Accuracy of Detection Rate and Intraoperative Sentinel Lymph Node Assessment in Early-stage Cervical Carcinoma

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Abstract

Objective: This article shows our experience on sentinel lymph node (SLN) biopsy in early-stage cervical carcinoma since the technique was introduced in our Institution. The main objective is to analyze the detection rate (DR) of metastatic SLNs**,** identifying prognostic factors for an increased risk of nodal metastases. Our second aim was to compare the accuracy of nodal metastases DR between intraoperative analysis and postoperative ultrastaging. **Materials and Methods:** Forty-one women with the International Federation of Gynecology and Obstetrics stages IA2-IIA1 who underwent laparoscopic surgical treatment applying the SLN technique, from December 2011 to June 2016, at La Paz University Hospital, were included. The sentinel node was identified using technetium and methylene blue dye or indocyanine green near-infrared fluorescent imaging, analyzed intraoperatively, and compared to deferred ultrastaging. **Results:** SLN DR was 100%, with a bilaterality rate of 83%. Twelve (26.8%) patients had metastatic nodes, 11 of them (91.7%) detected by SLN technique, of which 9 (81.8%) had only the sentinel node affected. False-negative rate was 2.4% after ultrastaging procedure. Metastatic SLN detection with ultrastaging was 45.5% higher than the intraoperative analysis, 63.6% of which had low tumor burden. The global detection of patients with nodal metastases after SLN technique was 21.9% higher than pelvic lymphadenectomy. **Conclusions:** Our preliminary results corroborate that SLN biopsy selectively maps metastatic nodes and ultrastaging increases the detection of metastatic SLNs, predominantly due to low tumor burden.

Keywords: Cancer staging, cervical cancer, lymphatic metastasis, lymphovascular space invasion, sentinel lymph node biopsys

Background

Systematic pelvic lymphadenectomy (PL) remains the standard in nodal staging for cervical cancer. Nodal status is a major prognostic factor for survival in patients with early-stage cervical cancer (ESCC)[1,2] and determines treatment planning.[3,4] However, almost 80% of patients do not have metastatic lymph node involvement, so PL could increase morbidity without benefit.[1,2] Therefore, sentinel lymph node biopsy (SLNB), defined as the first regional node that drains the tumor, has gradually gained acceptance as a future alternative instead of PL.[5] SLN mapping has the potential to decrease morbidity and optimize the pathologic assessment of identified nodal metastasis in women with cervical cancer.[1]

The intraoperative pathological analysis assumes a high-false-negative rate (FNR). The application of ultrastaging has led to an improvement, but the clinical impact of detect low tumor burden is still unclear.[3] In addition, it is known that lymphovascular space invasion (LVSI) is associated with a higher risk of lymph node metastasis (LNM);[6] however, other authors could not demonstrate such results.[7]

This cohort study represents a single-institution experience with SLNB in the management of ESCC. We hypothesized that the SLNB selectively detects metastatic nodes. Our main goal was to determine the detection rate (DR) of metastatic SLN, FNR, and analyze prognostic factors related to LNM. We also aimed to compare the accuracy of intraoperative analysis to the postoperative ultrastaging in detecting nodal metastases.

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Materials and Methods

Patients

Forty-one patients with the International Federation of Gynecology and Obstetrics ESCC were recruited. Patients underwent surgery with SLNB from December 2011 to June 2016 at La Paz University Hospital [Figure 1].

Eligibility criteria were histologically documented carcinoma of the cervix, clinical early-stage (IA1 with LVSI, IA2, IB1 or IIA1), without prior chemotherapy or pelvic radiotherapy (RT), and no contraindication to laparoscopy and signed informed consent. The Ethics Committee approved the study with reference number PI-1461. The informed consent was obtained in all patients.

Sentinel lymph node procedure

SLNs were detected with a dual technique, using a combination of a radiotracer (a colloid labeled with technetium-99 m (^{99m}Tc) with intraoperative methylene-blue dye (MB) in the first 25 (61%) patients or indocyanine green (ICG) in the following 16 (39%) patients. Radiotracer (^{99m}Tc-albumin nanocolloid; Nanocis^{R}, Schering, CIS BIO International, Gif-Sur-Yvette Cedex, France) was injected using a 2-day protocol. The day before surgery, a total dose of 148 MBq (4 mCi) was intracervically injected using a 20-Gauge hypodermic needle. A total volume of 2 ml was splitted in each of 4 quadrants (0.5 ml each) approximately 10 mm deep in the cervix stroma. First, a scan is done at 30 min and 2 h after the injection, and finally, a single-photon emission computed tomography/computed tomography (SPECT/CT) at 3 h.

Dyes used were 4 ml of MB Injection 10 ng/ml (Akorn Pharmaceuticals, Illinois, USA) or 2 ml of 10% ICG 25 mg (Pulsion Medical Systems AG, Munich, Germany)

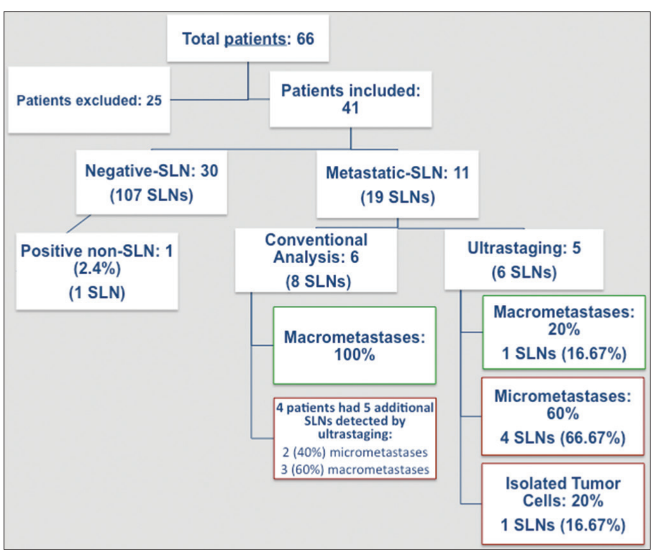

Figure 1: Flow chart of patients, cases included and sentinel lymph node pathological analysis. Sixty-six patients underwent surgery since December 2011 to June 2016 at La Paz University Hospital. Twenty-five cases were excluded, 15 by *in situ* carcinoma or locally advanced stage, 5 had been operated in another hospital, and 5 had incomplete data

diluted in 10 ml of sterile saline. The dye was injected intraoperatively, in the same manner as the radiocolloid, just before beginning surgery.

The detection and removal of SLNs were performed at the beginning of surgery. A window was opened in the peritoneum of the anatomical triangle formed among the infundibulum, round ligament, and iliac vessels, on both sides. We were guided to the exact point helped by preoperative lymphoscintigraphy and SPECT-CT information and intraoperative hand-held gamma probe (CdTe probe, Europrobe, Eurorad, Lyon, France) readout. We dissected the exact area where the SLN was located.

We localized, removed, and identified separately SLNs that were dyed, had the afferent channel stained, or were radioactive (except those with radiation level below 10% of the maximum detected).

If the SLN was negative, we continued with the standard procedure as planned, i.e., radical hysterectomy or trachelectomy with bilateral PL. If intraoperative histological analysis of the SLN was positive, surgical treatment of the primary tumor was canceled and a paraaortic transperitoneal dissection to the level of the left renal vein was performed and subsequent chemo RT (CRT). In case of pelvic lymph nodes suspected of metastasis, a debulking is performed.

Three specialized gynecologic pathologists performed all examinations. All the removed SLNs were intraoperatively analyzed by means of frozen section and imprint cytology of one section per node. If the thickness of the node was >5 mm, sections at 2–3 mm along the minor axis were performed. After negative intraoperative analysis, SLNs were embedded in paraffin and stained with hematoxylin-eosin (H and E) for ultrastaging. Thus, SLNs were sliced at 200-µm intervals for a total of four slides per block. At each level, two sections of 4-µm were taken: one section was examined with H and E, and the other section was processed using the immunohistochemical method for pancytokeratin AE1/AE3 (mouse monoclonal, clone AE1/AE3, prediluted, Dako, Glostrup, Denmark).

SLNs were considered positive if macrometastases (tumor deposit >2 mm in diameter), micrometastases (tumor deposit between 0.2 and 2 mm), or isolated tumor cells (small clusters of tumor cells ≤0.2 mm) were detected. Low burden disease was defined with the presence of micrometastases or isolated tumor cells.

Statistical analysis

The quantitative data were described with the median and interquartile range and qualitative data with absolute numbers and percentages. For univariate analysis, quantitative data were tested by one-way ANOVA or t-Student; and qualitative data by the Fisher's exact or the Chi-square (χ^2) test, depending on the size of the crosstab.

The Generalized Poisson Mixed Model for Overdispersed Count Data (GLMM) was performed to estimate the expected proportion of SLNs detected with radiocolloid and/or dye. For this model, it was considered best to use Poisson's distribution of logarithmic link function. The offset was the Neperian logarithm of total SLNs per patient. The deviance as the scale parameter for radiotracer and the scale parameters for the dyes were fixed at 0.49 and 0.25, respectively. All statistical analyses were performed using statistical software SPSS for windows, version 22.0 (Chicago, SPSS Inc., USA) and SAS Enterprise Guide 5.1 (Cary NC, SAS Institute Inc., USA). In particular, the procedure glimmix, from SAS, was used to perform GLMM. The two-sided test was used, and a $P < 0.05$ was considered statistically significant.

Results

General and histopathological characteristics are shown in Table 1. All 41 patients underwent preoperative SLN mapping with ^{99m}Tc-radiocolloid and intraoperative dye. At least, one SLN was identified in all patients, with bilateral detection in 34 (83%) cases.

One hundred and twenty-six SLNs were analyzed that means an average of 3.1 nodes per patient. The majority were located in external iliac (53.6%) and obturator (27.8%) areas [Figure 2]. Unusual SLN mapping was found in 18 (14.2%) SLNs (12 common iliac, 3 presacral, 1 paraaortic, and 2 parametrial). In four (22%) of these unusual-located SLNs, metastasis was present (3 common iliac and 1 presacral); but only 2 were intraoperatively detected.

Table 1: General and histopathological characteristics (*n*=41)

Variable	*n* (%) or median/(p25-p75)
Age (years)	46.2 (35.5-56.5)
<40	13 (31.7)
≥40	28 (68.3)
FIGO clinical stage	
IA2	5 (12)
IIA1	6 (15)
IB1	30 (73)
Tumor size (mm)	21.2 (12-27.5)
Histology	
Squamous carcinoma	30 (73.2)
Adenocarcinoma	9 (22)
Adenosquamous carcinoma	2 (4.9)
Tumor differentiation	
Well	7 (17.1)
Moderate	20 (48.8)
Poor	14 (34.1)
Deep stromal invasion (mm)	8.7 (3.5-12)
Positive LVSI	16 (39)
N° SLN/patient	3 (2-4)
Dye	
Methylene blue	25 (61)
Indocyanine green	16 (39)
Laterality drainage	
Unilateral	7 (17.1)
Bilateral	34 (82.9)
Pelvic lymphadenectomy (*n*)	36 (87.8)
N° pelvic lymph nodes/patient	16 (12-19)
Paraortic lymphadenectomy (*n*)	7 (17.1)
N° paraortic lymph nodes/patient	22 (15-29)

FIGO: International Federation of Gynecology and Obstetrics, LVSI: Lymphovascular space invasion, *n*: Number of patients, SLN = Sentinel lymph node

A total of 24 metastatic nodes in 12 patients were detected. Nineteen of them were metastatic-SLNs (19/126 = 15%), corresponding to 11 (11/41 = 26.8%) patients [Figure 1]. Four additional metastatic pelvic non-SLNs were detected in 2 patients with metastatic-SLNs. The remaining metastatic node (false-negative result) corresponds to a patient with bilateral-negative external iliac SLN, but a micrometastatic parametrial node in the surgical specimen was discovered during histopathological analysis.

Eight of 19 (42%) metastatic-SLNs were macrometastasis (MM) and detected intraoperatively in 6 patients, which represents 54.5% of the patients detected with LNM. The remaining 11 nodes (58%), corresponding to 9 patients, were detected by the ultrastaging procedure. In 5 of those 9 patients, we did not detect any positive metastatic node in a previous intraoperative analysis, which represents 45.5% of the patients detected with nodal metastasis. Six out of 9 patients presented low-tumor burden (2 with additional metastatic nodes were not intraoperatively detected) and the remaining 3 showed macrometastases (also 2 of them with additional metastatic nodes that were not intraoperatively detected). In the group of the 5 patients discovered by ultrastaging, 80% had low tumor burden nodal metastases (4 nodes in 3 patients with micrometastases and another node in a patient with isolated tumor cells).

Ultrastaging showed 4 (36.4%) SLNs with macrometastases, 6 (54.6%) SLNs with micrometastases, and 1 (9%) node with isolated tumor cells, so 63.6% (7/11) of cases presented low-burden disease.

The FNR of intraoperative pathological analysis was 14.6% (6/41) per patient versus 2.4% (1/41) after ultrastaging. Therefore, excluding the undetected case and two patients with positive PL, the SLNB detected 9 additional positive cases (21.9%, 9/41).

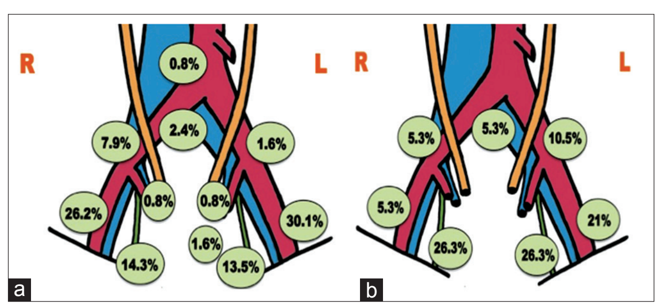

Figure 2: Sentinel lymph node mapping. (a) Distribution of all sentinel lymph nodes (*n* = 126); (b) distribution of metastatic-sentinel lymph nodes (*n* = 19). The obturator, external iliac, internal iliac, common iliac, presacral, and paraaortic areas were considered anatomical landmarks. Acronyms: R-right, L-left

Patients' characteristics according to metastatic-SLN are reported in Table 2. Seven patients underwent paraaortic lymphadenectomy, with an average of 22 nodes obtained per patient and no metastasis. Debulking of suspected pelvic lymph nodes and paraaortic lymphadenectomy was performed in 2 patients with intraoperative metastatic-SLN. In one of these patients, an additional positive pelvic lymph node was detected; the other patient only had a metastatic-SLN detected by ultrastaging.

There was no significant association between the detection of metastatic-SLN and age ($P = 0.25$), tumor size ($P = 0.28$), histology ($P = 0.61$), tumor differentiation ($P = 0.19$), or tumor markers (Squamous Cell Carcinoma – SCC and carcinoembryonic antigen – CEA) ($P = 0.51$). There was no correlation between the presence of LVSI and age ($P = 0.15$) or tumor size ($P = 0.74$), despite a trend that larger tumor size was associated with LVSI.

There was a statistically significant association between the detection of LVSI and metastatic-SLN involvement ($P = 0.003$) with a sensitivity of 78% and negative predictive value of 91%. Among the 16 patients (39%) with LVSI, 7 of them (43.8%) had metastatic-SLNs (63.6% of all patients with metastatic-SLN). Among the 23 patients (56.1%) without LVSI, metastatic-SLNs were detected in 2 (8.7%) patients. By estimating a risk, it was an 8-fold greater risk of a metastatic-SLN in a patient with LVSI than without LVSI.

Table 2: Patients' characteristics according to metastatic-sentinel lymph node

Variables (*n*=11 patients)	*n* (%)
Age (years)	
<40	6 (54.5)
≥40	5 (45.5)
Stage	
IA2	1 (9.1)
IB1	9 (81.8)
IIA1	1 (9.1)
Tumor size	
<2 cm	2 (18.2)
≥2 cm	4 (36.4)
Unknown	5 (45.4)
Histology	
Squamous carcinoma	9 (81.8)
Adenocarcinoma	2 (18.2)
Tumor differentiation	
Well	2 (18.2)
Moderate	3 (27.3)
Poor	6 (54.5)
LVSI	
Presence	7 (63.7)
Absence	4 (36.3)
Adjuvancy	
Radiotherapy[a]	2 (18.2)
Chemoradiotherapy	9 (81.8)

[a]Includes external radiation therapy and/or brachytherapy.
LVSI: Lymphovascular space invasion

After surgery, 14 (34.1%) patients were upstaged. Twelve (85.7%) of them had positive nodes, 11 (78.6%) detected by SLNB (9 (81.8%) with only the SLN involved), and a patient with a metastatic parametrial non-SLN. PL was performed in 36 patients, with additional nodal metastasis in 2 of them (5.5%). The SLNB detected 11 out of 41 included patients (26.8%); which means an increase of nine patients (21.3%) in the detection of nodal metastasis.

Adjuvant concomitant CRT was given to 9 patients with metastatic-SLNs. Two additional patients with low-burden metastatic-SLNs received adjuvant RT. In the remaining 30 patients without metastatic lymph node involvement, 12 received RT, 3 concomitant CRT, and 15 did not require adjuvant treatment.

The mean follow-up was 28.5 months (range 13–42). Four patients (9.8%) presented recurrences: 3 had a local relapse, and the remaining one showed nodal spread. Mean time to relapse was 31 months (range 8–71.5). No patient with metastatic-SLN relapsed or lost their life during the study. Overall survival (OS) was 95.1%, and disease-free survival was 90.2%.

Discussion

It is known that the nodal status defines the management strategy and prognosis in cervical cancer.[3,8] The main goal of the SLNB is to assess a selectively bilateral detection with the least morbidity as possible.[2,9] Selective lymph node mapping, of all suspected lymph nodes and those located in unusual lymphatic drainage,[10] is equivalent to a high precision lymphadenectomy.[1,8]

The feasibility of SLNB in cervical cancer has been well documented and established in clinical practice.[1,2] Our results were comparable with published data. It is described an SLN DR of 45%–100%, with bilaterality of 33%–81%[10,11] and mean number of SLNs per patient greater or equal to 2.[8,12]

Factors that modify the DR include the injection site, the type, and amount of tracer, the time between tracer injection and detection, surgeon's experience, and the cervical tumor lesion by itself.

One of the current common mistakes in performing SLNB technique is the lack of equanimity among methodology. The standard procedure accepted is a dual technique with radiocolloid and MB. This procedure was validated by the SENTICOL study with a sensitivity of 92%, negative predictive value 98.2%,[10,11,13] and FNR of 1.3%.[14]

Newly established in gynecologic oncology, real-time fluorescence mapping with ICG is a promising alternative with higher DR and accuracy, compared to the dual technique or MB alone.[2,9,15] Buda *et al*.[9] recently published data with a DR and bilaterality of 100% and 98.5%, respectively. In our

Institution, we used a combined technique (^{99m}Tc-radiocolloid with MB) with a 2-day-protocol. However, in accordance with the aforementioned excellent results achieved, we decide to replace MB for ICG fluorescent dye since October 2014.

Our patient mean tumor size was <3 cm. A recent analysis reported a DR of 95% and a sensitivity of 100% for tumor size ≤2 cm. Otherwise, tumor size >2 cm had a lower DR (80%) and sensitivity (89%).[16-18] The main cause is the anatomical distortion produced by increased tumor size, which can alter or block the lymphatic drainage.

First studies on SLN in cervical cancer had a high FNR, for example, 14.5% in Dargent *et al*. research.[19] In subsequent studies, FNR was <8%, with an average of 2.4%, these data are consistent with our results.[20,21] Currently, in "The Fluorescence Era," FNR is almost zero (0.04%).[9] Such low rate occurs in trained teams and generally related to parametrial nodes removed along with the surgical specimen,[22] which are not identified with the lymphoscintigraphy or gamma probe.[23] The incidence of parametrial involvement is very low in the subgroup of patients with a tumor size ≤2 cm, <10 mm of deep stromal invasion, and negative lymph nodes.[1,24] In our own results, 2 (1.6%) SLNs were located in the parametrium, but no one had metastasis. This is similar to 2.5% of parametrium nodes detected by Bats *et al*.,[8] but much <7%–11% theoretically reported.[2]

Removal of SLNs in the external iliac, interiliac, parametrial, and obturator areas enables evaluation of more than 80% of all SLNs.[1,5,8] As we described in our data, 84% of all SLNs and 80% of metastatic-SLNs were located in external iliac and obturator areas. A similar distribution has been obtained in other studies.[12,23]

SLNB increases the likelihood of identifying metastatic nodes with unusual lymphatic drainage outside the PL dissection area that would be missed. Unusual drainage outside the dissection area of PL to the common iliac, parametrium, presacral, and paraaortic areas has been described in 5%–20% of patients.[3] This would explain most of the recurrences in falsely considered nonmetastatic patients after PL.[10] In our analysis, 14.2% SLNs were located in unusual areas, 22% of which were metastatic, but only half of them were intraoperatively diagnosed.

The prevalence of nodal metastasis is usually <20% in ESCC.[3] SLNB represents an accurate method to identify the small-volume disease in those patients with ESCC.[9] Metastatic-SLNs are detected in 4.8%-31% of IA2-IB1 stages, being <15% if TS ≤2 cm.[1,25] In our sample, we have had a metastatic-SLN rate of 15% (19/126), with average tumor size <3 cm.

The main limitation against the SLNB standardization is the intraoperative identification of LNM.[3] Intraoperative analysis accurately detected MM, but there were a high FNR and inability to detect low-tumor burden.[3,13,26,27] In the Slama *et al*.[28] study, it has been reported that intraoperative sensitivity was 56%, with 8% of metastatic-SLNs with low-volume disease detected. As mentioned in our results, intraoperative analysis identified no micrometastases or isolated tumor cells, even being performed by an expert pathologist.

Pathological ultrastaging identifies low metastatic tumor burden in the SLNs, not detected by conventional pathology.[21] In concordance, our own results, using ultrastaging-detected metastases in 45.5% (5/11) of patients and 58% (11/19) of SLNs; showing higher results than intraoperative analysis. However, application of ultrastaging to all nodes or intraoperatively is not feasible yet.[1,8] This is why many authors consider that a two-step surgery[3] should be performed, instead of an intraoperative analysis of the SLN.[2]

Treatment and prognosis for patients with low lymph-node tumor burden still remains controversial.[3] Cibula *et al*.[21] concluded that micrometastases were an independent prognostic factor for OS while isolated tumor cells appeared to have no impact on survival, without modifying the adjuvant treatment. In Marchiolé *et al*. study,[29] micrometastases were linked to a higher 10-fold higher risk of recurrence and patients should receive adjuvant therapy, but it is still not clear whether if is better to administer RT or CRT.[1]

Main factors associated with tumor prognosis in cervical cancer are according to relevance: LNM, LVSI, tumor size, and deep stromal invasion.[30] Other controverted factors are age, close surgical margins, microscopic parametrial involvement, histology, and tumor differentiation.[7,31] In Zaganelli *et al*.[31] study, they described the association between LNM and a greater tumor size, the deep stromal invasion, the involvement of the parametrium or the vagina, and the presence of LVSI. However, there was no association with age, histology, tumor differentiation, or stage.[10]

LVSI is defined as the tumor cell invasion into blood or lymph vessels. LVSI represents a preliminary step for nodal metastases and tumor spread.[32] The presence of LVSI is an independent risk factor for LNM in ESCC[6,33-35] with an increased risk of nodal metastases, parametrial involvement,[36] and worse prognosis than in patients without LVSI,[7,37] regardless of density and location.[38-39] In Marchiolé *et al*.,[29] LVSI was present in 43% of ESCC, all metastatic-SLNs had LVSI, with a relative risk of 2.64 (P < 0.01) of recurrence. We estimated a probability of 8 times more likely to find a metastatic-SLN in the presence of LVSI (95% confidence interval [CI], 1.4–47.2; P = 0.019). Similar results were observed in Lécuru *et al*.[10] (95% CI, 2.2–30.6; P = 0.002).

This article represents our initial experience in the application of the SLNB in ESCC. Despite the small number of cases and therefore few events, our results are comparable to larger studies and recent reviews,[40] confirming that SLNB accurately predicts the status of the regional nodes.

Conclusions

Our results sustain that SLNB selectively maps metastatic nodes, which is an improvement over current methods.

Given PL does not seem to demonstrate an increased level of detection of LNM compared to SLNB, our hypothesis is that PL could be safely omitted in ESCC. However, we still need to improve intraoperative histological accuracy and standardize the technique, before consider the routine use of SLNB in these patients.

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Conflicts of interest

There are no conflicts of interest.

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