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Research Paper

Trends and Outcomes of Sentinel Lymph Node Biopsy in Early-stage Vulvar Squamous Cell Carcinoma: A Population-based Study

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Abstract

Purpose: To compare trends and outcomes between lymphadenectomy and sentinel lymph node biopsy (SLNB) in node-negative early-stage vulvar squamous cell carcinoma (SCC) using a population-based cancer registry.

Methods: Patients with vulvar SCC registered on the Surveillance, Epidemiology, and End Results program between 2003 and 2013 were identified. Statistical analysis was performed using Cox regression proportional hazards to calculate hazard ratio (HR) and 95% confidence interval (CI). A 1:1 propensity score matching (PSM) method was performed to minimize selection bias.

Results: A total of 1475 patients were identified, including 1346 (91.3%) who received lymphadenectomy and 129 (8.7%) who underwent SLNB. The proportion of patients receiving SLNB increased between 2008 and 2013 compared with the years 2003–2007 (13.9% vs. 3.7%, $p < 0.001$). Five-year cause-specific survival (CSS) in patients who received lymphadenectomy and SLNB was 91.8% and 92.9%, respectively ($p = 0.912$), and 5-year overall survival (OS) was 77.5% and 82.5%, respectively ($p = 0.403$). SLNB was not associated with an decrease in CSS (HR 1.024, 95% CI 0.474–2.213, $p = 0.952$) or OS (HR 0.874, 95% CI 0.541-1.410, $p = 0.581$) in univariate and multivariate analyses. A total of 115 pairs were selected by PSM and survival analysis also showed comparable CSS ($p = 0.481$) and OS ($p = 0.545$) between lymphadenectomy and SLNB.

Conclusions: There is an increasing trend toward SLNB in the treatment of patients with node-negative early-stage vulvar SCC, and survival is comparable between lymphadenectomy and SLNB.

Key words: Vulvar cancer, Squamous cell carcinoma, Lymphadenectomy, Sentinel lymph node biopsy, Survival

Introduction

Vulvar cancer is a rare gynecologic malignancy, accounting for approximately 3–5% of all gynecologic malignancies. Squamous cell carcinoma (SCC) contributes approximately 85–90% of all vulvar cancers (1,2). The incidence of vulvar cancer has increased in the last decade, probably due to a rise in human papilloma virus infection and lichen sclerosus, and prolonged human life expectancy, with

peak incidence in the seventh decade of life (1,3-5). The presence of lymph node involvement is the most important prognostic factor in vulvar SCC (1,6,7). Five-year survival rates were approximately 70–98% in node-negative patients, while only 12–41% for those with lymph node metastasis (7).

Systemic inguinofemoral lymphadenectomy is considered a standard surgical procedure for vulvar SCC patients with >1 mm depth of invasion. Currently, lymphatic mapping and subsequent sentinel lymph node biopsy (SLNB) is the standard procedure in early-stage breast cancer and melanoma (8,9). The incidence of inguinofemoral lymph node involvement for early-stage invasive vulvar SCC with clinically node negative is less than 30%; therefore, inguinofemoral lymphadenectomy could be omitted in about 70% of those patients, making SLNB an acceptable method in the management of early-stage vulvar SCC with negative groin nodes (10-12). In 2008, the GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V) I was a prospective international observational study, which included the patients with early-stage vulvar SCC with unifocal tumors less than 4cm in diameter who do not have evidence of suspicious groin nodes at palpation, the results showed that patients with a negative sentinel lymph node (SLN) appears to be safe to omit a complete inguinofemoral lymphadenectomy (13). In 2012, the results obtained in the gynecologic oncology group (GOG)-173 trial demonstrated similar results (14). Since these two seminal trials were published, the SLNB procedure has been integrated in the standard treatment for a selected group of patients with vulvar SCC world-wide (15). However, although complete lymphadenectomy results in a reduced quality of life (QoL), most early-stage vulvar cancer patients would choose complete lymphadenectomy over SLNB due to the fear of cancer recurrence (16).

Although several studies have found a low groin recurrence rate in patients undergoing SLNB (17-20), no randomized controlled trials have compared the effect of lymphadenectomy with SLNB on outcomes in vulvar SCC, because of the rarity of the disease. In this study, we used a population-based cancer registry (Surveillance, Epidemiology, and End Results, SEER) to compare trends and outcomes between lymphadenectomy and SLNB in node-negative early-stage vulvar SCC.

Materials and Methods

Patients

The SEER program, a database maintained by the National Cancer Institute, includes demographics, incidence, and cancer-specific survival data for approximately 28% of the United States population (21). Our study included patients with vulvar cancer registered on the database between 2003 and 2013. Patients who met the following criteria were included: 1) histologically confirmed vulvar SCC; 2) American Joint Committee on Cancer 6th edition tumor stage (T-stage) T1–2 with tumor size <4 cm; 3) node-negative disease who received lymphadenectomy or SLNB; 4) no preoperative or postoperative radiotherapy; 5) the availability of variables including age, race/ethnicity, grade, marital status, and the number of removed lymph nodes.

The following variables were collected from the SEER database: year of diagnosis, age, race/ethnicity, marital status, grade, T-stage, tumor size, and type of lymph node management. The primary survival outcomes of the study were cause-specific survival (CSS) and overall survival (OS). CSS was calculated as time from initial diagnosis to the date of death due to vulvar cancer. OS was calculated as the time between initial diagnosis and the date of death or last follow-up.

Statistical analysis

Descriptive statistics for patient demographics and clinicopathologic characteristics were analyzed for comparison between the types of lymph node procedure using Chi-square test and Fisher's exact test. A 1:1 match was used based on the propensity score matching (PSM) method to minimize selection bias using the following variables: age, race/ethnicity, grade, tumor size, and marital status (22,23). CSS and OS rates were calculated using the Kaplan–Meier method and compared using the log-rank test. Cox univariate and multivariate analyses were used to calculate hazard ratios (HRs) and their 95% confidence intervals (CIs) for adverse prognostic factors of survival outcomes. Statistical analyses were performed using SPSS version 22.0 (IBM Corporation, Armonk, USA) and a p value <0.05 was considered statistically significant.

Results

A total of 1475 patients who met the inclusion criteria were identified, with a median age of 65 years (range 23–101 years). The patient demographics and clinicopathologic characteristics are listed in Table 1. Of the 1475 patients, 1346 (91.3%) received lymphadenectomy and 129 (8.7%) underwent SLNB. The median number of lymph nodes removed in patients who underwent lymphadenectomy and SLNB was 9 (range 1–44), and 2 (range 1–11), respectively. The percentage of patients who received SLNB was significant increase between 2008 and 2013

compared with the years 2003–2007 (13.9% vs. 3.7%, $p < 0.001$) (Figure 1). Patients with stage T1 disease were more likely to have undergone SLNB ($p = 0.002$). There were no significant differences in age, race/ethnicity, and marital status between the two lymph node procedures.

Table 1. Characteristics of 1475 vulvar squamous cell carcinoma patients based on type of lymph node management.

Variables	*n*	SLNB	Non-SLNB	*p*
Age (years)				
< 50	236	20 (15.5)	216 (16.0)	0.809
50-64	488	46 (35.7)	442 (32.8)	
≥ 65	751	63 (48.8)	688 (51.1)	
Race/ethnicity				
Non-Hispanic White	1222	108 (83.7)	1114 (82.8)	0.066
Non-Hispanic Black	97	4 (3.1)	93 (6.9)	
Hispanic	112	9 (7.0)	103 (7.7)	
Other and unknown	44	8 (6.2)	36 (2.7)	
Grade				
Well differentiated	512	46 (35.7)	466 (34.6)	0.716
Moderately differentiated	744	67 (52.0)	677 (50.3)	
Poorly/undifferentiated	219	16 (12.4)	203 (15.1)	
T-stage (AJCC 6th)				
T1	899	95 (73.6)	804 (59.7)	0.002
T2	576	34 (26.4)	542 (40.3)	
Tumor size (mm)				
1-10	400	46 (35.7)	354 (26.3)	0.015
11-20	499	49 (38.0)	450 (33.4)	
21-30	404	23 (17.8)	381 (28.3)	
31-39	172	11 (8.5)	161 (12.0)	
Marital status				
Married	663	63 (48.8)	600 (44.6)	0.366
Divorced	208	17 (13.2)	191 (14.2)	
Single	236	14 (10.9)	222 (16.5)	
Widowed	368	35 (27.1)	333 (24.7)	

AJCC, American Joint Committee on Cancer; SLNB, sentinel lymph node biopsy; T, tumor.

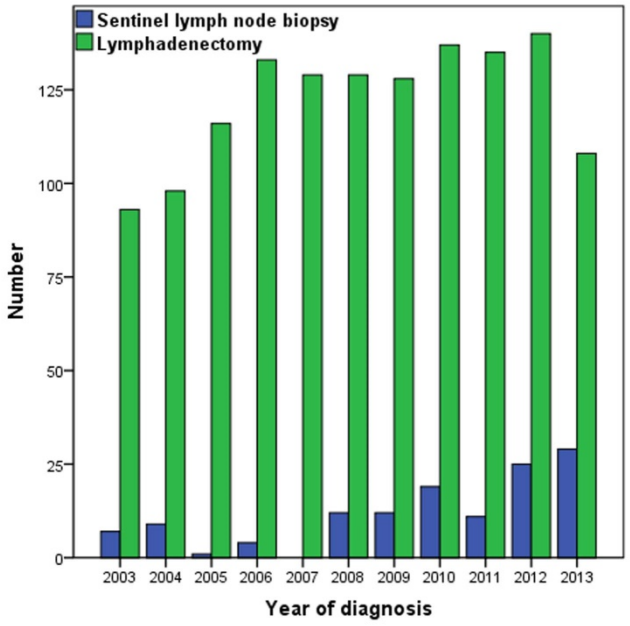

Figure 1. Number of patients who underwent lymphadenectomy and sentinel lymph node biopsy, 2003–2013.

The median follow-up time was 44 months (range 0–131 months). The 5-year CSS was 91.8% and 92.9% for lymphadenectomy and SLNB, respectively ($p = 0.912$) (Figure 2A), and 5-year OS was 77.5% and 82.5% for lymphadenectomy and SLNB, respectively ($p = 0.403$) (Figure 2B).

The univariate analysis results indicated that age, tumor size, and marital status were the prognostic factors affecting CSS and OS (Table 2). SLNB was not associated with decreased CSS (HR 0.958, 95% CI 0.445–2.061, $p = 0.912$) or OS (HR 0.817, 95% CI 0.508–1.315, $p = 0.405$). When adjusted for age, tumor size, race, grade, and marital status, multivariate analysis still suggested that SLNB did not affect CSS (HR 1.024, 95% CI 0.474–2.213, $p = 0.952$) or OS (HR 0.874, 95% CI 0.541–1.410, $p = 0.581$). Age, race, tumor size, and marital status were the independent predictors that influenced the survival outcomes (Table 3).

Table 2. Results of univariate analysis of 1475 vulvar squamous cell carcinoma patients.

Variables	CSS			OS		
	HR	95%CI	*p*	HR	95%CI	*p*
Age (years)						
< 50	1			1		
50-64	2.491	0.947-6.554	0.064	3.218	1.697-6.102	< 0.001
≥65	6.172	2.501-15.235	< 0.001	9.039	4.940-16.538	< 0.001
Race/ethnicity						
Non-Hispanic White	1			1		
Non-Hispanic Black	0.38	0.120-1.199	0.099	0.614	0.365-1.032	0.066
Hispanic	0.67	0.293-1.530	0.342	0.694	0.436-1.104	0.123
Other and unknown	1.914	0.887-4.128	0.098	0.875	0.465-1.644	0.677
Grade						
Well differentiated	1			1		
Moderately differentiated	1.274	0.824-1.970	0.277	1.104	0.865-1.410	0.426
Poorly/undifferentiated	1.520	0.866-2.667	0.145	1.157	0.829-1.614	0.392
T-stage (AJCC 6th)						
T1	1			1		
T2	2.396	1.638-3.505	< 0.001	1.985	1.596-2.469	< 0.001
Tumor size (mm)						
1-10	1			1		
11-20	1.919	1.010-3.647	0.046	1.513	1.082-2.116	0.016
21-30	2.946	1.566-5.543	0.001	2.241	1.607-3.126	< 0.001
31-39	5.538	2.845-10.781	< 0.001	3.452	2.382-5.001	< 0.001
Marital status						
Married	1			1		
Divorced	0.673	0.341-1.330	0.255	1.065	0.739-1.534	0.737
Single	0.75	0.399-1.411	0.373	0.834	0.565-1.233	0.364
Widowed	1.574	1.030-2.405	0.036	2.389	1.867-3.056	0
SLNB						
No	1			1		
Yes	0.958	0.445-2.061	0.912	0.817	0.508-1.315	0.405

AJCC, American Joint Committee on Cancer; CI, confidence interval; CSS, cause-specific survival; HR, hazard ratio; OS, overall survival; SLNB, sentinel lymph node biopsy; T, tumor.

Table 3. Multivariate analysis of 1475 vulvar squamous cell carcinoma patients.

Variables	CSS			OS		
	HR	95%CI	*p*	HR	95%CI	*p*
Age (years)						
< 50	1			1		
50-64	2.452	0.932-6.453	0.069	3.189	1.682-6.048	< 0.001
≥ 65	5.499	2.225-13.592	< 0.001	8.373	4.572-15.332	< 0.001
Race/ethnicity						
Non-Hispanic White	1			1		
Non-Hispanic Black	0.592	0.185-1.900	0.379	0.957	0.563-1.626	0.870
Hispanic	0.631	0.273-1.455	0.28	0.682	0.425-1.095	0.113
Other and unknown	2.201	1.010-4.798	0.047	1.098	0.581-2.074	0.774
Grade						
Well differentiated	1			1		
Moderately differentiated	1.243	0.800-1.932	0.334	1.044	0.816-1.337	0.732
Poorly/undifferentiated	1.486	0.840-2.627	0.173	1.102	0.784-1.547	0.576
Tumor size (mm)						
1-10	1			1		
11-20	1.646	0.863-3.140	0.13	1.344	0.960-1.881	0.085
21-30	2.368	1.244-4.507	0.009	1.753	1.253-2.451	0.001
31-39	4.696	2.392-9.220	< 0.001	2.917	2.011-4.230	< 0.001
Marital status						
Married	1			1		
Divorced	0.706	0.355-1.405	0.322	1.037	0.717-1.502	0.846
Single	0.782	0.412-1.487	0.454	0.896	0.603-1.333	0.589
Widowed	0.881	0.557-1.395	0.589	1.324	1.013-1.730	0.040
SLNB						
No	1			1		
Yes	1.024	0.474-2.213	0.952	0.874	0.541-1.410	0.581

CSS, cause-specific survival; CI, confidence interval; HR, hazard ratio; OS, overall survival; SLNB, sentinel lymph node biopsy.

Table 4. Characteristics of 115 matched pairs of patients

Variables	*n*	SLNB	Non-SLNB	*p*
Age (years)				
< 50	32	16	16	1
50-64	82	41	41	
≥65	116	58	58	
Race/ethnicity				
Non-Hispanic White	216	108	108	1
Non-Hispanic Black	2	1	1	
Hispanic	10	5	5	
Other and unknown	2	1	1	
Grade				
Well differentiated	80	40	40	1
Moderately differentiated	120	60	60	
Poorly/undifferentiated	30	15	15	
Tumor size (mm)				
1-10	80	40	40	1
11-20	88	44	44	
21-30	42	21	21	
31-39	20	10	10	
Marital status				
Married	116	58	58	1
Divorced	26	13	13	
Single	26	13	13	
Widowed	62	31	31	

SLNB, sentinel lymph node biopsy.

We matched the patients using PSM, resulting in matched cohorts of 155 patients with lymphadenectomy and 115 patients with SLNB. The PSM cohorts are summarized in Table 4. The survival analysis also showed comparable CSS (p = 0.481) (Figure 3A) and OS (p = 0.545) (Figure 3B) between lymphadenectomy and SLNB.

Discussion

In this study, we assessed the trends and outcomes of SLNB in patients with early-stage node-negative vulvar SCC, and our results showed an increasing trend toward SLNB, and survival outcomes were comparable between patients undergoing lymphadenectomy and SLNB in unmatched and matched populations.

The overall incidence of vulvar cancer increases with age, and our population-based study confirmed a median patient age of 65 years. Therefore, it is more important to investigate optimal treatment schedule to reduce the treatment-related complications and improve the QoL for this group of patients. Systemic inguinofemoral lymphadenectomy is considered the standard surgical procedure in patients with invasive vulvar SCC with >1 mm invasion. However, complete inguinofemoral lymphadenectomy may lead to a higher rate of complications, including wound breakdown (20–40%) and lymphedema (30–70%) (24). Moreover, less than one-third of patients have inguinofemoral lymph node involvement, meaning routine inguinofemoral lymph node dissection exposes a large number of patients to potentially avoidable surgical complications (25). Currently, lymphatic mapping and subsequent SLNB is the standard procedure in early-stage breast cancer and melanoma (8,9). Our results were similar to the previous study that the average number of removed lymph nodes was 9–10 for lymphadenectomy and 2–3 for SLNB (26), suggesting the extent of lymphadenectomy or SLNB in our population-based study was representative.

A population-based analysis from Germany by Rottmann *et al*. (27) found an increase in the proportion of patients with vulvar SCC undergoing SLNB, from 11.4% to 39.1% in the last two decades. A study from the United States by Cham *et al*. (17) also found that the proportion of vulvar cancer patients undergoing SLNB increased from 17.0% in 2006 to 39.1% in 2015. Groin recurrence and survival were not affected by these changes and were likely accompanied by an improvement in QoL (27). However, in our study, prior to 2008 only 3.7% of vulvar SCC patients underwent SLNB, and although the proportion of patients receiving SLNB increased to 13.9% after 2008, it was still lower than the aforementioned two studies. The rate of SLNB increased after 2008 following the publication of the

results of the GROINSS-V-I (13). A previous SEER study indicated that only 5.1% of patients received SLNB between 2004 and 2008 (28). It is still unclear why there are differences between the SLNB rate in our study and the studies by Rottmann *et al.*(27) and Cham *et al*. (17). The differences in the study population may be the main reason contributing to the conflicting results. In addition, the rarity of the disease may limit the potential for individual surgeons to develop the technical skills for SLNB procedure. An expert panel recommended in 2009 that surgeons conduct 10 SLNB procedures followed by complete lymphadenectomy to confirm SLNB findings before conducting SLNB alone for appropriately selected patients (29). Therefore, for gynecologic oncologists who rarely see patients with vulvar cancer, it is appropriate to refer patients to a high-volume center or surgeon. SLNB should still be considered as an experimental approach that should not be routinely performed by gynecologic oncologists outside referral centers.

There have been no randomized trials to compare the effect on outcomes between lymphadenectomy and SLNB in vulvar SCC due to the rarity of the disease. The results of GROINSS-V-I and GOG-173 trials showed that SLNB in vulvar cancer had a high sensitivity (92-94%) for the identification of SLN metastases and a low false-negative predictive value (2.0-2.9%) in a selected group of patients (13,14). Several studies have found that SLNB is the most cost-effective treatment strategy for management of early-stage vulvar cancer because of lower costs of primary treatment, lower risk of treatment-related complications, and better QoL (30-33). However, most of patients would choose complete lymphadenectomy over SLNB due to the fear of cancer recurrence (16). Therefore, more studies are needed to further delineate the application and outcomes of SLNB in vulvar cancer.

Groin recurrence rate was only 2.3% for unifocal vulvar disease in the GROINSS-V-I trial, and the 3-year disease-specific survival rate was 97% (13). After a median follow-up of 105 months, the isolated groin recurrence rate was 2.5% for SLN-negative patients, and the disease-specific survival rate was 91% at 10 years (18). Robison *et al.* (19) recently reported SLNB results for 69 patients and found groin recurrence was 5.3% in SLN-negative patients. A 20-year analysis of 128 patients by Brammen *et al.* (20) included 46 patients who received SLNB, and no groin recurrence was observed in these patients. The long-term results of SLNB procedure in patients with node-negative breast cancer was also shown an extremely low rate of axillary recurrence (0.2%) (34). In our study, the SLNB procedure was not associated with an increased risk of all-cause mortality compared with lymphadenectomy. Therefore, the advantages of the SLNB procedure must be disseminated for the benefit of as many patients as possible to decrease morbidity and improve QoL.

Currently, there are corresponding recommendations for patients who are eligible for SLNB. Patients with tumors that are unifocal, less than <4 cm in diameter, and with no evidence of

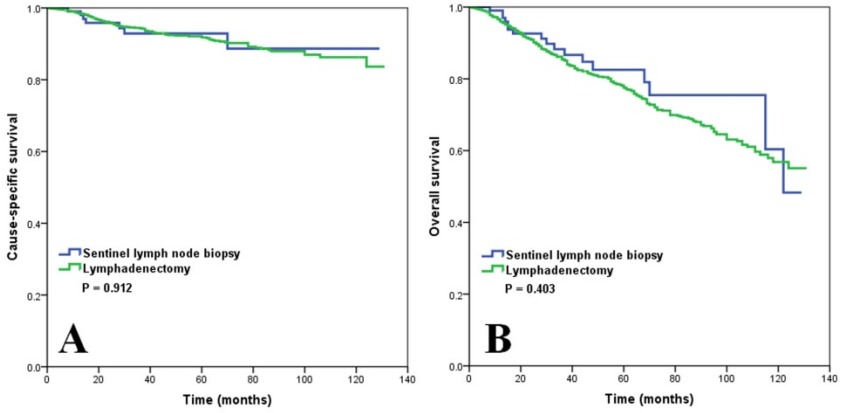

Figure 2. Survival comparison (A, cause-specific survival; B, overall survival) in patients with vulvar squamous cell carcinoma based on the type of lymph node management before propensity score matching.

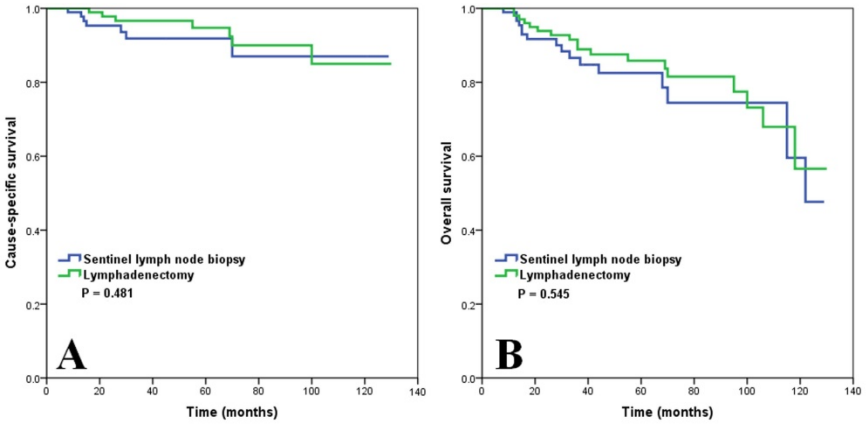

Figure 3. Survival comparison (A, cause-specific survival; B, overall survival) in patients with vulvar squamous cell carcinoma based on the type of lymph node management after propensity score matching.

lymph node involvement by preoperative assessment, are eligible for SLNB (35), while patients with multifocal disease, clinically suspicious groin nodes, or a tumor located in the midline are unsuitable (13,14,24). In addition, patients who have undergone preoperative radiotherapy/chemotherapy should probably be excluded because damage to the lymph vessels may affect the SLNB procedure (36).

We need to acknowledge several limitations to our study. First, it will have the inherent bias of any retrospective study. Second, details on the extent of lymphadenectomy, the method of SLN identification procedures, and the patterns of disease recurrence are lacking in the SEER database. In addition, the radiological staging and histopathological ultrastaging are also not included in the SEER database. However, due to the relatively rare incidence of the disease, it is difficult to conduct randomized controlled trials to compare the effect of lymphadenectomy and SLNB on patient survival. The primary strength of our study is that we used population-based data to compare the outcomes of the two types of lymph node management.

Conclusion

In conclusion, our results suggest an increasing trend toward SLNB in patients with node-negative early-stage vulvar SCC, and survival is comparable between patients undergoing lymphadenectomy and SLNB. Considering that most vulvar cancers are in the elderly, SLNB has an important part of the management of these patients to decrease surgery-related complications and improve the QoL. More prospective studies are needed to confirm our results.

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Competing Interests

The authors have declared that no competing interest exists.

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