Reflections on the current knowledge of epidemiology, treatment and prognosis for renal cell carcinoma
Hew, M.N.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CRITICAL APPRAISAL OF THE PADUA CLASSIFICATION AND ASSESSMENT OF R.E.N.A.L. NEPHROMETRY SCORE IN PATIENTS UNDERGOING PARTIAL NEPHRECTOMY

Miki Hew¹, Barbaros Baseskioglu², Kurdo Barwari¹, Priscilla Axwijk¹, Cavit Can³, Simon Horenblas³, Axel Bex³, Jean de la Rosette¹, Pilar Laguna¹

¹ Department of Urology, Academisch Medisch Centrum, Amsterdam, The Netherlands
² Department of Urology, Eskisehir Osmangazi University Medical Faculty, Eskisehir, Turkey
³ Department of Urology, Anthoni van Leeuwenhoek Ziekenhuis, Amsterdam, The Netherlands
INTRODUCTION

The current surgical recommendation for clinical T1a renal masses is partial nephrectomy (PN) \cite{1, 2}. In T1b an increasing trend exists towards the same surgical treatment when possible \cite{1, 2}. In these stages oncological outcomes after PN are similar to those of radical nephrectomy \cite{3-6} with advantages in terms of renal function preservation and derived medical morbidity \cite{7, 8}. Nevertheless perioperative complication rates, ranging from 19-25\%, are higher in PN, especially those related to bleeding and urinary leakage\cite{9}.

Recently Ficarra et al proposed a preoperative score system (PADUA classification) to predict the risk for perioperative complications in renal masses candidate for nephron sparing surgery (NSS)\cite{10}. The classification, based on radiological anatomical features and tumor size was developed in a population in which enucleation and renal compression were used during surgery. Also in 2009, an American group reported a similar scoring system (R.E.N.A.L. nephrometry score) that describes the surgical relevant anatomy of renal masses in an organized quantitative scoring system \cite{9, 11}. R.E.N.A.L. nephrometry has not been tested as predictive classification until date.

Our primary objective was to evaluate the ability of the PADUA classification and the R.E.N.A.L. nephrometry score to predict perioperative complications of PN. Secondary objectives were to assess their interobserver variability and their ability to predict the use of ischemia and ischemia time.

MATERIALS AND METHODS

Patients and tumors
Consecutive patients who underwent PN because of a renal mass were retrospectively identified in three academic institutions (January 1998 - June 2010).

Patient and tumor characteristics, surgical, perioperative information and pathological data were gathered from clinical files and databases in the different hospitals. PN was performed according to the standard protocols of the respective centres.


Chapter 3

Selection criteria
Patients were 18 years of age or older and preoperative cross sectional imaging (CT or MRI) were available at the moment of the analysis. Only cases with a single tumor operated on in a single session were included.

Measurements
Tumor stage was determined by TNM 2002 classification\(^1\). Comorbidity index was assigned according to Charlson\(^1\). Ischemia time was measured from the time of hilar clamping until opening the clamp. Complications were divided in intraoperative and postoperative complications (until 30 days after operation) and were classified according to Satava\(^8\) and to Dindo & Clavien respectively\(^9\). Transfusion need was used as a proxy for bleeding and categorized according to the time of administration in intraoperative (during/ immediately after surgery) or postoperative (from day 1 after surgery onwards).

Radiological characteristics of the renal masses were scored by a senior urologists according to PADUA classification\(^10\) and R.E.N.A.L. nephrometry score\(^11\) as described in the original articles (Addendum 1).

Inter-observer concordance for PADUA and R.E.N.A.L. scores was assessed among three urologists with different degree of expertise in a subcohort with full access to cross sectional imaging.

Statistical analysis
Univariate analyses were conducted using independent-samples T-tests for continuous variables and chi-squared tests for categorical variables. The continuous variables were age, BMI, ischemia time and CT and pathological (PA) tumor size. The categorical variables were gender, Charlson index, American Society of Anaesthesiologists (ASA) score, clinical stage, the use of ischemia, pT-stage, histological results and PADUA and R.E.N.A.L. scores.

Logistic regression analyses were used for evaluating the ability of the PADUA and R.E.N.A.L. score to predict perioperative complications, the use of ischemia, and perioperative transfusion. Multivariate analysis was controlled for co-linearity. Because PADUA and R.E.N.A.L. scores included similar components and size, three different models were constructed to avoid confounders. Linear regression analyses were used to evaluate the ability of the scores to predict ischemia time. We assessed inter-observer variation in PADUA and R.E.N.A.L. score assignment by means of Fleiss’ generalized kappa and Intra-class correlation coefficient (ICC).

A p-value <0.05 was considered statistically significant. Data was analyzed using SPSS 16.0 software.

RESULTS

134 cases of PNs were included. Clinical staging was T1a in 93 cases (69.4%), T1b in 34 cases (25.3%) and T2 in 7 cases (5.2%). Warm or cold ischemia was used in 83 cases (62%). In total we observed 41 complications (13 intraoperative and 28 postoperative) in 31 cases (23.1%). All intraoperative complications were transfusions (Satava II). Among the postoperative complications there were 6 blood transfusions, 6 urine leaks, 1 coecum perforation and 15 medical complications.

In univariate analyses only PADUA components polar location (tumors situated in mid -section were more prone to complications than tumors with a polar location, p=0.007), involvement of the urinary collecting system (UCS) (p=0.02) and size (p=0.03) and R.E.N.A.L. components radius (p=0.02) had a significant association with perioperative complications. The other components of PADUA and R.E.N.A.L. scores did not have any statistical significant association. Anterior or posterior location could not be defined in 11 cases.

In multivariate analysis PADUA score ≥ 10, RENAL score ≥ 9 and CT tumor size in cm, were independent predictors of complications when evaluated in three different models respectively. Age was an independent prognosticator for complications in the three models.

PADUA and R.E.N.A.L. scores were able to predict both perioperative and postoperative complications. Both scores predicted the ischemia time. R.E.N.A.L. predicted the use of ischemia. Size in cm predicted overall complications. The low incidence of intraoperative and postoperative urological complications precluded any statistical analysis.
Overall complication rate (in cases) n=31

- Intraoperative complication rate (in cases) n=13
- Postoperative complication rate (in cases) n=22

Minor Clavien grades (I-II) (in events) n=15
- Major Clavien grades (≥III) (in events) n=15

Table 1: Baseline clinical, operative, pathological data and PADUA and R.E.N.A.L. scores of 134 cases treated with partial nephrectomy. Groups according to the absence or presence of perioperative complications. *p<0.05 was considered statistically significant.

Table 2. Specification of perioperative complications, displayed in PADUA, RENAL and size categories. Complication rates are calculated with the total number of cases in the respective category. 13 Intraoperative complications were seen in 13 cases and 28 postoperative complications were seen in 22 cases (3 cases with 2 complications, one case with 4 complications). Clavien grades are displayed in absolute number of events and as percentages of the total postoperative complications.

Table 3. Multivariate analyses for predicting perioperative complications. As size is a component of PADUA and RENAL scores three different models were constructed to avoid confounding. OR- odds ratio, CI- confidence interval, R²- Nagelkerke R squared.
Fleiss’ generalized kappa in a subcohort of 92 tumors was 0.37-0.80 for the different components of the PADUA score and 0.23-0.73 for the R.E.N.A.L. nephrometry components. The ICC was 0.73 for the PADUA score and 0.70 for the R.E.N.A.L. score.

**DISCUSSION**

Predictive research needs to be reproducible and easy to apply, before widespread clinical use can be recommended. Especially when assessing images, small subjective or technical differences may play a role. We aimed to assess the predictive performance of the PADUA classification in a different setting than the developmental one and hypothesized that the R.E.N.A.L nephrometry score, originally reported as a descriptive classification, could also predict the risk of complications. Since both scores encompass the most important surgically relevant features, it would seem logical to foresee a similar predictive ability.

The univariate analysis showed a statistically significant difference in complication rate for age, clinical tumor size and for both median scores of PADUA and R.E.N.A.L. nephrometry score. These variables were statistically significantly higher in the group of patients with perioperative complications. However a correlation between the different components of the two scores and the presence of complications was not uniformly found, suggesting that the performance of the PADUA classification could be different in our setting when compared to the original cohort and that R.E.N.A.L. nephrometry may not be useful as a risk predictive tool either.

Nevertheless logistic regression showed that overall PADUA classification and R.E.N.A.L. nephrometry could predict the risk of perioperative complications at the expenses of the postoperative complications justifying a multivariate analysis. Regarding PADUA classification, only the highest category (score≥10) was an independent predictor of perioperative complications. When compared with the lowest score (6-7), patients with the highest score presented four-fold risk of complication. This increased risk was at the expenses of the operative and minor postoperative complications. No differences were found for the incidence of major complications (Clavien ≥ 3) between PADUA category ≥ 10 or <10 but the incidence of major complications was too low for a sound statistical analysis.
In contrast with the developmental PADUA cohort, our multicenter series included cases operated on with and without ischemia during a larger time interval and a lower rate of clinical T1a. The presence of slightly larger tumors in our cohort compared to the original one may be the source of discrepancy and may explain the lack of association of some of the individual components of the score with the presence of complications. Complication rate was similar in both cohorts and unlikely the reason for the lack of predictive value of the intermediate PADUA scores in our setting.

A previous attempt to validate the PADUA score included cases operated on under ischemia and a similar percentage of clinical T1b (26%) as in our series. In line with our findings the median total PADUA score was an independent predictor of complications. As in our series, this was evident when comparing score ≥ 10 with scores < 10. The absence of association between complications and the individual components of the PADUA score, except for renal sinus/urinary collecting system involvement and for tumor size was also evident in this previous report. In fact this is in line with the findings of a large multicenter analysis (n=1048), demonstrating that in PN increased blood loss, urinary leakage and transfusion rates are observed in tumors larger than 4 cm when compared with tumors smaller than 4 cm.

The predictive ability of R.E.N.A.L. nephrometry score has not yet been explored and the classification was not initially intended as a predictive system but as a standard quantification of renal tumor anatomical elements. In the words of the authors such a classification “will allow for a proper data set comparison and help in the surgical decision choice” 

As the features scored in R.E.N.A.L. nephrometry were quite similar to the ones presented in the PADUA classification we hypothesized that a predictive value could be anticipated. In spite of the notorious lack of association between most of the components of this quantitative classification and the presence of complications, in our cohort R.E.N.A.L. nephrometry score had a predictive ability for perioperative complications equal to the one of the PADUA score, with only a R.E.N.A.L. score (≥9) being an independent predictor for complications. Regarding the presence of major complications the same consideration as for PADUA classification apply to the RENAL nephrometry.

Because tumor size is a component of the two scores and furthermore significant in univariate analysis, to avoid confounding, three different logistic regression models were made. These models included only one score or size respectively and in each one age, significant in univariate analysis, was included. Of paramount importance is the fact that in all scores age was a predictive risk for perioperative complications and that the three models had a similar R². In other words the three models explain to the same extent the variance in outcomes (complications) and performed equally in predicting complications.

Only R.E.N.A.L. nephrometry score was able to predict the use of ischemia in our cohort. That PADUA did not predict ischemia, is most likely due to the fact that it was developed in a non-ischemia cohort. However the use of hilar clamping during PN is mainly a surgeon’s choice based on patient and tumor characteristics as well as intraoperative conditions. Renal compression seems perfectly acceptable when aiming to minimize parenchyma ischemia although its feasibility depends on tumor characteristics, mainly size and location. In the group of patients that underwent ischemia PADUA and R.E.N.A.L. increasing scores correlated with increasing ischemia time, reflecting potential surgical difficulties.

Our last objective was to assess the reproducibility of the two scores. Different individuals (urologists or radiologists) assigned scores in previous reports on PADUA classification, without mentioning the ICC. In our cohort a senior urologist gave definitive scores, but in a subcohort of available radiological images the score of the senior urologist was compared to the scores of two junior urologists. In our opinion a score or classification should lead to standardization and be “easy to use” by less experienced urologists. Overall ICC among the three urologists was substantial for both scores, indicating that the scores can be widely reproduced albeit variations in total score can still be expected depending on the observer. The rationale behind the exclusive involvement of urologists in the reproducibility assessment was that ultimately it is the surgeon who decides on the type of surgery. Involvement and proximity to the urinary system were the most difficult anatomical features to reproduce and influence the overall ICC. The question remains as if only those components that show substantial agreement should be taken into account in a classification. The degree of ICC needed to recommend the broad use of a score or classification in the urological community remains unknown, although it seems desirable to aim at the highest ICC possible. When quantifying agreement awareness is deemed to the fact that the use of
Kappa is influenced by distribution and still subject to chance, furthermore debatable in statistics milieu. Although it would seem logical that a higher Kappa and ICC ensure reproducible scoring systems, significance of agreement values is not universal and in fairness we cannot support or reject a scoring system based only in agreement values. For tumors growing from the tips of the renal poles a significant designation of anterior or posterior is not always feasible. In our series most of those had a polar location including the whole parenchyma thickness. In few cases anterior or posterior location could not be determined because the lack of clear demarcation of the lateral peritoneal reflection. However this feature did not contribute to the total score in any of the classification/score assessed and should not be relevant, except for those upper pole tumors where adjacent organs may be damaged during surgical maneuvers.

Limitations

Limitations of our study include the retrospective nature and the large inclusion period. Differences in tumor size and in the use of ischaemia may hinder the performance of PADUA classification in our series. Larger and homogeneous cohorts than the one hereby presented may suit better validation purposes. However homogeneity may also limit the application of a prognostic classification. In fact a previous validation of the PADUA classification in a larger and more homogenous cohort than ours showed similar results. We cannot rule out that the 2 highest categories of PADUA or R.E.N.A.L. nephrometry could have been predictive in a cohort with higher prevalence of cT1a tumors. Indeed the question arises if a predictive score should be developed for T1a and T1b independently or if either size alone is as good predictor as more elaborated classifications. A further limitation in our series might be the different precision in the CT threshold detection used for evaluation. While older images used 5 mm distant, most of the modern CTs used for staging and decision making are composed of 3 mm slices. This radiological variance could explain the poor inter-observer concordance for anatomic features involving renal sinus and involvement/proximity to the collecting system. The use of transfusion as proxy for perioperative bleeding hinders any comparison as its use is subject to multiple factors (preoperative Hb levels, cardiac status and individual policies). Furthermore the incidence of transfusion was too low to statistic conclusion.

CONCLUSIONS

Only the highest score of PADUA and R.E.N.A.L. scores predicted overall complication risk in our PN series. The intermediate scores failed to predict the risk of complications. A similar predictive value was observed for tumor size. The reproducibility of the PADUA and R.E.N.A.L. scores is substantial, but its broad clinical use for standardization and data set comparison deserves further refinement and evaluation.

REFERENCE LIST


