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INVESTIGATIVE AND CLINICAL UROLOGY
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Current status of robotic partial nephrectomy in Japan

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The safety and efficacy of robot-assisted partial nephrectomy (RAPN) has been reported in Western countries. However, there are no similar reported studies of RAPN in Japan. Although common medical services are covered by public health insurance in Japan, RAPN had not been approved as a listed treatment for public insurance. We conducted a prospective clinical trial to confirm the efficacy and safety of RAPN in Japan. The aim of the present review article is to describe current status of RAPN in Japan and to introduce a part of clinical results obtained from the clinical trial. Based on the favorable results obtained in this clinical trial, RAPN was approved in April 2016 by the Japanese Ministry of Health, Labour and Welfare to be covered by public health insurance. This change allows access to RAPN to everyone in Japan, regardless of wealth. The RAPN techniques used in Japan are also reviewed.

Keywords: Health insurance; Minimally invasive surgical procedures; Nephrectomy; Renal cell carcinoma

INTRODUCTION

Renal cell carcinoma (RCC), which accounts for 2% to 3% of all malignant neoplasms in adults, is one of the most lethal of the common urologic cancers [1,2]. RCCs arise from the proximal tubules or more distal components of the nephron. They account for about 85% of all malignant renal neoplasms [3,4]. In Japan, the total number of patients suffering from malignancies of the kidney in 2011 was approximately 25,000 (19,000 males and 6,000 females). This is an increase from 1996, when the number of individuals with renal malignancies was 15,000 (10,000 males and 5,000 females). Kidney cancer affects more men than women. In 2013 the total number of fatalities from RCC was 4,439 (3,032 males and 1,407 females); approximately 90% of these patients were over 60 years of age. Although early-stage RCC shows no signs, various symptoms arise as the cancer progresses, such as macroscopic hematuria, pain or palpable masses. With advances in diagnostic imaging, many asymptomatic RCCs have been discovered incidentally in their early stages with ultrasonography or computed tomography [5,6]. The 5-year survival rate of RCC is approximately 70%. Reported survival is near 90% in stage I, 70% in stage II, 50% in stage III, and 20% in stage IV [5]. In recent years molecular targeted therapies for RCC have been developed. However, treatment response to these therapies has been limited for advanced or metastatic RCC. Currently the most effective treatment modality for non-metastatic RCC is surgical resection.

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SURGICAL TREATMENT FOR CLINICAL T1 RCC

Traditionally the standard surgical treatment for clinical stage T1 RCC has been radical nephrectomy, in the absence of concerns about renal function on the contralateral side. Partial nephrectomy was performed only in cases with complicating factors, such as solitary kidney, renal insufficiency, or bilateral RCC. Partial nephrectomy, however, has become more commonly performed for kidney tumors 4 cm or less in diameter, even in patients with normal contralateral kidney function [7]. The long-term oncological outcomes of partial nephrectomy through laparoscopic or open surgery are excellent and hardly differ from those of radical nephrectomy. The cancer-specific 5-year survival rate after partial nephrectomy in patients with RCC is 89% to 96% [8-11]. There are other reasons for this change in treatment approach: approximately 10% of small tumors are benign, and with radical nephrectomy there is a risk of deterioration in renal function resulting from hyperfiltration in the single kidney postoperatively.

In 2011 the Japanese Urological Association published a treatment guideline for kidney cancer [6]. The guideline recommends partial nephrectomy for T1a tumors (≤4 cm) as standard of care, because the procedure achieves equivalent cancer control and has good results in preserving renal function, compared with radical nephrectomy. However, there have been few reports on cancer control and postoperative renal function after partial nephrectomy for tumors greater than 4 cm in diameter. Therefore, it is too early to judge whether partial nephrectomy works well in the long term. In contrast, the 2014 National Comprehensive Cancer Network guideline recommends partial nephrectomy or nephrectomy as standard surgical treatment for tumors between 4 and 7 cm in diameter [12], because they achieve equivalent cancer control [13,14]. The European Association of Urology guidelines for kidney cancer also recommend partial nephrectomy for T1 renal tumors (<7 cm) [15]. As these guidelines show, partial nephrectomy through laparoscopic surgery or open surgery controls cT1 kidney cancers as well as radical nephrectomy and is associated with a good long-term prognosis for renal function. Robot-assisted partial nephrectomy (RAPN) for cT1 kidney cancer patients may also be useful. Choi et al. [16] reported that RAPN is preferable to laparoscopic partial nephrectomy (LPN), with a lower conversion rate to radical nephrectomy, favorable renal function as indicated by 1estimated glomerular filtration rate (eGFR), shorter length of hospital stay, and shorter warm ischemia time.

PUBLIC HEALTH INSURANCE AND ADVANCED MEDICAL TREATMENT IN JAPAN

Every person in Japan is covered by some form of public insurance and thus can receive necessary medical services at low cost by paying insurance premiums and co-payments (10% to 30% of charges). In addition, the Japanese health insurance system offers "free access," which means that everyone can receive medical services at any medical institution nationwide. People are protected by the universal health insurance system, in which everyone can receive high-quality medical services at a predetermined cost, regardless of their income or type of work. However, because of increases in national medical expenditure, the financial management of universal health care has been increasingly challenging in recent years and thus measures to curtail this trend have become an urgent issue.

A system of mixed medical services, with both publically and privately funded services, is not accepted in Japan. Therefore, having a treatment recognized by insurance is an important step for that treatment to spread to the public. To be covered by insurance, the safety and validity of a treatment need to be demonstrated in a prospective clinical trial in Japan. The only robot-assisted surgery covered by medical services in Japan until April 2016 was robot-assisted radical prostatectomy.

Advanced medical treatment in Japan means accepting the combination of advanced medicine and covered medical services. Treatments need to be evaluated to determine whether they should be covered by public insurance in the future. The goals of this approach are securing public safety, preventing increased costs for the patient, extending patients' choices, and improving convenience for the public.

CLINICAL TRIAL OF RAPN IN JAPAN

To evaluate whether RAPN should be covered by public insurance in Japan, we conducted a multi-institutional, prospective, nonrandomized clinical trial to assess its efficacy and safety. RAPN is an innovative technology aimed at cancer control, postoperative renal function preservation, and minimized invasiveness. The forceps used on the robotic arm in RAPN are highly flexible compared with those used in conventional laparoscopic surgery. With the removal of the tremor of the surgeon, minute surgery is accurately reproduced. This enables not only precise tumor excision in a limited space but also dissection and suturing of fine vessels and urinary tracts. This approach also minimizes bleeding and tissue damage and reduces the

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ischemic time. Thus robot-assisted laparoscopic surgery is expected to be advantageous for cancer control and renal function preservation. In highly challenging cases such as hilar tumors or endophytic tumors, which are considered very difficult to resect with a laparoscopic approach, RAPN enables tumor resection equivalent to open surgery, with minimal invasion. Considering these facts, radical tumor resection and preservation of renal function were chosen as the primary endpoints of this trial. We defined radical tumor resection and preservation of renal function as: (1) no conversion to laparoscopic or open surgery, (2) negative surgical margins, and (3) warm ischemic time under 25 minutes.

Before this trial started, about 75 RAPNs had been performed in Japan (as of the end of December 2012, according to a survey by the Japanese Society of Endourology). From 2011 to January 2013 Kobe University Hospital performed RAPN in 26 patients whose kidney tumors were surgically removable and who wanted to receive this surgery at their own expense. Our study revealed that RAPN resulted in less blood loss, no extension of ischemic time, and good postoperative renal function compared with conventional LPN and open partial nephrectomy (OPN). Although it takes time to master the techniques of RAPN, we believe that the learning curve is shorter than that for laparoscopic surgery. The spread of RAPN, with its low invasiveness, high cancer cure rates, and simultaneous preservation of renal function, will contribute to the radical curability of cancer in patients with localized renal cancer, will help avoid postoperative chronic kidney disease (CKD) and will provide good long-term prognosis, thus improving public health.

1. Effectiveness

The endpoint of effectiveness (both renal function preservation and curative resection) was compared with the "historical control," which was LPN performed at multiple institutions in Japan (541 institutions, 1,375 cases). The achievement rate of both renal function preservation and radical resection, which were the primary endpoints of the present trial, was 91.3% (95% confidence interval, 84.1–95.9). This value significantly exceeded the threshold level (23.3%) determined beforehand ($p<0.001$).

Renal ischemic time under 25 minutes is an important indicator of renal function preservation. According to the existing research, patients with less than 25 minutes of renal ischemic time have significantly less impaired renal function 6 months postoperatively and significantly lower incidence of CKD (CKD stage IV; <30% eGFR), compared with those having ischemic time over 25 minutes. A multi-institutional observational study used as a historical control suggested that with LPN the renal ischemia time was 25 minutes or less in 25% of patients at most. When planning this project, we hypothesized that increasing the percentage of patients with renal ischemic time of 25 minutes or less by 5% to 10% (corresponding to the number needed to treat=10–20) with the RAPN protocol would be clinically significant. To achieve a significant change in medical economics it was determined that an increase of 15% would be required, taking into account the incremental costs related to the introduction of this novel treatment. Accordingly, the expected percentage of RAPN patients with renal ischemic time within 25 minutes was set at 40%. Additionally we anticipated that approximately 37.2% of patients would achieve the primary endpoint of both renal function preservation and curative resection, taking into account that in some cases RAPN would need to be converted into conventional laparoscopic or open surgery, or would have positive surgical margins. In the present prospective trial, 91.3% of patients achieved both renal function preservation and curative resection, far exceeding our expectations.

Thus, the results of this trial revealed good efficacy with RAPN, compared with the historical control. The historical control used to set the basis of threshold was reported in 2012 based on data from a multi-institutional observational study on LPN (54 institutions, 1,375 cases) conducted in Japan from 1998 to 2008 [17]. That study reported that ischemic time in laparoscopic surgery had decreased in recent years. Therefore, when comparing the results of the two studies, it may be necessary to consider differences in the technical maturity between the present and the time when the multi-institutional joint observational study on LPN was performed. However, even if this difference in technical maturity is taken into consideration, the results of the present study show an obvious advantage of RAPN.

When ischemic time alone was examined, we found a clear shortening compared with historical controls (mean±standard deviation: 19.0±6.4 minutes for RAPN, 41±19 minutes for LPN). There were no positive surgical margins. The reported rates of positive surgical margins with LPN were 0% to 4% [18-24]; the rate of the historical control was 1.7%. These values indicate the effectiveness of RAPN for cancer control. These excellent results were due to the features of a robot-assisted approach, such as precise 3-dimensional visualization, highly flexible forceps with 7 degrees of freedom, and the correction of tremor. Although it is difficult to perform LPN in some cases, depending on conditions such as tumor diameter or location even in the case of T1 tumors, RAPN had good results, with no big difference in achievement rate regardless of the diameter or location of the tumor.

When an analysis object group (full analysis set) was evaluated with the R.E.N.A.L. nephrometry score, which is an index of the difficulty of partial nephrectomy mainly based on tumor location and diameter [25], we found 38 low-complexity cases (36.9%), 62 intermediate-complexity cases (60.2%) and 3 high-complexity cases (2.9%). These percentages are comparable to the patient composition in past reports (48 low-score cases [44%], 57 intermediate-score cases [53%], and 3 high-score cases [3%]), which reveals that arbitrary patient selection was not performed. In addition, although we have only short-term results at present, there was no report of death, and the probability of survival for 90 days after surgery was 100.0%. A comparison of outcomes in past studies and in the present trial is shown in Table 1. Longer average length of hospital stay observed in the present study was due to Japanese public health insurance system; burden of hospitalization cost is light in Japan. Observation is ongoing in this trial.

The positive surgical margins rate in this study was 0%. Compared with the results of the historical control (1.7%), this result suggests the effectiveness of RAPN. With respect to the tumor location, the protocol treatment was performed evenly in all locations and the achievement rate of the primary endpoint was as high as 87.5%–93.7%, irrespective of tumor location. As mentioned above, in cancer control (negative margin rate) and renal function preservation (ischemic time within 25 minutes), RAPN achieved better results than conventional laparoscopic surgery. Comparison of surgical efficacy in reported and present studies were shown in Table 1. Achievement of primary outcome according to background characteristic factors was shown in Table 2.

2. Safety of RAPN in Japanese trial

The operative time (mean±standard deviation) in this trial was 3.89±1.10 hours; blood loss was 60.78±94.50 mL. Compared with clinical studies on RAPN performed in other countries and those on LPN in Japan, surgery time was almost the same (historical control, 4.32±1.52 hours). Blood loss, however, was less with RAPN than with the conventional surgical procedure (210±426 mL for historical control). Among safety analysis object groups, the rate of adverse events during the operation was 53.3% (56 of 105), which was high compared with the rate of postoperative complications (10.6% [11 of 104]).

The serious adverse event in this study was postoperative renal arterial aneurysm (9 cases). Renal artery aneurysm is a known complication after OPN or LPN. When the renal artery is damaged during suturing after tumor resection, or if insufficient hemostasis in the thin vulnerable renal artery results in rebleeding when blood flow increases after surgery, hematoma around an artery in resected defects can form a pseudoaneurysm. The main sign of pseudoaneurysm is macrohematuria. In this study we examined the relationships between pseudoaneurysm and sex, age, body mass index, anamnesis, tumor location, and Renal Nephrometry Score. No correlation was found with any of these factors. Three cases of aneurysm, however, were reported from a single institution. Those cases might have resulted from inexperience of the surgeon.

The reported probability of symptomatic aneurysm with signs such as macrohematuria is 0.4%–4.2% in OPN, 1.0%–12.0% in LPN, and 0.2%–10.2% in RAPN. These numbers, however, vary depending on the report [26-32]. In one study in Japan, asymptomatic renal pseudoaneurysm was detected with enhanced computed tomography in 17 out of 117 early postoperative patients (15%) after RAPN [33]. According to that report, arterial embolization was performed in 1 case that had bleeding and in 11 cases to prevent future bleeding (size≥4 mm), though they were asymptomatic. The other 5 cases were followed up and regressed naturally. Therefore, even though pseudoaneurysm can occur, small pseudoaneurysms generally follow a course of natural regression. The number that could have become symptomatic and caused clinical problems was 12. Therefore the estimated incidence of symptomatic aneurysm is 10.2% (12 of 117). In the present study pseudoaneurysm occurred in 8 cases (7.6%), indicating that renal pseudoaneurysm did not occur frequently.

The preferred treatment of pseudoaneurysm is coil embolization via arterial catheter because of its low invasiveness and high success rate. However, invasive laparotomy is sometimes required [26,44]. All cases of pseudoaneurysm in the present study were mild and recovered with minimally invasive catheter coil embolization. This is because the artery that caused rebleeding was quite small and hemostasis of the main arteries was ensured with the precise manipulation of the robot-assisted approach. Pseudoaneurysm is an adverse event that can occur after RAPN; this possible complication must be kept in mind during postoperative patient care, and must be treated quickly and appropriately when it does occur.

Another complication of partial nephrectomy is urine leakage. When open tumor resection of the renal pelvis or calyx is performed, urine can leak into the abdominal cavity

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Table 1. Comparison of surgical efficacy in reported and present studies

Study	No. of patients		Mean WIT (min)		Mean operative time (min)		Mean EBL (mL)		Mean LOS (d)		PSM (n)	
	RPN (n=1,134)	LPN (n=978)	RPN	LPN	RPN	LPN	RPN	LPN	RPN	LPN	RPN	LPN
Alemozaffar et al. [34]	25	25	-	-	232	224	178	154	2.5	2.7	-	-
Masson-Lecomte et al. [18]	220	45	20.4	24.3	168	200	245	268	5.5	6.8	18	2
Williams et al. [35]	27	59	18.5	28	-	-	-	-	-	-	-	-
Ellison et al. [19]	108	108	26.8	28.2	215	162	368	400	2.7	2.2	6	6
Hyams et al. [36]	20	20	-	-	231	259	-	-	2.3	2.8	-	-
Long et al. [20]	199	182	22.4	23.2	197	241	280	325	3.5	3.8	2	2
Lucas et al. [21]	27	15	25	29.5	190	195	100	100	2	3	1	0
Lavery et al. [22]	20	18	22.7	24.7	189	180	93	140	2.6	2.9	0	0
Pierorazio et al. [37]	48	102	-	-	-	-	-	-	-	-	2	1
Seo et al. [23]	13	14	35.3	36.4	153	118	284	264	6.2	5.3	0	0
Boger et al. [38]	13	46	-	-	168	171	100	100	2	2	-	-
Choi et al. [39]	13	31	35.5	32.4	296	286	289	205	-	-	-	-
Haber et al. [24]	75	75	18.2	20.3	200	197	323	222	4.2	4.1	0	0
Benway et al. [40]	129	118	19.7	28.4	189	174	155	196	2.4	2.7	-	-
Jeong et al. [41]	31	26	20.9	17.2	170	139	198	208	5.2	5.3	-	-
Kural et al. [42]	11	20	-	-	185	226	286	388	3.9	4.3	5	1
Wang et al. [43]	40	62	19	25	140	156	136	173	2.5	2.9	1	1
Aron et al. [44]	12	12	23	22	242	256	329	300	4.7	4.4	1	-
Present study	103		19.0		170		61		10.0		0	

WIT, warm ischemia time; EBL, estimated blood loss; LOS, length of stay; PSM, positive surgical margin; RPN, robot-assisted partial nephrectomy; LPN, laparoscopic partial nephrectomy.

Table 2. Achievement of primary outcome according to background characteristic factors

Factor	No. of cases	Achievement both of renal functional preservation and surgical margin negative, No. of cases (%)
Overall	103	94 (91.3)
Age (y)		
<30	0	0 (0)
≥30, <40	6	5 (83.3)
≥40, <50	10	9 (90.0)
≥50, <60	26	23 (88.5)
≥60, <70	39	39 (100)
≥70	22	18 (81.8)
Sex		
Male	77	71 (92.2)
Female	26	23 (88.5)
Previous abdominal surgery		
Absent	83	77 (92.8)
Present	20	17 (85.0)
Body mass index (kg/m^2)		
<18.5	6	6 (100)
≥18.5, <25	66	60 (90.9)
≥25, <30	25	23 (92.0)
≥30, <35	6	5 (83.3)
≥35	0	0 (0)
R.E.N.A.L. nephrometry score		
High (≥10, ≤12)	3	2 (66.7)
Intermediate (≥7, ≤9)	62	56 (90.3)
Low (≥4, ≤6)	38	36 (94.7)
Side		
Right	46	43 (93.5)
Left	57	51 (89.5)
ASA physical status		
I	48	41 (85.4)
II	52	52 (100)
III	1	1 (100)
IV or more	0	0 (0)

ASA, American Society of Anesthesiologists.

from the suture line, and can cause clinically significant effects. In the historical control, urine leakage was found in 2.5% of all patients and in 1.7% of those who were grade 3 or higher. There were no reports of urine leakage in our trial. This is a point that should be noted, because it shows the advantages of robotic assistance. Robotic assistance allows easy and accurate suturing compared with a conventional laparoscopic approach, enables surgery to be performed with an enlarged field of view, and provides secure suturing in the case of open resection of the renal pelvis or calyx.

Other defined adverse events in this trial were bleeding, venous thrombosis, pulmonary embolism, wound infection, multiorgan damage, renal hypertension, wound infection, and acute renal dysfunction. The events reported during the observation period were 29 cases of bleeding (27.6%) and 3 of acute renal dysfunction (2.9%). In the patients with acute renal dysfunction, the serum creatinine level rose transiently, with a decrease in eGFR. Each of these cases recovered without becoming critical. The frequency and outcome of bleeding and acute renal dysfunction were not different from those of other treatments in this domain. The rate of adverse events was evaluated according to background factors. No factors correlating with adverse events were identified, although the number of examples of each background factor varied. The adverse events that occurred most frequently in the perioperative period were wound complications (31 cases), macrohematuria (22 cases), and fever (13 cases), all of which occur frequently with any

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surgical procedure.

eGFR, which is an indicator of renal function, never fell below 60 mL/min/1.73m^2 in any patient after protocol treatment and showed recovery with passage of time, indicating preservation of renal function. Thus RAPN appears to effectively preserve renal function. Moreover, in 91.3% of cases resection and suturing were performed within 25 minutes, which is considered the cutoff for ideal ischemic time. Minimizing renal ischemia time leads to long-term preservation of renal function and to the control of progression to CKD, contributing significantly to the improvement in patients' quality of life.

Among safety analysis object groups, 146 postoperative adverse events were reported in 56 patients, yielding a complication rate of 53.3% (56 out of 105 cases). The adverse event that occurred most frequently in the perioperative period was wound complications (31 cases, 29.5%), followed by macroscopic hematuria (22 cases, 21.0%) and fever (13 cases, 12.4%). The perioperative critical adverse event that occurred most frequently in this trial was symptomatic pseudoaneurysm in 8 cases (7.6%). It is known, however, that renal pseudoaneurysm sometimes occurs after partial nephrectomy. The incidence of pseudoaneurysm in this trial was not particularly high. Comparison of safety outcomes of previous and current studies were shown in Table 3.

3. Conclusions of the clinical trial

Fourteen Japanese institutions participated in this trial. The console surgeons were required to have experienced more than 10 cases of RAPN. Furthermore, they were required to meet the following conditions: experience of more than 10 cases of laparoscopic or open partial nephrectomy, more than 30 cases of laparoscopic or open radical nephrectomy, more than 20 cases of robot-assisted radical prostatectomy, and approved as laparoscopic surgeon by the Japanese Society of Endourology. Although the experience of 10 cases of RAPN cannot be considered vast experience, 91.3% of patients attained the primary endpoint.

Although mastering this technology takes some training and technical experience, as with open surgery or conventional laparoscopy, it is possible to gain the skills in a short period of time. Accordingly RAPN is considered to be a useful surgical technique to minimize invasiveness, provide radical cancer curability and preserve renal function. Surgery for renal hilar tumors and full endophytic-type tumors has been considered difficult with a conventional laparoscopic approach. In the future, however, a robotic approach will make it possible to remove such tumors with minimal invasiveness, which has previously been attained

Table 3. Comparison of safety outcomes of previous and current studies

Study	No. of patients		Conversion rate to open surgery		Conversion ratio to radical surgery		Complication CD I–II (n)		Complication CD III–V (n)	
	RPN (n=1,152)	LPN (n=1,088)	RPN	LPN	RPN	LPN	RPN	LPN	RPN	LPN
Masson-Lecomte et al. [18]	220	45	7	5	–	–	24	7	21	7
Williams et al. [35]	27	59	-	-	-	-	5	12	-	-
Ellison et al. [19]	108	108	-	-	-	-	40	33	8	7
Long et al. [20]	199	182	-	-	2	21	53	47	11	9
Lucas et al. [21]	27	15	-	-	1	0	3	1	1	0
Haber et al. [24]	75	75	0	1	-	-	10	9	2	1
Benway et al. [40]	129	118	2	1	-	-	-	-	-	-
Jeong et al. [41]	31	26	-	-	1	0	-	-	-	-
Kural et al. [42]	11	20	0	2	-	-	-	-	-	-
Wang et al. [43]	40	62	1	2	-	-	-	-	-	-
Aron et al. [44]	12	12	-	-	-	-	-	-	-	-
Present study	103	-	0	-	0	-	56	-	8	-

CD, Clavien-Dindo classification; RPN, robot-assisted partial nephrectomy; LPN, laparoscopic partial nephrectomy.

only through open surgery.

This study found that RAPN achieves minimal invasiveness, good cancer control, and renal function preservation, indicating that this technology will improve the surgical treatment of patients with nonmetastatic RCC, will decrease the occurrence of postoperative CKD, and will improve long-term prognosis. RAPN will contribute considerably to the public health, which will lead to reduced medical expenses.

RAPN LISTED ON JAPANESE PUBLIC HEALTH INSURANCE AND FUTURE PERSPECTIVE

Based on the above trial results, RAPN was approved by the Japanese Ministry of Health, Labour and Welfare in April 2016 to be covered by public health insurance in Japan. This inclusion allows any person in Japan to receive RAPN, regardless of wealth. Further clinical trials involving complex renal tumors are warranted.

CONFLICTS OF INTEREST

The authors claim no conflicts of interest.

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