

# Diagnosis of Prostate Cancer: Repeated Transrectal Prostate Biopsy or Transurethral Resection

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**Background:** Transrectal ultrasound-guided biopsy of the prostate is the major method by which prostate cancer is diagnosed. However, many patients might be overlooked with the initial biopsy. Not uncommonly, patients need repeated biopsies when they continue to exhibit suspicious clinical signs. This may cause psychological stress to both patients and doctors. The purpose of this study was to determine how many repeat transrectal biopsies are adequate for prostate cancer detection and when to switch to transurethral resection.

**Methods:** We retrospectively studied a cohort of 2,996 patients who had undergone prostate biopsy. If the biopsy specimen was negative for malignancy, patients were given the choice of either being managed with observation or undergoing transurethral resection of the prostate (TURP) if indicated. If there was a high suspicion of cancer, patients were advised to undergo additional biopsies. The primary endpoint of this study was a diagnosis of cancer.

**Results:** The cancer detection rate was 22.9% (685 of 2,996 patients) in specimens taken during the first transrectal biopsy, 8.7% in those taken during the second biopsy (32 of 336 patients), and 6.1% in those taken during the third biopsy (6 of 98 patients). The cancer detection rate of TURP after 1 negative biopsy result was 9.3% (35 of 375 patients), and that after 2 negative biopsy results was 17.1% (6 of 35 patients). TURP-derived specimens that were pathologically diagnosed as malignant had lower Gleason grade on average, no matter how many repeat biopsies there were in patients whose previous transrectal biopsy specimens were negative for malignancy ( $p=0.002$  for 2 negative biopsy results and  $p=0.007$  for 3 negative biopsy results).

**Conclusion:** The chance of detecting malignancy beyond a third transrectal biopsy procedure is low. TURP, therefore, might be an alternative procedure for obtaining tissue for pathologic diagnosis, especially in patients with rising prostate-specific antigen levels and comorbid illnesses such as obstructive symptoms. [*J Chin Med Assoc* 2008;71(9):448–454]

**Key Words:** biopsy, prostatic neoplasms, prostate-specific antigen, transurethral resection of the prostate

## Introduction

Serum prostate-specific antigen (PSA) assay is broadly used to screen for prostate cancer in men over the age of 50 years. PSA level  $>4$  ng/mL is an indication for prostate biopsy. However, about 20–30% of cancers might not be detected in biopsy specimens that are taken during the initial biopsy.<sup>1</sup>

Many have tried to improve the detection rate of prostate cancer from prostate biopsy. For example, Gore et al suggested a 10-core biopsy strategy.<sup>2</sup> This

protocol has improved the cancer detection rate by 25.5% without significant morbidity.<sup>3</sup> Other studies have reported that the cancer detection rate can be significantly improved by lowering the PSA cut-off value to 2.5 ng/mL, or by evaluating the ratio of free PSA to total PSA.<sup>4</sup> However, many patients with high suspicion of cancer are suggested to have repeat biopsies.<sup>5</sup> Urologists are commonly consulted about how many biopsies are adequate to confirm or rule out a diagnosis of prostate cancer, especially in men with rising PSA levels.



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E-mail: jshuang@vghtpe.gov.tw • Received: June 25, 2008 • Accepted: July 29, 2008

The present study was performed to investigate the natural history of a cohort of patients who had undergone at least 1 transrectal ultrasound-guided (TRUS) prostate biopsy. The patients chose to have repeated TRUS biopsy or transurethral resection of the prostate (TURP) or just a follow-up policy at office visits. Among these patients, we compared the characteristics of biopsy methods in cancer detection rate.

## Methods

We retrospectively reviewed 2,996 consecutive cases who had undergone TRUS biopsy in our institution between January 2000 and May 2005. Indications for biopsy included serum PSA > 4.0 ng/mL or abnormal digital rectal examination (DRE).

All transrectal biopsies were performed with a spring-lodged autonomic biopsy gun equipped with an 18-gauge Tru-Cut biopsy needle (C.R. Bard Inc., Covington, USA; length of sample notch: 1.9 cm), under the guidance of an ultrasound scanner (7 MHz biplane-probe; B-K Medical A/S, Herlev, Denmark). Specimens were taken by the 6-core biopsy protocol, and suspected nodules were taken separately under finger-guided biopsy.

Prostate volume was calculated by the ellipsoid prostate formula (width × length × height × 0.52). PSA density was calculated by dividing total PSA value by prostate volume. When the biopsy results were negative for malignancy, patients were advised to have their PSA level measured at follow-up 3 months later, and if PSA remained elevated, repeat biopsy was suggested. Patients with voiding difficulty, evaluated by the International Prostate Symptom Score (IPSS) and urine flow rates, were advised to undergo TURP. The TURP procedure was comprised of removing the adenoma from the transitional zone and the resection plane advanced to the surgical capsule.

In patients without obstructive symptoms, PSA values were regularly measured at 3- to 6-month intervals. If any abnormality (either change in PSA or DRE) was encountered, patients were recommended to have another biopsy or TURP. The endpoint of the study was defined as: (1) when a diagnosis of cancer was made, by either TRUS biopsy or TURP; (2) when TURP was completed.

All statistical analyses were performed using SPSS version 11.0.1 (SPSS Inc., Chicago, IL, USA) for Windows. Comparison of the cumulative detection rate of prostate cancer diagnosed by TRUS biopsy and TURP was obtained using the Kaplan-Meier method. The differences in newly diagnostic detection rate of each

session between TRUS biopsy and TURP were evaluated using the  $\chi^2$  test. Mann-Whitney U test was used to evaluate the significance of the differences between these 2 groups in the second and third sessions.

## Results

The median age of the 2,996 men was 74 years (range, 24–99 years). Stratifying by indications for biopsy, we found that 1,035 (34.5%) had PSA > 10 ng/mL, 1,549 (51.7%) had PSA between 4 and 10 ng/mL, and 412 (13.8%) had PSA < 4 ng/mL but with suspicious DRE.

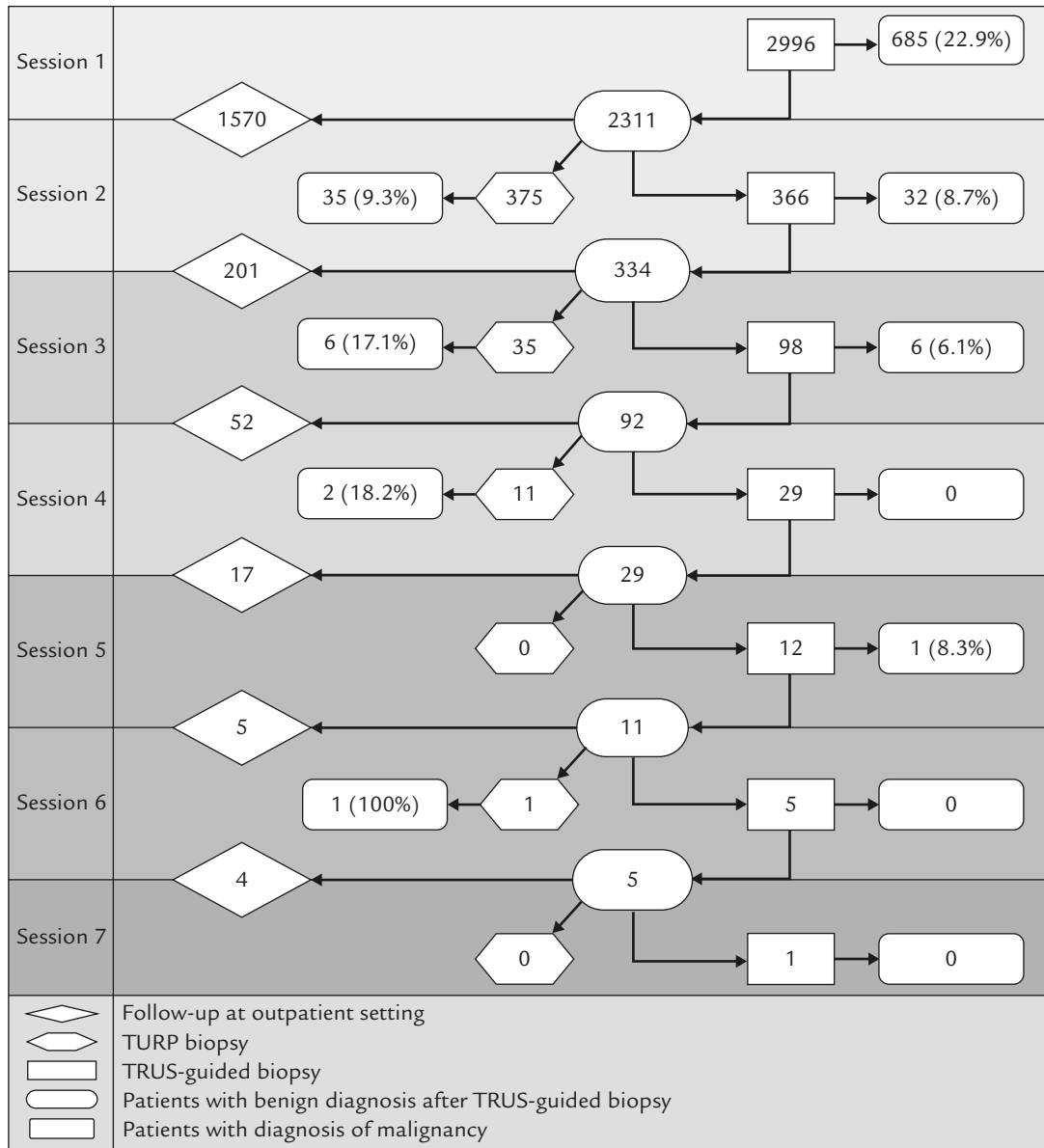
A total of 768 (25.6% of total included cases) patients were diagnosed to have prostate cancer during the study period. The cumulative prostate cancer detection rate by TRUS biopsy was 24.2% (724 of 2,996). The individual detection rates in each individual TRUS biopsy session were 22.9% (685 of 2,996) in the first session, 8.7% (32 of 366) in the second session, 6.1% (6 of 98) in the third, 0% (0 of 29) in the fourth, 8.3% (1 of 12) in the fifth, 0% (0 of 5) in the sixth, and 0% (0 of 1) in the seventh (Figure 1).

In patients who received TURP, the cumulative cancer detection rate was 10.4% (44 of 422). The individual detection rate was 9.3% (35 of 375) in the second session, 17.1% (6 of 35) in the third session, 18.2% (2 of 11) in the fourth, 0% (0 of 0) in the fifth, and 100% (1 of 1) in the sixth session. The mean prostate specimen weight resected by TURP was 25.2 g (range, 5–108 g).

Although the results showed no statistically significant difference in the cumulative cancer detection rate by TRUS biopsy or TURP, there was a trend that cancer detection rate by TURP was greater than that by TRUS biopsy, especially in the second and third sessions of diagnosis (Figure 2).

In the first session (TRUS biopsy only), a total of 685 cancers (22.9%) were found (685 of 2,996 men). By stratifying the cancer detection rate according to serum PSA levels, malignancy was detected in 14.8% (61/412) of patients with PSA < 4 ng/mL, while it was detected in 13.7% (212/1,549) of patients with PSA 4–10 ng/mL, and in 41% (412/1,035) of patients with PSA > 10 ng/mL. In the second session, there was no significant difference in cancer detection rate between the TRUS biopsy and TURP methods across different PSA ranges (PSA < 4 ng/mL, 3.3% *vs.* 9%; PSA 4–10 ng/mL, 6.1% *vs.* 6.6%; PSA > 10 ng/mL, 14.5% *vs.* 11.9%; Table 1).

In prostate cancer patients, there was no difference in the demographic characteristics (age, prostate



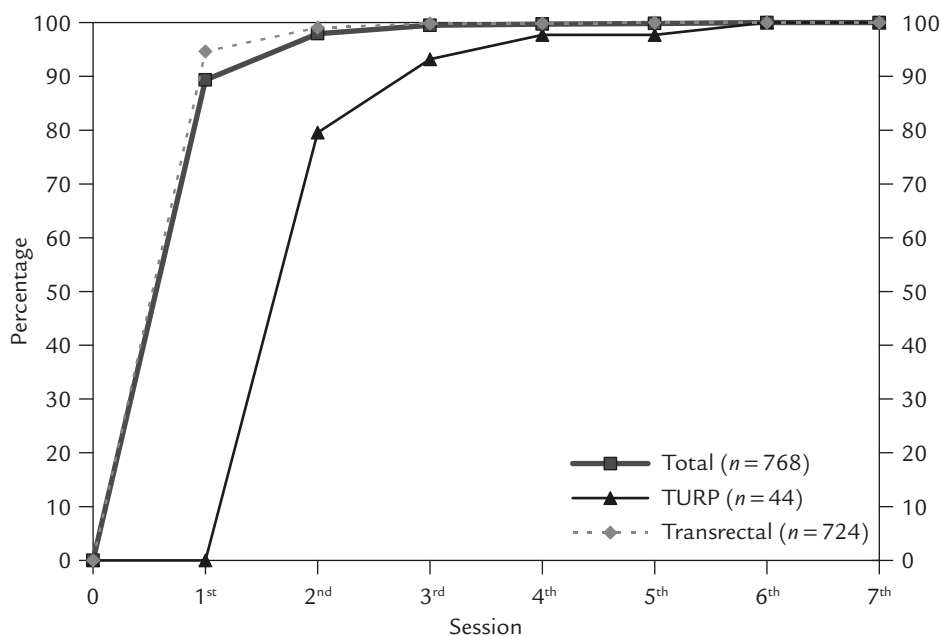
**Figure 1.** Flowchart of patients receiving diagnostic sessions.

volume, PSA density) between the TRUS biopsy and TURP methods (Table 2). In addition, serum PSA levels before each session of assessment were examined. We found no difference between patients who had TRUS biopsy and TURP for the second session ( $21.3 \pm 40.7$  vs.  $19.7 \pm 34.5$ ,  $p=0.85$ ). However, the PSA levels before biopsy were lower in patients who underwent TURP than in those who had TRUS biopsy in the third session ( $16.9 \pm 9.8$  vs.  $8.4 \pm 5.8$ ,  $p < 0.05$ ). We also found that Gleason grades were significantly lower in TURP-diagnosed cancer than those detected transrectally (for the second session,  $6.7 \pm 1.0$  vs.  $5.9 \pm 1.5$ , Mann-Whitney U test,  $p=0.007$ ; after the second session,  $7.6 \pm 1.3$  vs.  $5.2 \pm 1.0$ ,  $p=0.002$ ).

Of the patients who chose follow-up only, 6.3% had their PSA increase by more than 50% of their initial values, 25% had their PSA levels drop back to the normal range, and 66% had their PSA levels fluctuate within 50% of their initial values at the end of the study.

## Discussion

The cancer detection rate of 1-time TRUS prostate biopsy ranges from 22% to 34%.<sup>1,6</sup> The rate found in this study (22.9%) fits within that range. However, single-session sextant biopsy might miss at least 20–30%



**Figure 2.** Cumulative cancer detection curves of the different biopsy methods.

of detectable prostate cancer.<sup>7</sup> Thus, repeated biopsies are necessary when indicated. Roehl et al reported that cancer detection rates were 34% on the first TRUS biopsy, 19% on the second biopsy, 8% on the third biopsy, and 7% on the fourth biopsy.<sup>1</sup> Durkan and Greene reported that 31% (15 of 48) of the prostate cancers diagnosed in their patients was from specimens taken during second- or third-session sextant biopsy.<sup>8</sup> In our study, the cumulative cancer detection rate (Figure 2) by both TRUS biopsy and TURP was estimated to be approximately 98% during the first 2 sessions. The prostate cancer detection rate by TRUS biopsy in our study was 22.9% in the first session and 8.7% in the second session. Although the cancer detection rate from the first biopsy was similar to that reported in the literature, the positive rate in the second biopsy in our study was much lower than that shown in other studies. This finding might be due to the fact that some of our patients chose to receive TURP rather than undergo repeat TRUS biopsy. The other possibility is that the biopsy protocol used in this study was systemic sextant biopsy as proposed by Hodge et al.<sup>9,10</sup> Although a 10-core or 12-core biopsy strategy increases the cancer detection rate, it was reported in a prospective randomized trial comparing 6 versus 12 prostate biopsy cores that the overall cancer detection rate was not materially increased by 12-core biopsy.<sup>11,12</sup> We examined another patient cohort ( $n=474$ ) who received a 12-core biopsy protocol to compare the prostate cancer detection rate. The detection rate was 30.6% in the first session, which was similar to previous reports.<sup>12,13</sup>

Although an increase of 7.7% in detection rate was observed, the percentage of “significant” prostate cancer did not show any significant difference between the 6-core and 12-core biopsy groups (58.4% vs. 59.3%, respectively, unpublished data).<sup>14</sup>

Some studies have emphasized lowering the PSA cut-off value from 4.0 ng/mL to 2.5 ng/mL in order to increase the cancer detection rate. For example, Catalona et al reported that men with PSA levels of 2.5–4.0 ng/mL had an appreciable prevalence (22%) of detectable cancer.<sup>15</sup> However, data for Asian or Chinese people are lacking in the English literature. In our study, we noted that the repeat TRUS biopsy rate decreased dramatically after the second session. Furthermore, the ethnic characteristic of our patients (100% Han Chinese) might also explain the discrepant findings, such as decrease of prostate cancer detection by the TRUS procedure in the second session.

Presti et al advocated performing biopsy with a minimum of 8 cores, and increasing the number of cores taken at the lateral aspect of the peripheral zone.<sup>7</sup> Epstein et al, who performed sextant biopsies and posterolateral needle biopsies on 150 radical prostatectomy specimens, also support the importance of taking biopsy for the lateral prostate. They determined that maximum cancer detection results from combining both techniques.<sup>16</sup> Stewart et al proposed using a saturation needle biopsy technique under anesthesia in the operating room.<sup>17</sup> They took additional biopsy cores from the transition zone and detected prostate cancer in 96% of the specimens taken during the first

**Table 1.** Cancer detection rate from different diagnostic sessions with transrectal ultrasound-guided (TRUS) biopsy or transurethral resection of the prostate (TURP), stratified by prostate-specific antigen (PSA) levels

Session of biopsy	No. cancer/No. total (%)					
	Transrectal biopsy group			TURP biopsy group		
	PSA (ng/mL)		Total	PSA (ng/mL)		Total
<4	4-10	>10		<4	4-10	
1 <sup>st</sup>	61/412 (14.8)	212/1,549 (13.7)	412/1,035 (41)	4/48 (9)	16/209 (6.6)	15/118 (11.9)
2 <sup>nd</sup>	1/30 (3.3)	13/212 (6.1)	18/124 (14.5)	1/3 (33.3)	5/19 (26.3)	0/13 (0)
3 <sup>rd</sup>	0/3 (0)	2/64 (3.1)	4/31 (12.9)	0/0 (0)	1/4 (25)	1/7 (14.3)
4 <sup>th</sup>	0/0 (0)	0/12 (0)	0/4 (0)	0/0 (0)	0/0 (0)	0/0 (0)
5 <sup>th</sup>	0/0 (0)	0/3 (0)	1/2 (50)	0/0 (0)	0/0 (0)	0/0 (0)
6 <sup>th</sup>	0/1 (0)	0/2 (0)	0/2 (0)	0/0 (0)	0/0 (0)	1/1 (100)
7 <sup>th</sup>	0/0 (0)	0/1 (0)	0/0 (0)	0/0 (0)	0/0 (0)	0/0 (0)

**Table 2.** Characteristics of patients with prostate cancer diagnosed by transrectal ultrasound-guided (TRUS) biopsy or transurethral resection of the prostate (TURP) in different diagnostic sessions\*

	At 2 <sup>nd</sup> session						At ≥3 <sup>rd</sup> session					
	Total patients		Cancer patients		p	p	Total patients		Cancer patients		p	p
	TRUS	TURP	TRUS	TURP			TRUS	TURP	TRUS	TURP		
Cancer detection rate (%)	32/366 (8.7%)	35/375 (9.3%)	0.088 <sup>†</sup>	6/98 (6.1%)	6/35 (17.1%)	0.343 <sup>†</sup>						
Age (yr)	73.1±6.3	74.7±5.6	0.89 <sup>‡</sup>	71.9±10.2	72.7±6.2	0.62 <sup>‡</sup>						
Total PSA (ng/mL)	12.3±18.1	10.9±15.1	0.34 <sup>‡</sup>	73.4±5.4	78.0±9.0	0.21 <sup>‡</sup>						
Ratio (%) of free PSA to total PSA	20.5±8.6	24.7±10.4	0.92 <sup>‡</sup>	19.7±34.5	16.9±9.8	0.049 <sup>‡</sup>						
Estimated volume of prostate gland (mL)	42.8±24.9	48.0±24.3	0.02 <sup>‡</sup>	24.8±10.4	17.3±6.0	0.33 <sup>‡</sup>						
PSA density	0.28±0.26	0.26±0.70	0.76 <sup>‡</sup>	38.5±15.9	47.4±21.6	0.93 <sup>‡</sup>						
Gleason grades	6.7±1.0	5.9±1.5	0.007 <sup>‡</sup>	0.26±0.21	0.22±0.13	0.33 <sup>‡</sup>						
				0.26±0.21	0.22±0.13	0.33 <sup>‡</sup>						
				7.6±1.3	5.2±1.0	0.002 <sup>‡</sup>						

\*Data presented as mean ± standard deviation; <sup>†</sup>χ<sup>2</sup> test; <sup>‡</sup>Mann-Whitney U test. PSA = prostate-specific antigen.



2 biopsy sessions. However, the complication rate was high (12%), and urinary retention occurred in 4.5% of the patients.

In addition, the choice of TURP procedure was due to obstructive symptoms rather than randomization. Furthermore, not all patients underwent repeated TRUS biopsy or TURP after negative TRUS biopsies. Therefore, it is difficult to demonstrate the real sensitivity or specificity of TRUS biopsy. Actually, most patients in the follow-up group had fluctuating PSA levels. These patients might have had only latent cancers of low clinical significance or other benign disorders that contributed to their serum PSA levels.

It is still not easy to answer how many biopsies a patient should undergo. We found that patients with consistently negative biopsy results show a higher rate of malignancy after subsequent TURP; this finding is also reported in other studies.<sup>18-22</sup> This might be because tissue removed by TURP is chiefly from the transition zone. In our study, after the third session, cancer detection rate increased steeply in the TURP group. This finding implies that we should focus on tissue from the transition zones in patients with negative findings from the second and third TRUS biopsies. Therefore, for patients with repeated negative biopsy results, TURP should be offered as an alternative when there is a high suspicion of cancer.

Epstein et al demonstrated in a 10-year study that benign biopsy specimens are more likely to be obtained from larger prostate glands or from patients when cancer is located in the anterior region of the transitional zone or the lateral regions.<sup>23</sup> Philip et al also emphasized the importance of targeting the anterior zone in transurethral biopsies or resections.<sup>18</sup> Based on those findings, Kitamura et al suggested using TURP for detecting cancer in patients with peripheral zone and transitional zone biopsy specimens that are negative for malignancy.<sup>24</sup> In particular, they reported that the prostate cancer diagnosed from TURP specimens is usually organ-confined. Interestingly, in our study, cancers detected by TURP had lower Gleason grades and were associated with lower PSA levels than cancers detected by TRUS biopsy, especially in later sessions. This implies that the proportion of latent cancer might be higher among these patients who had previous negative TRUS biopsy results (Table 2). In our study, patients receiving TURP did not have larger prostate glands than those who had TRUS biopsy only (see Table 2).

In conclusion, for patients who have had 2 negative biopsies, TURP should be considered as an alternative option for biopsy. However, if these patients do not present with obstructive symptoms and are reluctant

to undergo TURP, then these patients could be managed with observation, including monitoring of serum PSA or undergo additional TRUS biopsy of tissue at the transition zone. From our data, 3 consecutive biopsy procedures may be indicated for high-risk patients. Since very little benefit can be expected from fourth or further TRUS biopsies, TURP biopsy is an alternative diagnostic procedure for patients with persistently high PSA and for those with comorbid illnesses such as obstructive symptoms.

## Acknowledgments

The authors thank Ms Hui-Chen Lee for her valuable assistance in statistical analysis. This study was supported, in part, by a grant (VGH 93-248) from Taipei Veterans General Hospital to William J.S. Huang.

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