatively short period due to the pandemic in patients with kidney tumors may cause worse oncological outcomes. Therefore, according to the results derived from our database with a substantial number of patients, we strongly recommend that these patients undergo surgery as soon as possible.

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### Ethics

**Ethics Committee Approval:** This study is structured as a database report and therefore, ethical committee approval was not sought.

**Informed Consent:** Database report.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: İ.T., S.S., H.Ö., B.A., G.A., S.B., E.S., Y.B., V.İ., Concept: S.Ç., İ.T., Design: S.Ç., İ.T., Data Collection or Processing: S.Ç., İ.T., S.S., H.Ö., B.A., G.A., S.B., E.S., Y.B., V.İ., Analysis or Interpretation: S.Ç., İ.T., T.A.Ö., F.G., Literature Search: S.Ç., Writing: S.Ç., İ.T.

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