

The variation of selective uNGAL levels after robot-assisted partial nephrectomy: Early results of a prospective single center study

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Summary *Objectives: Acute kidney injury (AKI) secondary to nephron-sparing surgery represents a significant problem in order to preserve renal function. Since serum creatinine alone underestimates the early detection of AKI several biomarker have been investigated. Neutrophil Gelatinase-Associated Lipocalin (NGAL) is considered a good biomarker for AKI.*

Materials and methods: We report our experience in 28 patients affected by localized renal cell carcinoma and submitted to robot-assisted partial nephrectomy (RAPN). In each patient selective urinary NGAL levels were dosed before surgery, then 2 and 48 hours after the procedure, through a ureteral catheter inserted into the excretory axis of the operated kidney. Moreover, we evaluated split renal function of the preserved renal parenchyma by a 99mTC-DTPA renal scintigraphy, performed before surgery and three months later.

Results: AKI was diagnosed, according to internationally criteria, in 3 patients (10.7%). The baseline selective urinary NGAL level was 20.02 ng/ml. This level significantly increased after surgery with a selective urinary NGAL level that reached 56.36 ng/ml ($p < 0.0001$). Moreover, a significant reduction in 99mTC-DTPA clearance of the operated kidneys after three months was detected ($p < 0.0001$).

Conclusions: Selective urinary NGAL assay represent a sensitive biomarker of acute kidney injury after robotic nephron sparing surgery, capable of predicting the functional outcome of the operated kidney.

KEY WORDS: Neutrophil Gelatinase-Associated Lipocalin (NGAL); Acute kidney injury (AKI); Robot-assisted partial nephrectomy (RAPN).

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INTRODUCTION

Partial nephrectomy (PN) is the treatment of choice for cT1 (< 7 cm) renal tumors because has demonstrated to offer oncological control equal to that of radical nephrectomy (RN) with superior functional outcomes (1-3).

The major goal of the nephron-sparing surgery is maximizing renal function preservation. The three main drivers of post-PN functional recovery, in order of importance, are pre-PN function, remnant vascularized nephron mass, and ischemia time (4) Nowadays robot-

assisted partial nephrectomy (RAPN) is generally preferred by several worldwide centers (5-6) which can performed either with or without hilar clamping. However unclamping hilar control techniques seem to be safe and feasible approaches, with potentially superior functional outcomes, and non-inferior oncological outcomes, when compared with main artery clamping (7). The direct surgical injury and nephron loss that occurs during PN are associated with the risk of occurrence of acute kidney injury (AKI) and chronic kidney disease (CKD). Current criteria for AKI diagnosis and classification depend on serum creatinine (sCr) changes and urine output. (8) Unfortunately, the evaluation of kidney injury by sCr alone underestimates the early diagnosis of AKI, a serious complication after renal surgery, associated with prolonged hospitalization, high morbidity and mortality. The early phase of AKI is accompanied with few symptoms or may be completely asymptomatic (9). Several biomarkers have been investigated in order to identify and anticipate the diagnosis of AKI. Among the others Neutrophil Gelatinase-Associated Lipocalin (NGAL) was extensively evaluated as biomarker of AKI and predictor of CKD (10, 11). NGAL is a ubiquitous 25-KDa protein which expression increases greatly in the presence of a renal damage after ischemia reperfusion injury and nephrotoxicity (12). Nowadays NGAL is considered a biomarker for AKI that has been extensively evaluated in adult and pediatric cardiopulmonary bypass patients (13), kidney transplant patients (14), and patients in intensive care units (15). Production of NGAL is upregulated following renal injury, and consequently detectable in serum and urine hours prior to sCr increases (16). The aim of this study was to evaluate urinary NGAL (uNGAL) both as a marker for early AKI in patients undergoing RAPN for a cT1 renal cell carcinoma and as a marker able to predict the loss of function of the operated kidney.

MATERIALS AND METHODS

In this prospective study 28 patients undergoing partial robot-assisted nephrectomy for cT1 renal cell carcinoma

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at “*Francesco Miulli*” Hospital from June 2017 to December 2017 were enrolled. After approval from the institutional review board, we obtained written consent from all patients. The preoperative clinical tumor staging workup included *computed tomography* (CT) or *magnetic resonance imaging* (MRI) of the abdomen and pelvis and chest radiography. We included patients with a solitary renal cortical tumour of ≤ 7 cm and imaging of a normal contralateral kidney before surgery. The patient’s age, gender, Charlson comorbidity index score, preoperative sCr, preoperative eGFR: *estimated Glomerular Filtration Rate* (eGFR), intra and postoperative data and pathologic features (tumor size, PADUA score, histologic type, and Fuhrman’s nuclear grade) were collected. We evaluated the post-operative onset of AKI according to KDIGO criteria (8). In each patient was collected *serum Neutrophil Gelatinase-Associated Lipocalin* (sNGAL) and selective *urinary Neutrophil Gelatinase-Associated Lipocalin* (uNGAL) before surgery, 2 and 48 hours after nephron-sparing surgery. In particular uNGAL was dosed on the urine collected selectively through a ureteral catheter inserted into the excretory axis of the operated kidney, before surgery. NGAL was measured into the serum and urine with a commercially available enzyme-linked immunosorbent assay kit (*Human NGAL ELISA kit- KIT 036 RUO- Bioporto Diagnostics*). The assay is a sandwich ELISA performed in microwells coated with a monoclonal antibody to human NGAL. Bound NGAL is detected with another monoclonal NGAL antibody labeled with biotin and the assay is developed with horseradish peroxidase (HRP)-conjugated streptavidin followed by the addition of a color-forming substrate. The enzymatic reaction is stopped chemically, and the color intensity is read at 450 nm. Furthermore preoperatively, the split renal function of the operated kidneys was measured by a ^{99m}Tc -DTPA renal scan. After 3 months we detected the functional loss of the operated kidneys through a second control ^{99m}Tc -DTPA renal scan. Sequential kidney scintigraphy is a method of choice for both static and dynamic determination of kidney function separately. Statistical Analysis: We used one-way ANOVA in order to analyze post-operative dosage variations of uNGAL and sNGAL as well as compare functional outcomes after on-clamp or off-clamp *robot-assisted partial nephrectomy* (RAPN). Statistical significance was considered at $p < 0.05$. Linear regression was applied to determine the correlation of selective urinary NGAL assay 48 hours after surgery with the variation of ^{99m}Tc -DTPA clearance three months after surgery. The analysis was performed by using the statistical MedCalc software (*Version 18.2.1, MedCalc, Inc., Belgium*).

RESULTS

Twenty-eight patients were included, mean age was 62.6 (35-88) years. Table 1 resumes baseline characteristics and main intraoperative and perioperative data (Table 1). Seventeen patients underwent off-clamp

RAPN while the remaining eleven patients were submitted to on-clamp RAPN. The choice of hilar clamping during RAPN was performed according to the surgeon’s experience and the characteristics of the tumor. In patients who underwent on-clamp RAPN, the mean warm ischemia time was 12.6 minutes (Table 2).

Table 1.
Pre- and peri-operative characteristics of patients undergoing RAPN for cT1 RCC.

Sex	Male: 15 (53.5%) Female: 13 (46.5%)
Age	62.6 years (35-88)
RCC histotype	Clear cell Rcc: 24 (85.7%) Chromophobe Rcc: 3 (10.7%) Papillary Rcc: 1 (3.6%)
Fuhrman grade	I: 15 (53.5%) II: 13 (46.5%)
pT1	a: 22 (78.5%) b: 6 (21.5%)
Mean tumor diameter (cm)	3,1 (1.2-6.5)
PADUA score	6-7: 15 (53.6%) 8-9: 10 (35.7%) ≥ 10 : 3 (10.7%)
Surgical technique	Off-clamp RAPN: 17 (60.7%) On-clamp RAPN: 11 (39.3%)
Medium Warm Ischemia Time (min)	12,6 (7-22)
Post-operative AKI	3 (10.7%)
Charlson Comorbidity Index	2.32 (0-6)
Preoperative eGFR (ml/min/1.73 m ²)	87.03 (34-115)
Preoperative sCr (mg/dl)	1.07 (0.63-1.73)
Preoperative uNGAL (ng/ml)	20.02 (36.8-4.9)
Preoperative operated kidney Cl ^{99m}Tc -DTPA (ml/min)	37.45 (58.7-14.2)
<small>RCC = renal cell carcinoma; RAPN: Robot-Assisted Partial Nephrectomy; AKI = Acute Kidney Injury; eGFR = estimated glomerular filtration rate; sCr = serum creatinine; uNGAL = urinary Neutrophil Gelatinase-Associated Lipocalin; Cl = clearance; ^{99m}Tc-DTPA= Technetium-99m-diethylenetriaminepentaacetic acid.</small>	

Table 2.
Pre- and peri-operative characteristics of patients undergoing off-clamp vs on-clamp RAPN.

	off-clamp RAPN	on-clamp RAPN	p
No.	17	11	
Sex			
male	8	9	
female	7	4	
Age (years)	65.8 (35-86)	57.6 (40-88)	0.097
Mean tumor diameter (cm)	2.89 ± 1.56	3.6 ± 1.51	0.832
PADUA score	7.23 ± 1.67	8.72 ± 1.67	0.070
Charlson Comorbidity Index	2.58 ± 1.66	1.90 ± 2.16	0.136
Preoperative sCr (mg/dl)	1.08 ± 0.31	0.88 ± 0.24	0.218
Preoperative eGFR (ml/min/1.73 m ²)	72.58 ± 24.40	86.45 ± 26.81	0.880
Preoperative uNGAL (ng/ml)	20.52 ± 15.91	19.25 ± 6.73	0.079
Preoperative operated kidney CL ^{99m}Tc -DTPA (ml/min)	35.79 ± 14.11	40.00 ± 10.85	0.181
AKI	2 (11.7%)	1 (9%)	0.831
<small>RAPN: Robot-Assisted Partial Nephrectomy; AKI = Acute Kidney Injury; eGFR = estimated glomerular filtration rate; sCr = serum creatinine; uNGAL = urinary Neutrophil Gelatinase-Associated Lipocalin; Cl = clearance; ^{99m}Tc-DTPA= Technetium-99m-diethylenetriaminepentaacetic acid.</small>			

The sNGAL baseline level was 169.5 ng/ml and did not change postoperatively ($p = 0.13$). The selective uNGAL baseline level was 20.02 ng/ml and showed a not negligible increase at 2 and 48 hours after surgery (Figure 1). Variation after 48 hours after surgery was statistically significant ($p < 0.0001$). However no statistically significant differences emerged between patients subjected to on-clamp vs off-clamp RAPN (66.17 ng/ml vs 50.02 ng/ml; $p = 0.242$). According to KDIGO criteria for AKI, we detected postoperative AKI in 3 of 28 patients, using sCr dosage 48 hours after surgery. Comparing the pre-operative creatinine with the 48-hours postoperative one, no statistically significant difference was found ($p = 0.0669$). Before comparing patients undergoing on-clamp and off-clamp robot-assisted partial nephrectomy (Table 2), we evaluated the homogeneity of the two groups through ANOVA. They were homogeneous for eGFR pre-intervention ($p = 0.88$), preoperative sCr ($p = 0.218$), maximum tumor size ($p = 0.83$), PADUA score ($p = 0.07$), preoperative uNGAL ($p = 0.07$), Charlson Comorbidity Index ($p = 0.13$), age ($p = 0.09$) and pre-operative selective ^{99m}Tc -DTPA clearance ($p = 0.831$). Evaluating postoperative functional outcome of the oper-

ated kidneys at three months we highlighted a statistically significant reduction in ^{99m}Tc -DTPA clearance of the operated kidneys 3 months after surgery ($p < 0.0001$), with a mean functional loss of the operated kidneys by 8.2% (mean change in ^{99m}Tc -DTPA clearance of -3.081 ml/min). Stratifying the cohort according to the execution of clamping technique (on-clamp vs off-clamp RAPN), there was no statistically significant differences between the two groups ($p = 0.414$) as far as the variation of ^{99m}Tc -DTPA clearance of the operated kidneys. Finally, we evaluated the correlation between the variation in ^{99m}Tc -DTPA clearance 3 months after surgery with the selective dosage of uNGAL at 48 hours from surgery (Figure 2), finding a statistically significant association between the two variables ($R^2 = 0.2391$, $p = 0.0083$). This correlation has not been highlighted by comparing the variation in ^{99m}Tc -DTPA clearance 3 months after surgery with sCr dosage 48 hours postoperatively ($R^2 = 0.12$, $p = 0.0669$).

Figure 1. Postoperative selective urinary excretion of NGAL (mean values).

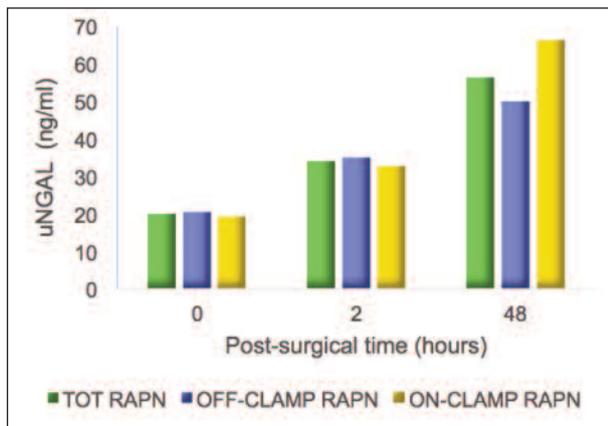
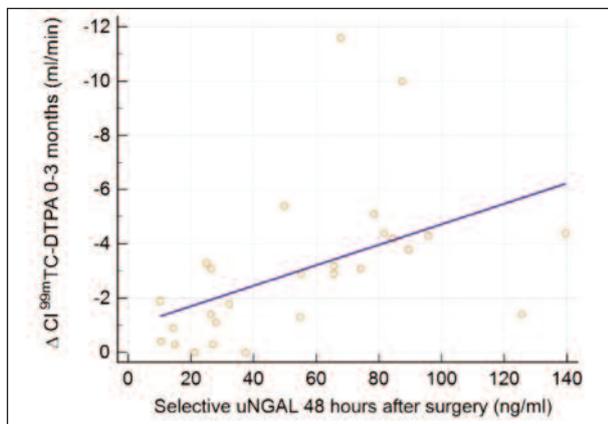


Figure 2. Correlation between the variation in ^{99m}Tc -DTPA clearance 3 months after surgery with the selective dosage of uNGAL at 48 hours from surgery.



DISCUSSION

Urological patients represent a population at risk of AKI which can affect long-term renal function (17). The risk of occurrence of AKI in patients undergoing partial/radical nephrectomy and nephroureterectomy is about 43.1% (18). Currently, AKI is defined according to KDIGO criteria based on sCr changes and urine output, which arise after renal damage (8). AKI observed in renal surgery patients is largely related to direct renal damage. In particular, after a partial nephrectomy, AKI is caused by direct removal of renal parenchyma and damage of the remaining tissue from hyperfiltration or ischemia (19, 20). AKI does not act exclusively on the renal parenchyma but also systemically through the release of inflammatory cytokines (21). The post-operative onset of AKI leads to an increase in post-surgical complications, a lengthening of hospitalization time, an increase in the postoperative mortality rate and a significant increase in health care expenditure with an additional risk of CKD (9, 22, 23). Since traditional definitions of AKI seem to be not very sensitive until the healthy nephrons are reduced by 50%, a growing interest towards biomarkers able to evaluate even slight worsening of renal function represents an expanding research area (24, 25).

Neutrophil gelatinase-associated lipocalin (NGAL) represents an acute renal injury marker that the latest *Acute Dialysis Quality Initiative* (ADQI) guidelines recommend use in patients with suspected AKI (26). Baseline reference values of sNGAL are 86.3 ng/ml in men and 88.9 ng/ml in women while uNGAL has a reference value of 5.7-17.7 ng/ml, but they may increase > 10-fold in serum and > 100-fold in urine following an acute injury. (27) However, human clinical studies have shown conflicting results on the potential clinical use of this biomarker for the assessment of acute kidney injury. *Abassi* has shown that the severity of acute renal injury after nephron sparing surgery is quantitatively correlated to the urinary dosing of NGAL (28). In contrast, *Sprengle* highlighted that changes in urinary NGAL dosage of patients undergoing partial nephrectomy are comparable to those of patients undergoing thoracic surgery (29).

In addition, *Kyo Chul Koo* examining 176 patients who underwent partial open and laparoscopic nephrectomy, had not shown that uNGAL could represent a predictive marker of both postoperative AKI and CKD 6 months after surgery (30). To the best of our knowledge the current report represents the first prospective study that evaluates postoperative AKI and the functional outcome after 3 months from surgery, adopting selective uNGAL assay. First of all, we showed a statistically significant increase in the selective dosage of uNGAL after 48 hours from surgery. This result was not confirmed for the serum NGAL assay after 48 hours from surgery. Probably sNGAL dosage is significantly affected by postoperative blood loss (not considered in this study), as well as could be influenced by the patient's hydration status. For this reason, we decided to focus our interest on the uNGAL. Comparing selective uNGAL assay 48 hours after surgery between patients undergoing on-clamp and off-clamp RAPN, we did not find a statistically significant difference. In fact, it seems that hilar clamping does not influence the increase in selective uNGAL dosage and therefore the severity of the acute post-operative renal injury. On the other hand, the diagnosis of AKI using the KDIGO criteria allowed to diagnose postoperative AKI in only 3 patients, suggesting a lack of sensitivity of the diagnostic criteria worldwide used for AKI. Later we highlighted a worsening of renal function of the operated kidneys 3 months after surgery, through a sequential renal scintigraphy performed before and 3 months after surgery. This result should be explained not as a failure of nephron sparing surgery but as an effect of the high sensitivity of renal scintigraphy in detecting even small changes in renal function compared to the use of sCr. Indeed, the curvilinear relationship between serum creatinine and eGFR may lead to the lack of detection of early stages of AKI or CKD (31). The choice of the third post-operative month for the execution of the control scintigraphy, follows the KDIGO recommendations (8). Comparing patients undergoing on-clamp and off-clamp RAPN, there are no differences in losses of ^{99m}Tc -DTPA clearance 3 months after surgery. This result could be due either to the short post-operative follow-up period but also to the limited warm ischemia time of on-clamp procedures (the mean warm ischemia time was 12.6 minutes). As we know, warm ischemia time is an important, modifiable predictor of postoperative renal function. In particular, warm ischemia time should not exceed 25 minutes, to avoid a short and long-term reduction in renal function (32). The statistically significant association between the reduction in ^{99m}Tc -DTPA clearance 3 months after surgery with the selective dosage of uNGAL at 48 hours from surgery, highlighted a direct relationship between these two predictors. The limitations of this report should be acknowledged. First, the small number of patients as well as the short time of postoperative follow-up (3 months) limited the power of the analyses. Second, the normalized uNGAL (the ratio of urine NGAL to urine creatinine) was not used in this study; moreover, the postoperative urine collection for uNGAL was performed selectively through a ureteral catheter inserted into the excretory axis of the operated kidney, unlike previous studies where urine

was collected from the urethral catheter (28-30). Further studies are needed to understand the clinical use of the uNGAL although it seems clear the importance of implementing the definition of AKI with the introduction of new biomarkers. The importance of reno-protective surgery is not in question in this report but we tried to demonstrate the lack of sensitivity of traditional methods. Our findings support the concept that the development of reno-protective techniques can prevent the onset of small changes in postoperative renal function, not detected with the sCr dosage, but which may impact on the functional outcome of the operated kidney.

CONCLUSIONS

Selective uNGAL assay represent a sensitive biomarker in detecting postoperative AKI in patients submitted to RAPN for a cT1 renal cell carcinoma. Furthermore, selective uNGAL assay may be consider a predictive biomarker of CKD after nephron-sparing surgery. In our opinion KDIGO criteria for AKI should be implemented with the clinical use of biomarkers such as uNGAL.

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