

Cancer-specific Survival Outcomes Among Patients Treated During the Cytokine Era of Kidney Cancer (1989-2005)

A Benchmark for Emerging Targeted Cancer Therapies

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BACKGROUND. The management of renal cell carcinoma (RCC) is evolving toward less extirpative surgery and the use of targeted therapy. The authors set out to provide a benchmark against which emerging therapies should be measured.

METHODS. A prospective database including clinical and pathological variables for 1632 patients with RCC treated between 1989 and 2005 was queried. Patients were stratified using the University of California-Los Angeles Integrated Staging System (UISS) into low-, intermediate-, and high-risk groups. Disease-specific survival (DSS) was measured. Response to systemic therapy for patients with advanced disease was assessed.

RESULTS. Nephrectomy was performed in 1492 patients. Overall 5-, 10-, and 15-year DSS was 55%, 40%, and 29%. For localized disease, 5- and 10-year DSS for UISS low-, intermediate-, and high-risk groups was 97% and 92%, 81% and 61%, and 62% and 41%, respectively. For metastatic disease, 5- and 10-year DSS for UISS low-, intermediate-, and high-risk groups was 41% and 31%, 18% and 7%, and 8% and 0%, respectively. Patients with metastatic disease receiving immunotherapy (n = 453) had complete response in 7% (median survival [MS], 120+ months), partial response in 15% (MS, 42.8 months), stable disease in 33% (MS, 38.6 months), and progressive disease in 45% (MS, 11.6 months).

CONCLUSIONS. Most patients with localized RCC do well with surgery alone, but effective adjuvant therapy is needed for patients identified as at high risk for recurrence. For advanced disease, newer targeted and potentially less toxic treatments should be at least as effective as those achieved with aggressive surgical resection and immunotherapy. *Cancer* 2008;113:2457-63. © 2008 American Cancer Society.

KEYWORDS: survival, kidney cancer, interleukin-2, immunotherapy.

With over 51,000 new cases and 13,000 deaths expected in the United States in 2007, renal cell carcinoma (RCC) represents the most lethal urologic malignancy.¹ The surgical and medical treatment paradigms for RCC are evolving. Increased use of imaging has resulted in a stage migration, making more cases amenable to partial nephrectomy or minimally invasive or ablative treatments such as cryoablation. In addition, the Food and Drug Administration (FDA) has recently approved sorafenib, sunitinib, and temsirolimus—3 agents that target specific molecular aberrations in neoplastic cells—for the treatment of advanced RCC. These agents are changing the treatment paradigm for metastatic RCC by replacing

the near-exclusive use of interleukin-2 (IL-2) and interferon-alpha (IFN- α) with an approach targeted to tumor characteristics.

The field of kidney cancer is undergoing dramatic changes, and it is as yet still unclear how these changes are affecting patient outcome. No randomized controlled trials compare the results of resection and ablation, and therefore it remains unknown whether the long-term cancer control outcomes are similar for localized RCC. In addition, no phase III trials have evaluated the new targeted agents against IL-2, previously the only FDA-approved drug for metastatic RCC. Many new trials have been initiated to compare combinations of these agents with immunotherapy, but none compare the efficacy against the previous standard of care, which offered patients infrequent but durable, long-term complete treatment responses.

A critical assessment of the potential improvement in the new treatment era necessitates a comparison to a known benchmark. Therefore, we comprehensively describe a large single-center experience with the clinical management and cancer control outcomes among patients with kidney cancer treated at University of California-Los Angeles (UCLA) Medical Center from 1989 to 2005. During this time, the uniform principle that was applied to the management of patients with RCC included radical surgical resection and aggressive use of immunotherapy. In addition, we have updated our prognostic model that facilitates patient stratification, guides surveillance, and enrollment in adjuvant clinical trials.

MATERIALS AND METHODS

Patients

The prospective, institutional review board approved, UCLA kidney cancer database comprises 1825 patients treated for a solid renal tumor at UCLA from 1989 to 2005. RCC was found in 1632 patients (89%), representing the study cohort. Patients were categorized by year of RCC diagnosis into the following periods: pre-1991, 1991-1995, 1996-2000, and 2001-2005. Five-year increments were arbitrarily chosen to facilitate a description of the changes in patient characteristics and outcomes over time. Patients were categorized as asymptomatic unless symptoms specifically attributed to RCC were present. Symptoms included gross hematuria, flank pain, weight loss >10% within 6 months, abdominal pain, back pain, and abdominal mass. Surgical management was categorized as partial or radical nephrectomy and as including or excluding adrenalectomy

and lymphadenectomy. TNM stage was defined according to the 2002 American Joint Committee of Cancer classification,² the grade according to the Fuhrman system,³ and the histological type according to the World Health Organization classification.⁴ Nonclear cell RCC specimens were re-reviewed by a single expert in genitourinary pathology (J.W.S.) to confirm their histologic classification. Localized disease was defined as the absence of lymph node involvement and metastases (N0M0). Performance status was determined prospectively using the Eastern Cooperative Oncology Group (ECOG PS) criteria. We further classified patients into 1 of 6 risk groups (low-, intermediate-, or high-risk localized and low-, intermediate-, or high-risk metastatic) based on the previously described UCLA Integrated Staging System (UISS).⁵ Briefly, the UISS combines ECOG PS, TNM stage, and Fuhrman grade to stratify patients undergoing nephrectomy for nonmetastatic (N0M0) or metastatic RCC into 6 groups based on risk of death from RCC.

Statistical Method

The points of interest included temporal trends in presentation, management, and disease-specific survival (DSS). DSS was calculated from date of diagnosis to date of death or last contact. Patients dying from other causes were censored at time of death. Surviving patients were censored at last contact. Life tables were used to determine the proportions of surviving patients at specific time points and calculation of standard error.

Student *t* test and the chi-square test were used to compare continuous and categorical data, respectively. We estimated survival functions using the Kaplan-Meier method and performed univariate comparisons for disease-specific survival with the log-rank test. We then fit a multivariate Cox proportional hazard model to identify patient and/or tumor characteristics independently associated with DSS. Concordance statistics were calculated to evaluate the predictive accuracy of prognostic models. All statistical tests used a significance level of .05. The statistical software SPSS (SPSS Inc., Chicago, Ill) was used for analyses.

RESULTS

From 1989 to 2005, 1632 patients, 1099 (67%) male and 533 (33%) female, were treated for RCC at UCLA. The median age was 60 years (range, 11 years-94 years). ECOG PS was 0 in 787 (48%), 1 in 738 (45%), 2 in 93 (6%), and 3 in 14 patients (1%).

TABLE 1
Patient and Tumor Characteristics

	Pre-1991 (n=205)		1991-1995 (n=468)		1996-2000 (n=523)		2001-2005 (n=436)		Total (n=1632)		P
	n	%	n	%	n	%	n	%	n	%	
RCC	205	96.7	468	93.2	523	89.4	436	82.9	1632	89.4	<.001
Non-RCC benign	5	2.4	21	4.2	45	7.7	72	13.7	143	7.8	
Non-RCC malignant	2	0.9	13	2.6	17	2.9	18	3.4	50	2.7	
Detection											<.001
Incidental	77	37.6	138	29.5	162	31.0	193	44.3	570	34.9	
Symptomatic	128	62.4	330	70.5	361	69.0	243	55.7	1062	65.1	
TNM stage											<.001
I	56	27.3	109	23.3	163	31.2	177	40.6	505	30.9	
II	30	14.6	36	7.7	32	6.1	37	8.5	135	8.3	
III	77	37.6	87	18.6	77	14.7	75	17.2	316	19.4	
IV	42	20.5	236	50.4	251	48.0	147	33.7	676	41.4	
Fuhrman grade (n=1499)											<.001
G1	26	15.4	41	10.3	65	14.4	47	10.8	179	12.3	
G2	87	51.5	190	47.5	219	48.6	180	41.5	676	46.5	
G3	51	30.2	155	38.8	141	31.3	138	31.8	485	33.4	
G4	5	3.0	14	3.5	26	5.8	69	15.9	114	7.8	
Histological subtype (n=1555)											<.001
Clear cell	181	90.5	385	88.1	383	79.3	330	75.9	1279	82.3	
Papillary	13	6.5	35	8.0	62	12.8	62	14.3	172	11.1	
Chromophobe	1	0.5	10	2.3	26	5.4	31	7.1	68	4.4	
Collecting duct	0	0.0	1	0.2	2	0.4	1	0.2	4	0.3	
Unclassified	5	2.5	6	1.4	10	2.1	11	2.5	32	2.1	
Type of Nephrectomy											<.001
Partial	19	9.6	48	11.7	88	19.5	168	38.7	323	21.6	
Radical	178	90.4	361	88.3	364	80.5	266	61.3	1169	78.4	
Adrenalectomy	168	85.3	336	82.2	296	65.5	143	32.9	943	63.2	<.001

RCC indicates renal cell carcinoma.

Five hundred seventy (35%) patients were asymptomatic at the time of diagnosis, whereas 1062 patients (65%) presented with symptoms, most frequently gross hematuria (24%), flank pain (20%), weight loss >10% within 6 months (17%), abdominal pain (15%), back pain (10%), and abdominal mass (5%). The percentage of patients presenting with symptoms decreased with time ($P < .001$) (Table 1).

TNM Stage and Histological Type

TNM stage was I, II, III, and IV in 31%, 8%, 19%, and 41%, respectively. The percentage of patients with stage I RCC increased over time ($P < .001$). The proportion of patients treated for stage IV RCC at UCLA first increased but has decreased more recently. Fuhrman grade was G1, G2, G3, and G4 in 12%, 46%, 33%, and 8%, respectively. The most common histological type was clear-cell RCC (82%), which decreased during latter periods accompanied by a corresponding increase in the proportion of papillary and chromophobe RCC. In addition, the percentage

of patients undergoing nephrectomy for benign lesions increased over time.

UISS

One thousand four hundred fifty-three patients undergoing nephrectomy were eligible for risk-group assessment. Nine hundred eleven (63%) patients presented with nonmetastatic RCC, with 36% classified as low risk, 51% as intermediate risk, and 13% as high risk. Among 542 (37%) patients presenting with metastases, 14% were classified as low risk, 75% as intermediate risk, and 11% as high risk.

Management

Nephrectomy was performed in 1492 (91%) patients. Patients not undergoing nephrectomy had either unresectable metastatic RCC (96%) or poor performance status (4%). Radical nephrectomy was performed in 78% and partial nephrectomy in 22%. A limited or extended lymphadenectomy was performed in 58% and adrenalectomy in 63%. The proportion of patients undergoing radical (vs partial)

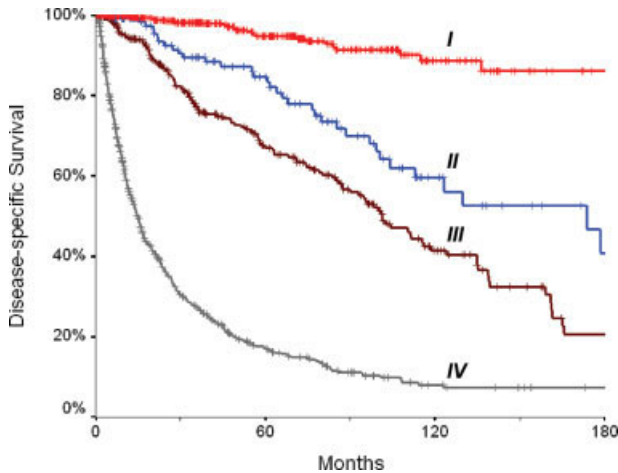


FIGURE 1. Disease-specific survival is shown according to TNM stage for all patients with renal cell carcinoma (N = 1632).

nephrectomy ($P < .001$) and concomitant adrenalectomy ($P < .001$) or lymphadenectomy ($P < .001$) decreased over time (Table 1).

The first-line treatment for 667 evaluable patients who presented with stage IV RCC consisted of nephrectomy and metastasectomy (3%), nephrectomy followed by immunotherapy (46%), nephrectomy alone (31%), immunotherapy alone (9%), or palliative care only (11%). Immunotherapy consisted of high-dose IL-2 (45%), IFN- α (7%), combination IL-2/IFN- α (34%), or other (14%).

Outcome

At the time of analysis, 41% of patients had died of RCC after a median of 18 months. The median follow-up for 960 (59%) censored patients was 38 months, and the 5-, 10-, and 15-year DSS rates for all patients were 55%, 40%, and 29%, respectively. The median survival was 82 months. Survival for each TNM stage is depicted in Figure 1.

Patients who underwent nephrectomy were analyzed according to UISS risk group (Table 2, Fig. 2). For patients with nonmetastatic RCC, 5-, 10-, and 15-year DSS rates were 85%, 68%, and 54%, respectively. For patients presenting with metastatic RCC, the 1-, 2-, 5-, 10-, and 15-year DSS rates were 59%, 41%, 20%, 10%, and 9%, respectively (median survival, 17 months). According to the UISS, 5-year DSS rates for low-, intermediate-, and high-risk localized RCC were 97%, 81%, and 62%, respectively. For patients with low-, intermediate-, and high-risk metastatic RCC at the time of nephrectomy, the 5-year DSS rates were 41%, 18%, and 8%. Among patients in the same UISS risk category, no difference in survival

TABLE 2
Disease-specific Survival According to University of California-Los Angeles Integrated Staging System Risk Group for Patients With Renal Cell Carcinoma Who Underwent Nephrectomy (n=1453)

Nonmetastatic or Metastatic	Risk Group	n	RCC Deaths	RCC Time	Survival Rate (% \pm SE)	Median Survival (mo \pm SE)
Nonmetastatic	Low risk	326	8	5 y	97 \pm 1	nr
				10 y	92 \pm 3	
				15 y	92 \pm 3	
	Intermediate risk	464	98	5 y	81 \pm 2	174 \pm 19
				10 y	61 \pm 4	
				15 y	45 \pm 6	
	High risk	121	45	5 y	62 \pm 5	95 \pm 20
				10 y	41 \pm 7	
				15 y	20 \pm 10	
Metastatic	Low risk	78	38	1 y	86 \pm 4	45 \pm 4
				5 y	41 \pm 7	
				10 y	31 \pm 8	
	Intermediate risk	406	302	1 y	59 \pm 3	17 \pm 2
				5 y	18 \pm 2	
				10 y	7 \pm 2	
	High risk	58	39	1 y	19 \pm 7	6 \pm 3
				5 y	8 \pm 5	
				10 y	0	

RCC indicates renal cell carcinoma; SE, standard error; nr, not reached.

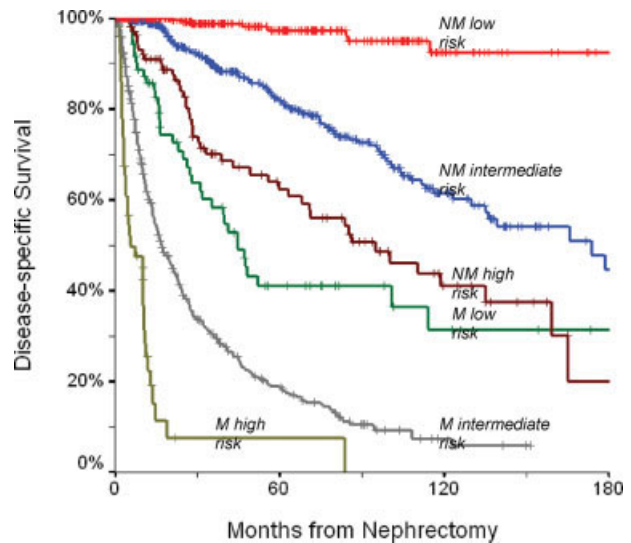


FIGURE 2. Disease-specific survival is shown according to the University of California-Los Angeles Integrated Staging System for all patients who underwent nephrectomy (n = 1453). M indicates metastatic; NM, nonmetastatic.

was seen when stratified according to year of nephrectomy.

Survival differed among patients with stage IV RCC with regard to first-line treatment. Nephrectomy

TABLE 3
Response to Immunotherapy According to First-Line Immunotherapy

Response	HD IL-2 n=212	IFN- α n=30	IL-2 and IFN- α n=157	Other n=54	Total n=453	Median Survival, mo
PD	110 (52%)	10 (33%)	55 (35%)	28 (52%)	203 (45%)	11.6
SD	51 (29%)	13 (43%)	55 (35%)	22 (41%)	151 (33%)	38.6
PR	25 (12%)	6 (20%)	33 (21%)	3 (6%)	67 (15%)	42.8
CR	16 (8%)	1 (3%)	14 (9%)	1 (2%)	32 (7%)	120+

HD indicates high dose; IL-2, interleukin-2; IFN- α , interferon-alpha; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

and metastasectomy provided the best DSS, with a median survival of 57 months. The median DSS for patients receiving nephrectomy and immunotherapy was 21 months, which was significantly better than the DSS for patients treated only with immunotherapy (10 months) or nephrectomy (11 months). Seventy-five patients received palliative care only, and their median survival time was 4 months. The overall response rate to immunotherapy was 22%: 15% partial (PR) and 7% complete (CR). The partial and complete response rates for high-dose IL-2, IFN- α , and combination IL-2/IFN- α were 12% and 8%, 20% and 3%, and 21% and 9%, respectively. An additional 33% experienced stable disease (SD), and 45% showed progression (PD). Median survival (in months) was 120+, 42.8, 38.6, and 11.6 for patients with CR, PR, SD, and PD, respectively (Table 3).

A multivariate Cox proportional hazards model was fit, and revealed ECOG PS, symptomatic presentation, TNM stage, Fuhrman grade, and nephrectomy as independent prognostic factors of survival. On the basis of concordance statistics, UISS predicted outcomes better than TNM staging.

DISCUSSION

It is imperative to evaluate the efficacy of new treatments in relation to an established benchmark. Individualized treatment approaches need to demonstrate comparable efficacy to what has been achieved with a uniform, aggressive approach in a general RCC patient population. We therefore performed a comprehensive analysis of 1632 patients treated for RCC with a consistent approach from 1989 to 2005 at a single-institution, RCC referral center. This report provides a description of the presentation, treatment, prognosis, and outcomes of patients with RCC through the cytokine era.

The last 20 years have seen substantial changes in the management of RCC. The increased utilization of imaging has led to an increased proportion of patients with incidentally detected tumors amenable to less

invasive surgical approaches. In addition, the surgical approach has become less radical, with the elimination of routine adrenalectomy and lymphadenectomy and the increased utilization of partial nephrectomy when feasible. At the same time, advances in our understanding of RCC genetics and molecular pathways have dramatically altered the medical management of patients with advanced disease.

Standard treatment for localized RCC for the past few decades has been radical nephrectomy. Long-term data regarding the efficacy for partial nephrectomy has demonstrated similar excellent oncologic results, and this may have become the new standard of care.⁶⁻⁸ Techniques such as cryotherapy and radiofrequency ablation have emerged as new techniques for the treatment of small renal masses. Despite excellent efficacy, these treatments have only short-term follow-up available for comparisons.^{9,10} Before considering these treatments similar, long-term data are necessary and must be compared with an existing benchmark.

Cytoreductive nephrectomy was not believed to improve survival before the immunotherapy era.¹¹ With the advent of immunotherapy, the role of nephrectomy for metastatic RCC was readdressed in 2 randomized studies demonstrating a survival advantage with surgery.^{12,13} Although nephrectomy followed by systemic therapy remains the standard approach for metastatic RCC, some patients with metastatic RCC can be cured by surgery alone. Although the number of these patients is small, metastasectomy provides favorable long-term survival rates, especially for patients with solitary lung metastases.¹⁴⁻¹⁷ These carefully selected patients with minimal metastatic disease should undergo nephrectomy and metastasectomy. The role of cytoreductive nephrectomy in conjunction with new targeted agents has not been established, however, and surgery remains the de facto standard of care in the absence of level I evidence.¹⁸

Immunotherapy has shown efficacy in treatment of metastatic RCC, with some durable remissions. The initial series with immunotherapy presented data demonstrating a high response rate to INF- α .^{19,20} However, later cohorts revealed response rates of only 10%, a slight improvement in survival, and rare complete responses.^{21,22} Consequently, IFN- α has not been approved by the FDA as monotherapy for treatment of RCC. High-dose IL-2, however, produces response rates of 15% to 30%, including some long-term remissions, and was approved for the treatment of metastatic RCC in 1992.²³⁻²⁶ In conjunction with cytoreductive nephrectomy, IL-2 may be more efficacious than IFN- α .²³ Although a large number of patients do not respond to IL-2, clinical

characteristics such as good performance status, clear cell histology, absence of nodes or sarcomatoid features, and limited disease burden may predict improved response.²⁶⁻²⁸ In addition, high tumor expression of carbonic anhydrase IX may be a biomarker associated with enhanced response to IL-2 and improved survival.^{29,30}

The FDA has recently approved 3 agents for the treatment of advanced RCC: sorafenib, sunitinib, and temsirolimus. These new agents target specific molecular pathways in neoplastic cells and have been replacing IL-2 as the first-line treatment for the majority of patients, as clinical responses are observed in a large number of patients. No comparative trials have evaluated the new targeted agents against IL-2 or the safety of cytokines after tyrosine kinase inhibitor failure. With the new agents, complete responses are rare, and most patients die of their disease.³¹⁻³³ Many new trials have been initiated to compare combinations of these agents with immunotherapy, but none compare the efficacy against the previous standard of care, IL-2. Our data clearly demonstrate that long-term survival with cytokines is achievable. In the absence of phase III trials, the long-term efficacy of sunitinib, sorafenib, and temsirolimus should be viewed in context of an established benchmark of the previous era.

The combination of cytokines and angiogenesis inhibitors holds significant promise. Recently, Ryan et al showed that combination sorafenib and IFN- α produced a response rate of 19%, which was greater than expected with either sorafenib or IFN- α alone.^{33,34} In addition, Escudier et al showed a response rate of 31% for the combination of bevacizumab and IFN- α , much higher than the response rate of 13% for IFN- α alone.³⁵ Other clinical trials have been initiated to assess the combination of the new agents with IL-2.

As new regimens for RCC have been developed, risk stratification based on clinical and pathologic variables has grown in importance. Although TNM stage is a strong tool for prognostication, it does not reflect the full heterogeneity of RCC.³⁶ At our institution, we have combined TNM stage, Fuhrman grade, and ECOG PS into the UISS. This system stratifies patients with localized or metastatic disease into low-, intermediate-, and high-risk groups based on risk of death from RCC and has been externally validated by other large cohorts,³⁷ and we present our series with longer follow-up. Interestingly, the high-risk localized and low-risk metastatic patients appeared to have similar prognoses when observed up to 15 years. These patients identified with high-risk localized disease are ideal candidates for adjuvant clinical trials.

In our study, despite excellent outcomes noted in low-risk localized and metastatic subjects, the overall long-term survival of patients with RCC is fair. The 5-, 10-, and 15-year DSS rates are 55%, 40%, and 29%, respectively. Patients undergoing nephrectomy for localized RCC, conversely, show relatively good survival. Patients with stage I RCC (T1N0M0) have the most favorable prognosis, with only 11% and 14% of the patients suffering RCC-specific death by 10 and 15 years, respectively. Patients with stage II RCC (T2N0M0) have somewhat diminished 10- and 15-year DSS rates of 60% and 41%, respectively, whereas patients with stage III RCC have 10- and 15-year DSS rates of only 42% and 21%. These data indicate that nephrectomy alone is not sufficient to cure all patients with clinically localized RCC and that effective adjuvant therapies are needed for those with high-risk disease.

Several limitations must be addressed regarding our analysis and inference that the data qualify as a benchmark. This is a single-institutional study from a major referral center of advanced disease. However, although this may be a limitation, the single-center experience is also a strength in that we have followed a consistent therapeutic approach of aggressive surgical resection and immunotherapy. However, the surgical strategy, although consistently aggressive upfront resection, has changed over time, as evidenced by our decreased rates of adrenalectomy and lymph node dissection. In addition, the use of our data as a benchmark for ablative techniques may be difficult using the UISS, as a pathologic specimen is not available; however, it is anticipated that the majority of these patients would likely be considered low-risk localized.

CONCLUSIONS

The medical and surgical management of RCC is evolving as the understanding of the disease improves. We present long-term, single-institution data to provide a thorough understanding of the results that have been achieved until now using a consistent, aggressive approach for localized and metastatic disease. These results demonstrate excellent surgical outcomes in low-risk localized patients, the need for effective adjuvant therapies in high-risk localized patients, and impressive long-term survival in metastatic patients that respond to cytokine therapy. These results may serve as a benchmark to compare the results of emerging medical and surgical treatments. With longer follow-up, the UISS continues to assist with the identification of appropriate patients at risk for death from RCC for novel adjuvant therapies.

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