

Clinical-Kidney cancer
Management of high complexity renal masses in partial nephrectomy:
A multicenter analysis

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Abstract

Objective: To determine the safety and efficacy of performing partial nephrectomy (PN) on patients with high nephrometry score tumors.

Patients and methods: We used a prospectively maintained multi-institutional kidney cancer database to identify 144 patients with R.E.N.A.L. nephrometry score ≥ 10 who underwent PN for a cT1-cT2 renal mass. Baseline demographics and clinical characteristics, tumor characteristics, perioperative, and pathological outcomes were analyzed and reported. Trifecta achievement, defined by warm ischemia time < 25 minutes, no perioperative complications, and negative surgical margins, was the primary outcome. We assessed the relationship of baseline clinical and tumor characteristics data to trifecta achievement and perioperative complications.

Results: Baseline median eGFR was 84.57 ml/min/1.73 m², with 119 (84.39%) patients having normal baseline kidney function. The median clinical tumor size was 4.95 cm, with 74 (51.75%) being completely endophytic and 58 (41.73%) located on the hilum. The median ischemia time was 20 minutes. Median estimated blood loss was 150 ml. Twelve patients (8.33%) had intraoperative complications. No patient had a conversion to open surgery. Postoperative, perioperative, and major complication rate were 10.42%, 17.3%, and 2.34% respectively. Thirty-six patients (37.89%) developed postoperative acute kidney injury and 28 (20.90%) developed new-onset CKD at a median follow-up of 6 months. Eight patients (5.56%) had a positive surgical margin. Trifecta was achieved in 89 (61.81%) patients. There was no significant difference in baseline, clinical, and tumor characteristics between those that achieved trifecta and in those where trifecta was not. Pathologic tumor stage was the only factor significantly associated with trifecta achievement ($P = 0.025$).

Conclusion: In treating complex renal tumors, PN should be performed when possible. Although this remains a challenging procedure, with experience and appropriate case selection, the trifecta outcome can be achieved in a significant number of patients with high renal score lesions. © 2019 Elsevier Inc. All rights reserved.

Keywords: Renal cell carcinoma; Nephrometry; Partial Nephrectomy; RENAL score; Trifecta

1. Introduction

The majority of renal tumors are diagnosed as organ confined disease [1]. In cT1a setting, partial nephrectomy (PN) yields superior functional outcome compared to radical

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nephrectomy (RN) with comparable oncologic outcome, and therefore is the preferred treatment technique [2]. However, controversy continues with regards to the utility of PN in larger tumors. Superior functional outcome of PN may result in a potential overall survival (OS) benefit via decreased metabolic and cardiovascular morbidity [3]. However, the only randomized clinical trial in the literature failed to demonstrate any OS benefit to PN [4]. Furthermore, there are technical challenges resulting in an increased complication rate associated with PN in treating cT1b and cT2 renal masses [5]. Therefore, PN has not been widely adopted in these larger tumors. Regardless, guidelines suggest that PN should be favored over RN in cT1b patients when feasible [2].

However, size alone is not enough to warrant PN. Other tumor characteristics such as endophytic, central, and hilar location cause technical challenges in tumor excision and kidney reconstruction [6]. Therefore, we need to account for the anatomical complexity of a tumor. Anatomical classification systems have been proposed in the past to better evaluate the complexity of renal masses [7,8]. A high RENAL nephrometry score has been shown to be associated with complications, warm ischemia time (WIT), and functional outcome [9,10].

Anatomical complexity also affects the decision to perform minimally invasive surgery. European Association of Urology Guidelines suggests that the decision to perform robotic or open PN should be based on the surgeon's skill and expertise. Since the adoption of the robot, utilization of minimally invasive PN has increased nationwide [11], including intermediate and high complexity renal masses [12]. In this study, we sought to determine the safety and efficacy of performing robotic PN (RPN) in patients with high nephrometry score tumors.

2. Patients and methods

2.1. Data source

Our IRB approved multi-institutional database of 2,553 patients undergoing RPN was utilized for analysis. Data from 6 surgeons was available and all PN were performed between 2006 and 2018. In an attempt to minimize selection bias, patients were excluded if they had end-stage renal disease ($n = 3$), a solitary kidney ($n = 6$), or had a clinical stage greater than cT2aNOM0 ($n = 5$). Additionally, RPN patients with a R.E.N.A.L. nephrometry score less than 10 ($n = 2303$), patients that underwent intraoperative conversion from RPN to RRN ($n = 2$) and those with incomplete data to meet the criteria for trifecta achievement were also excluded ($n = 90$). After exclusion, there were 144 patients that met eligibility criteria.

2.2. Variables

Baseline characteristics included age, gender, body mass index (BMI), Charlson-comorbidity index (CCI),

Table 1

Baseline demographic, clinical and tumor characteristics of patients undergoing RAPN for high complexity renal mass

Variables	N (%)
Number of patients	144
Age (year) ^a	59 ± 12
Male gender	83 (57.64%)
Body mass index ^a (kg/m ²)	30.35 ± 6.63
Hypertension	82 (56.84%)
Diabetes	34 (23.61%)
CCI ^b	3 (2, 4)
Baseline Creatinine (mg/dL) ^b	0.90 (0.73, 1.09)
Baseline eGFR (ml/min/1.72 m ²) ^b	84.57(24.78, 104.74)
Baseline CKD stage*	
> Grade 3	119 (84.40%)
Grade 3	22 (15.60%)
ASA score ^b	3 (2, 3)
Tumor laterality	
Right	70 (52.24%)
Left	64 (47.76%)
Tumor size (cm) ^b	4.95 (3.25, 6.30)
Growth pattern*	
<50% Endophytic	5 (3.50%)
>50% Endophytic	64 (44.76%)
Completely Endophytic	74 (51.75%)
Hilar tumor*	58 (41.73%)

ASA = American society of Anesthesiologist; CCI = Charlson's comorbidity index; CKD = chronic kidney disease; cm = centimeter; eGFR = estimated glomerular filtration rate; min = minutes; mg/dl = milligram per deciliter.

* Missing data.

^a Continuous variable presented as mean ± standard deviation.

^b Continuous variable presented as median (interquartile range).

hypertension, diabetes mellitus, baseline estimated glomerular filtration rates (eGFR), baseline chronic kidney disease (CKD) stage and American Society of Anesthesiologists (ASA) score. eGFR was calculated using Modification of Diet in Renal Disease formula [13]. Tumor characteristics included clinical tumor size, tumor laterality, tumor growth pattern and proximity to the hilum. Perioperative outcomes included operative time, WIT, estimated blood loss (EBL), intra and postoperative complication rate (any, major [Clavien≥3]) according to Clavien-Dindo classification [14], conversion to open surgery, and length of stay. Renal Functional outcome data evaluated included rates of acute kidney injury (>25% reduction in eGFR from baseline to discharge, as described in RIFLE Criteria) [15], eGFR at discharge, last follow-up eGFR, and the development of de novo CKD. Pathology data included pathologic tumor size, stage, tumor histology, tumor behavior, Fuhrman grade, and margin status. Oncologic outcome variables included recurrence and death.

2.3. Outcome

Trifecta achievement as an outcome was used, defined by negative surgical margins, no perioperative

complications and WIT ≤ 25 minutes. Trifecta achievement was categorized as either achieved or not achieved.

2.4. Statistical analysis

Categorical variables were reported as frequencies and proportions. Continuous variables were reported as medians and interquartile range if the variable was not normally distributed and as means and standard deviations, where the distribution was normal. The relationship between baseline data, clinical and tumor characteristics with Trifecta achievement, and perioperative complications were assessed using Chi-square test of independence, Fishers exact (where cell count was less than 5), student *T* test (for normally distributed variables) and Mann-Whitney U test (when normal distribution was not met). Missing data were handled using a pairwise analysis method. All analysis was conducted using STATA version 14.1 (College Station, TX), and statistical significance was determined at *P* value < 0.05 .

Table 2

Perioperative and functional outcome of patients who underwent RAPN for high complexity renal mass

Variables	N (%)
Operative time (min) ^b	216 (165, 262)
Warm ischemia time (min) ^b	20 (15, 26)
Estimated blood loss (ml) ^b	150 (75, 300)
Intraoperative complication	12 (8.33%)
Postoperative complication	15 (10.42%)
Blood transfusion	1 (0.69%)
Major complication (Clavien ≥ 3) ^{c,*}	3 (2.34%)
Trifecta achievement	89 (61.81%)
Length of hospital stay (days) ^b	1 (1, 2)
eGFR (ml/min/1.72 m ²)	
At discharge ^b	65.42 (51.75, 83.73)
Last follow-up GFR ^b	67.61 (54.01, 83.73)
Postoperative AKI (RIFLE STAGE 1) [*]	36 (37.89%)
De novo CKD [*]	28 (20.90%)

AKI = acute kidney injury; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; min = minutes.

* Missing data.

^b Continuous variable presented as median (Interquartile range).

^c Clavien-Dindo classification greater or equal to grade III.

Table 3

Relationship between baseline demographic, clinical and tumor characteristics and perioperative complication of patients who underwent RAPN for high complexity renal mass

Variables	Perioperative complications		<i>P</i> value
	No	Yes	
Number of patients	119	25	
Age (year) ^a	58 ± 12	62 ± 13	0.243
Male gender	65 (54.62%)	18 (72.00%)	0.110
Body mass index ^a (kg/m ²)	30.31 ± 6.27	30.55 ± 8.29	0.871
Hypertension	65 (54.62%)	17 (68.00%)	0.219
Diabetes	27 (22.69%)	7 (28.00%)	0.570
CCI ^b	3 (2, 4)	4 (2, 4)	0.693
Baseline creatinine (mg/dL) ^b	0.90 (0.73, 1.06)	0.90 (0.70, 1.18)	0.782
Baseline eGFR (ml/min/1.72m ²) ^b	83.63 (70.17, 104.74)	91.49 (70.03, 105.71)	0.709
Baseline CKD stage [*]			
Grade 1 and 2	100 (84.75%)	19 (82.61%)	0.759
Grade 3	18 (15.25%)	4 (17.39%)	
ASA score ^b	3 (2, 3)	3 (3, 3)	0.056
Tumor laterality			
Right	60 (53.57%)	10 (45.45%)	0.486
Left	52 (46.43%)	12 (54.55%)	
Tumor size (cm) ^b	4.50 (3.10, 6.30)	5.30 (4.00, 6.60)	0.257
Growth pattern [*]			
<50% Endophytic	5 (4.24%)	0 (0.00%)	0.665
>50% Endophytic	51 (43.22%)	13 (52.00%)	
Completely Endophytic	62 (52.54%)	12 (48.00%)	
Hilar tumor [*]	50 (43.48%)	8 (33.33%)	0.384

ASA = American society of Anesthesiologist; CCI = Charlson's comorbidity index; CKD = chronic kidney disease; cm = centimeter; eGFR = estimated glomerular filtration rate; min = minutes; mg/dl = milligram per deciliter.

P value for all categorical variables were determined using Chi-square test or Fisher's exact test

P value is significant at < 0.05 .

* Missing data.

^a Continuous variable presented as mean ± standard deviation and *P*-value was determined by 2-tailed *t* tests.

^b Continuous variable presented as median (Interquartile range) and *P*-value was determined by Mann-Whitney –U test.

3. Results

3.1. Patient and tumor characteristics

Of the 144 patients that underwent RAPN for highly complex tumors, 83 (57.63%) were males. The mean age of patients was 59 ± 12 years. The mean BMI of patients was 30.35 ± 6.63 kg/m². Eighty-two (56.84%) patient had hypertension, while 34 (23.61%) had diabetes. The median CCI was 3. Patients had a median baseline creatinine of 0.90 mg/dl, with a median eGFR of 84.57 ml/min/1.73 m². A total of 119 (84.39%) patients had a normal baseline kidney function. The median clinical tumor size was 4.95 cm, with 74 (51.75%) being completely endophytic and 58 (41.73%) located on the hilum. Other patient characteristics are reported in [Table 1](#).

3.2. Perioperative outcome

The median operative time and median ischemia time were 216 and 20 minutes respectively. Median EBL was 150 ml. No patient had a conversion to open surgery. Intraoperative, postoperative, and major complication rate were 8.33%, 10.42%, and 2.34% respectively. Only 1 patient received blood transfusion (0.69%). The median length of hospital stay was 1 (IQR 1, 2) days ([Table 2](#)).

Twenty-five patients had perioperative complications ([Table 3](#)). Perioperative complications were not significantly associated with other baseline, clinical, and tumor characteristics: age ($P=0.243$), gender ($P=0.110$), BMI ($P=0.871$), hypertension ($P=0.219$), diabetes ($P=0.570$), CCI ($P=0.693$), baseline creatinine ($P=0.782$), baseline eGFR ($P=0.709$), baseline CKD ($P=0.796$), tumor laterality ($P=0.297$), tumor size ($P=0.257$), growth pattern ($P=0.665$), and hilar tumor ($P=0.384$).

3.3. Renal functional outcome

The median postoperative eGFR at discharge was 65 ml/min/1.72 m², with 36 patients (37.89%) developing postoperative acute kidney injury. Twenty-eight (20.90%) developed new-onset CKD, and the median postoperative eGFR at last follow-up was 67.61 ml/min/1.72 m² at a median follow-up of 6 months ([Table 2](#)).

3.4. Pathologic and oncologic outcome

Pathological and oncologic outcomes are reported in [Table 4](#). The median pathologic tumor size was 5.0 cm. One hundred and sixteen (85.93%) tumors were malignant, and 84 (60.87%) had a clear cell histology. Twenty-five (20.00%) had a pathologic tumor stage of ≥ 2 , and 30 (29.30%) tumors had a Fuhrman grade of 3 to 4. Eight patients (5.56%) had a positive surgical margin. Follow-up recurrence data were available for 110 patients, and 8

Table 4

Pathological and oncological outcomes of patients who underwent RAPN for high complexity renal mass

Variables	N (%)
Pathologic tumor size (cm) ^b	5 (1.3, 15)
Malignant tumor*	116 (85.93%)
Histology*	
Clear cell	84 (60.87%)
Papillary	16 (11.59%)
Chromophobe	8 (5.80%)
Angiomyolipoma	3 (2.17%)
Oncocytoma	7 (5.07%)
Other	20 (14.49%)
pT stage*	
T1a	59 (47.20%)
T1b	41 (32.80%)
T2a	9 (7.20%)
T2b	6 (4.80%)
T3a	10 (8.00%)
Fuhrman grade*	
I	13 (12.62%)
II	60 (58.25%)
III	26 (25.24%)
IV	4 (3.88%)
Positive surgical margin*	8 (5.56%)
Recurrence*	8 (7.27%)
Death*	2 (5.13%)

cm = centimeter; pT = pathologic tumor.

* Missing data.

^b Continuous variable presented as median (Interquartile range).

(7.27%) had recurrence. Similarly, only 2 (5.13%) deaths were reported from 39 available survival data.

3.5. Trifecta achievement

Trifecta was achieved in 89 (61.81%) patients. There was no significant difference in baseline, clinical, and tumor characteristics between those that achieved trifecta and in those where trifecta was not: age ($P=0.634$), male gender ($P=0.066$), BMI ($P=0.143$), hypertension ($P=0.105$), diabetes ($P=0.416$), CCI ($P=0.760$), baseline eGFR ($P=0.661$), and tumor size ($P=0.075$). Other baseline, clinical, and tumor characteristics and their association with trifecta are reported in [Table 5](#). Pathologic tumor stage was the only factor, significantly associated with trifecta achievement ($P=0.025$). There was no significant difference between trifecta achievement and other pathological outcomes: pathological tumor size ($P=0.125$), malignant tumor ($P=0.127$), histology ($P=0.326$), and Fuhrman grade ($P=0.282$) ([Table 6](#)).

4. Discussion

Anatomically complex masses pose technical difficulties in tumor resection and renorrhaphy, which results in an increased parenchymal excision, complication rate, and WIT [9]. This was the case with our cohort, with a

Table 5

Relationship between baseline demographic, clinical and tumor characteristics and trifecta achievement of patients who underwent RAPN for high complexity renal mass

	Trifecta		P value
	Achieved	Not achieved	
N	89 (61.81%)	55 (38.19%)	
Age (years) ^a	59 ± 13	61 ± 12	0.634
Male gender	46 (51.69%)	37 (67.27%)	0.066
Body mass index ^a	29.72 ± 6.18	31.42 ± 7.27	0.143
Hypertension	46 (51.69%)	36 (65.45%)	0.105
Diabetes	19 (21.35%)	15 (27.27%)	0.416
CCI ^b	3 (2, 4)	3 (2, 4)	0.760
Baseline Creatinine (mg/dL) ^b	0.90 (0.72, 1.05)	0.91 (0.74, 1.10)	0.308
Baseline eGFR (ml/min/1.72m ²) ^b	84.57 (70.17, 106.77)	85.02 (70.27, 100.24)	0.661
Baseline CKD stage*			
> Grade 3	76 (85.39%)	23 (82.69%)	0.670
Grade 3	13 (14.61%)	9 (17.31%)	
ASA score ^b	3 (2, 3)	3 (2, 3)	0.523
Tumor laterality			
Right	44 (53.66%)	26 (50.00%)	0.679
Left	38 (46.34%)	26 (50.00%)	
Tumor size (cm) ^b	4.40 (2.90, 5.60)	5.30 (3.80, 6.80)	0.075
Growth pattern*			
<50% Endophytic	5 (3.50%)	0 (0.00%)	0.173
>50% Endophytic	37 (42.05%)	27 (49.09%)	
Completely Endophytic	46 (52.27%)	28 (50.91%)	
Hilar tumor*	33 (38.82 %)	25 (46.30%)	0.384

ASA = American society of Anesthesiologist; CCI = Charlson's comorbidity index; CKD = chronic kidney disease; cm = centimeter; eGFR = estimated glomerular filtration rate; mg/dl = milligram per deciliter; min = minutes; N = number of observations.

P value for all categorical variables were determined using Chi-square test or Fisher's exact test

P value is significant at <0.05.

* Missing data.

^a Continuous variable presented as mean ± standard deviation and P value was determined by 2-tailed t tests.

^b Continuous variable presented as median (Interquartile range) and P value was determined by Mann Whitney – U test.

51% rate of completely endophytic and a 41.7% of hilar tumors. Despite these unfavorable characteristics, median WIT was 20 minutes. There are studies in literature in which PN is associated with an increased rate of complications in patients with complex renal masses, measured by both PADUA and RENAL scores [16,17]. In our study, the benefit or parenchymal preservation did not come at the expense of a high complication rate. Overall complication rate was 10%, and major complication rate was only 2.3%. Median operative time was 216 minutes, which is considered to be long for a standard RPN. However, median EBL was only 150 ml and median length of stay was 1 day. Our results show that RPN can be performed with an acceptable complication rate in complex renal masses. None of the baseline clinical factors were predictive of complication rate.

In addition to complications, controversy exists in literature regarding the potential oncological risks of performing PN on complex renal masses [18]. The functional benefit should not come at the expense of an increased PSM rate. In our series, PSM rate was 5.5% and recurrence was seen in 5.5% of patients, both of which were comparable to contemporary series in literature [19,20]. Overall, pathological

stage was the only factor that was associated with trifecta achievement in univariate analysis. Even though tumor size was not predictive of trifecta achievement, there was a significantly higher rate of pT1a patients in the trifecta achieved group. Furthermore, rate of pT3a upstaging was 6.9% of our cohort, which is significantly higher than the national average of 1.9% [21]. Given the association between pT3a upstaging and worse survival, urologists should be careful about this possibility when operating on complex renal masses [22].

The largest study in literature with a similar design has been published by the ROSULA Collaborative group, who reported the results of 298 patients who underwent RPN for cT2 renal tumors. They have reported a slightly longer WIT with 25 minutes and higher complication rate (22% postoperative and 5% intraoperative complications). However, major complication rate was only 5%, which is an acceptable rate. Their results demonstrated that pT stage was associated with overall complication rate, whereas our results showed that pT stage was associated with trifecta achievement [20]. Overall, their message was similar with our in that PN can be performed in select cases with acceptable outcomes.

Table 6

Relationship between pathologic outcomes and trifecta achievement of patients who underwent RAPN for high complexity renal mass

Variables	Trifecta		P value
	Achieved	Not achieved	
Pathologic tumor size (cm) ^b	3.9 (2.7, 15.0)	4.5 (3.0, 6.2)	0.125
Malignant histology*	68 (81.93%)	48(92.81%)	0.127
Histology*			
Clear cell	48 (57.14%)	36 (66.67%)	0.326
Papillary	10 (11.90%)	6 (11.11%)	
Chromophobe	3 (3.57%)	5 (9.26%)	
Angiomyolipoma	2 (2.38%)	1 (1.85%)	
Oncocytoma	6 (7.14%)	1 (1.85%)	
Other	15 (17.86%)	5 (9.26%)	
pT Stage*			
T1a	43 (58.90%)	16 (30.77)	0.025
T1b	20 (27.40%)	21 (40.38%)	
T2a	3 (4.11%)	6 (11.54%)	
T2b	3 (4.11%)	3 (5.77%)	
T3a	4 (5.48%)	6 (11.54%)	
Fuhrman grade*			
I	10 (15.87%)	3 (7.50%)	
II	32 (50.79%)	28 (70.00%)	
III	18 (28.57%)	8 (20.00%)	
IV	3 (4.76%)	1 (2.50%)	

cm = centimeter; pTumor = pathologic tumor.

P value for all categorical variables were determined using Chi-square test or Fisher's exact test.

P value is significant at <0.05.

* Missing data.

^b Continuous variable presented as median (Interquartile range) and P value was determined by Mann-Whitney – U test.

The main benefit of performing PN over RN is the functional kidney volume preservation, which, in theory, should result in a decreased rate of AKI at discharge and subsequent de novo CKD [23]. However, despite successful renal parenchymal preservation, we have seen a 36% rate of AKI at discharge and 20% consequent de novo CKD rate. These rates are not surprising, since increased RENAL score is known to contribute to a significant decrease in eGFR through ischemic insult and higher parenchymal loss [23,24]. Current evidence suggests that surgically induced CKD may not be as harmful as medical CKD on metabolism, cardiovascular system, and OS [25,26]. Therefore, these numbers should not discourage urologists from performing PN, due to the increased risks.

The aforementioned data demonstrate the importance of performing PN when possible. We did not compare PN vs. RN in our cohort due to lack of RENAL score data. In a 1:2 propensity score matched analysis of 120 patients, Yoo et al., who reported a 13.5% risk of CKD in PN group compared to 40.7% in the RN group. They have also reported that the benefit of PN over RN on CKD disappears in patients with T1b tumors when RENAL score is over 8 [27]. However, their analysis differed with ours in that they limited their analysis to T1b patients whereas we did not. In addition, their cohort only included 40 patients with T1b disease, which needs validation by a larger cohort.

Furthermore, we should not forget the importance of factors such as age and baseline kidney function when we are analyzing functional outcome [28].

Most series in literature are not comprised of exclusively robotic cases [12,29]. This was not a surprising finding since this cohort is made up very challenging cases. Evidence in literature regarding PN in complex renal masses is limited, and studies regarding the safety of PN in large (cT1b and/or cT2) masses are predominantly open series [5]. In treating renal masses, oncological outcome is the number one priority so the decision between PN and RN should take precedence over the decision between open and minimally invasive techniques. However, in the last decade there has been a paradigm shift in PN toward minimally invasive surgery. Therefore, efforts must be made to minimize morbidity and achieve faster convalescence.

There are several weaknesses to our study. Like other studies in literature, our results are based on retrospective observational data [18], which creates an inherent selection bias. In our cohort, only 2 cases were converted to RN, which is not a realistic rate in clinical practice. Moreover, our series is comprised of very high volume surgeons, which makes our results less generalizable. Furthermore, we did not do a PN vs. RN analysis since we lacked the RENAL score data on many patients. Even if we did not lack such data, RENAL score is not an optimal measure of

tumor complexity since larger tumors tend to be more exophytic, which decreases the RENAL score [8]. Our follow up period was not sufficient enough to perform a strong oncological or functional outcome analysis. However, our data was sufficient to demonstrate the perioperative outcome. On the other hand, our analysis was performed on an extensive, granular database of multi-institutional design, which is a significant strength of our results.

5. Conclusion

In treating complex renal tumors, PN should be performed when possible. Although this remains a challenging procedure, with experience and appropriate case selection, the trifecta outcome can be achieved in a significant number of patients with high renal score lesions.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.urolonc.2019.04.019>.

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