The Prognostic Impact of Early Change in ^{18}F-FDG PET SUV After Neoadjuvant Chemotherapy in Patients with Locally Advanced Breast Cancer

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SUV, which is an indicator of the degree of glucose uptake in ^{18}F-FDG PET, can be applied as a prognostic factor in various malignant tumors. We investigated the prognostic impact of early changes in ^{18}F-FDG PET uptake in patients with locally advanced breast cancer who received neoadjuvant chemotherapy. **Methods:** We retrospectively identified 87 patients who were treated with neoadjuvant chemotherapy followed by surgery for locally advanced breast cancer. All patients underwent ^{18}F-FDG PET at baseline and after 3 cycles of neoadjuvant chemotherapy, and the SUV_{max} of the primary tumor was assessed in each scan. Pathologic slides were retrospectively reviewed, and the residual cancer burden (RCB) index was calculated to estimate pathologic response. RCB-0 indicates no residual disease; patients with residual disease were categorized as RCB-1 (minimal residual disease), RCB-2 (moderate residual disease), or RCB-3 (extensive residual disease). **Results:** There was a negative correlation between reduction in SUV_{max} and RCB index ($r = -0.408$; $P < 0.001$). On multivariate analysis, ΔSUV_{max} was a significant independent prognostic factor for recurrence-free and overall survival, and the respective adjusted hazard ratios were 0.97 (95% confidence interval, 0.95–0.99; $P = 0.001$) and 0.97 (95% confidence interval, 0.95–0.99; $P = 0.015$). When patients were categorized into groups according to pathologic response (RCB index $\leq$ 1 vs. $\geq$ 2) and metabolic response ($\Delta SUV_{max} \leq 66.4\%$ vs. $> 66.4\%$), metabolic responders had significantly better recurrence-free and overall survival than metabolic nonresponders among poor-pathologic-response patients. In contrast, among metabolic responders, there was no survival difference according to pathologic response. **Conclusion:** The early change in ^{18}F-FDG PET SUV_{max} after third-cycle neoadjuvant chemotherapy is an independent and good prognostic marker beyond pathologic response in patients with locally advanced breast cancer. We suggest that in these patients, the use of ΔSUVmax should be considered not only for the assessment of tumor response but for the prediction of posttreatment outcome.

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In patients with locally advanced breast cancer, neoadjuvant chemotherapy has been widely accepted as a standard treatment because it can improve the surgical options and provide survival outcomes equivalent to those of conventional adjuvant chemotherapy (*1–3*). Moreover, neoadjuvant chemotherapy can assess sensitivity to chemotherapy, which can be helpful in modifying subsequent treatment according to an individual's response (*4*).

Pathologic complete response (pCR) has been used as a surrogate marker for treatment outcome in some subtypes of breast cancer, because in these subtypes the survival outcome has been better for women who had pCR than for those who did not (*5–8*). Breast cancer, however, is a heterogeneous disease with varying biologic characteristics, and the pathologic response to neoadjuvant chemotherapy is not always matched by prognosis. A recent metaanalysis found that in subgroups having slowly proliferating tumors, such as luminal-type, pCR did not correlate with prognosis (*7,8*). Among the tools to evaluate pathologic response, the residual cancer burden (RCB) index has been adopted for neoadjuvant chemotherapy. This index has a scoring system more advanced than the simple dichotomization of response as pCR or residual disease only (*9*), and it can provide strong prognostic information derived from the primary tumor dimensions, the cellularity of the tumor bed, and the axillary nodal burden.

^{18}F-FDG PET is a molecular imaging modality that reflects the biologic characteristics of a tumor and can predict its behavior and the patient's prognosis (*10–12*). In addition, ^{18}F-FDG PET is a sensitive technique for assessing response to therapy; studies have found that early changes in ^{18}F-FDG uptake by tumors after 1 or 2 courses of neoadjuvant chemotherapy can predict pathologic response (*13–16*). The aim of the present study was to investigate the prognostic impact of early changes in ^{18}F-FDG uptake in breast cancer patients who received neoadjuvant chemotherapy, especially compared with the RCB index.

MATERIALS AND METHODS

Patients

Between January 2004 and December 2011, 196 women with clinical stage II or III primary breast cancer received neoadjuvant chemotherapy. Of these, 87 patients who underwent ^{18}F-FDG PET/CT before starting the therapy and again after the third cycle were identified. Patients with distant metastasis or bilateral breast cancer were excluded. The study was approved by the institutional review board of Gangnam Severance Hospital, Yonsei University, Seoul, Republic of Korea, in accordance with good clinical practice guidelines and the Declaration of Helsinki, and the requirement to obtain informed consent was waived.

The clinical data of each patient were reviewed, and the pathologic findings were recorded. The modified Scarf–Bloom–Richardson system was used for tumor grading. Expression of estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (HER2), and Ki-67 was evaluated using formalin-fixed, paraffin-embedded tissue obtained from core biopsy or surgery. Immunohistochemistry staining was performed with appropriate antibodies for estrogen receptor (6F11; Novocastra), progesterone receptor (16; Novocastra), HER2 (4B5; Ventana Medical Systems), and Ki-67 (MIB-1; Dako). Estrogen receptor and progesterone receptor were determined by nuclear staining, which was scored from 0 to 8 using the system of Allred et al. (*17*). The results were categorized as positive when the total score, expressed as the sum of the proportion score and the intensity score, was 3 or greater. For HER2 evaluation, membranous staining was graded as 0, 1, 2, or 3 (*18*). A tumor with a score of 3 was considered positive, and equivocal results (in the case of a score of 2) were further tested by fluorescent in situ hybridization to confirm HER2 amplification (PathVysion HER2 DNA probe kit; Abbott-Vysis). The patients were categorized into 4 intrinsic subtypes using a Ki-67 cutoff of 14%, according to the criteria recommended by the St. Gallen panelists (*19*).

Neoadjuvant Chemotherapy

All but two of the patients received anthracycline-based neoadjuvant chemotherapy. The other two were treated with cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2), and 5-fluorouracil (600 mg/m^2) every 4 wk. Sixty-eight women received doxorubicin (50 mg/m^2) and docetaxel (75 mg/m^2) every 3 wk; 19 received cyclophosphamide (600 mg/m^2), doxorubicin (60 mg/m^2), and 5-fluorouracil (600 mg/m^2) every 4 wk; and 2 received doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 wk. After completion of the neoadjuvant chemotherapy, the patients underwent breast-conserving surgery or mastectomy with axillary lymph node dissection, followed by anti-HER2 therapy, endocrine therapy, or radiotherapy according to the standard guidelines.

^{18}F-FDG PET or PET/CT Method

The patients had fasted for at least 6 h and had a blood glucose level of less than 140 mg/dL before the ^{18}F-FDG (5.5 MBq/kg of body weight) was intravenously administered. Sixty minutes afterward, whole-body emission scans were obtained on an Allegro PET camera (Philips) (for patients imaged before 2008) or PET/CT scans were obtained on a hybrid scanner (Biograph 40 TruePoint or Biograph mCT 64; Siemens Healthcare Solutions USA, Inc.) (for patients imaged between 2008 and 2011). Whole-body CT images were obtained first for attenuation correction using automatic dose modulation with a reference of 40 mA and 120 kV without contrast enhancement. Then, PET data were acquired from the skull base to the proximal thigh for 3 min per bed position in 3-dimensional mode. The PET images were reconstructed using ordered-subset expectation maximization. For semiquantitative evaluation, SUV_{max} was calculated by measuring ^{18}F-FDG uptake by the primary tumor in the region of interest, as follows: SUV_{max} = [maximal radioactivity concentration in region of interest]/[injected dose/patient's weight (kg)]. The percentage reduction in SUV_{max} (ΔSUV_{max}) after the third cycle of chemotherapy was calculated as [100 × (baseline SUV_{max} − third-cycle SUV_{max})]/baseline SUV_{max}.

Pathology Assessment

All hematoxylin- and eosin-stained slides from the surgical specimens were reviewed, and the pathologic responses were evaluated. pCR was defined as no evidence of residual invasive cancer in the breast or axillary lymph nodes. Residual ductal carcinoma in situ was also defined as pCR. The RCB index was determined as described by Symmans et al. (*9*). Briefly, RCB index is derived from the primary tumor dimensions, the cellularity of the tumor bed, and the axillary nodal burden. RCB-0 indicates no residual disease; RCB-1, minimal residual disease; RCB-2, moderate residual disease; and RCB-3, extensive residual disease.

Statistical Analysis

To determine the optimal cutoff for ΔSUV_{max}, we applied the method of Contal and O'Quigley, which uses an algorithm that maximizes the hazard ratio (*20*). Recurrence-free survival was measured from the date of the first curative surgery to the date of the first tumor recurrence, including locoregional recurrence, distant metastasis, or death. Overall survival was measured from the date of the first curative surgery to the date of the last follow-up or until death from any cause during the follow-up period. The Kaplan–Meier method was used to estimate recurrence-free and overall survival. Multivariate Cox proportional-hazards regression was used to examine risk factors that showed statistical significance on univariate analysis. The concordance index, which is a measure of discrimination for model validation, was also examined.

All statistical analyses were performed using SPSS, version 18.0 (SPSS Inc.), and R (http://www.r-project.org) software. A P value of less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

Patient Characteristics

The clinicopathologic characteristics of the 87 patients are presented in Table 1. There were 17 patients with pCR and 6 patients with minimal residual disease (RCB-1). The median follow-up period was 61 mo (10–107 mo), during which 24 patients (27.6%) had recurrence and 15 patients (17.2%) died. All deaths were associated with breast cancer.

Relationship Between ΔSUV_{max} and pCR

The mean ΔSUV_{max} of the 87 patients was 69.1% (range, 4.2%–100%). Patients with pCR had a higher mean ΔSUV_{max} than those without pCR (81.6 vs. 66.0, $P = 0.016$). There was a negative correlation between ΔSUV_{max} and RCB index ($r = -0.408$; $P < 0.001$). The mean ΔSUV_{max} (±SD) was 81.5% ± 21.1 in RCB-0 patients, 76.0% ± 15.8 in RCB-1 patients, 71.4% ± 22.9 in RCB-2 patients, and 52.9% ± 24.5 in RCB-3 patients (Fig. 1).

Prognostic Impact of ΔSUV_{max}

On univariate analysis, an increased risk of recurrence was associated with advanced clinical N stage ($P < 0.001$), subtype ($P = 0.003$), and ΔSUV_{max} ($P < 0.001$) (Table 2). On multivariate analysis, clinical N stage, subtype, and ΔSUV_{max} were significant independent prognostic factors for recurrence-free survival, and the concordance index for this model was 0.82 (Table 3).

On univariate analysis for overall survival, the significant factors were clinical T stage ($P = 0.045$), N stage ($P = 0.005$), subtype

TABLE 1
Characteristics of the 87 Patients

Characteristic	Data
Age (y)	
Mean	46.1
Range	26–73
≤50	60 (69.0%)
50	27 (31.0%)
RCB index	
RCB-0	17 (19.5%)
RCB-1	6 (6.9%)
RCB-2	42 (48.3%)
RCB-3	22 (25.3%)
Clinical T stage	
I	12 (13.8%)
II	61 (70.1%)
III	9 (10.3%)
IV	5 (5.7%)
Clinical N stage	
I	53 (60.9%)
II	12 (13.8%)
III	22 (25.3%)
Modifier Bloom–Richardson score	
I	10 (11.5%)
II	29 (33.3%)
III	19 (21.8%)
Estrogen receptor	
Positive	36 (41.4%)
Negative	51 (58.6%)
Progesterone receptor	
Positive	29 (33.3%)
Negative	58 (67.7%)
HER2	
Positive	42 (48.3%)
Negative	45 (51.7%)
Ki-67	
High	30 (34.5%)
Low	56 (64.4%)
Subtype	
Luminal A	22 (25.3%)
Luminal B	17 (19.5%)
HER2	27 (31.0%)
Triple-negative	21 (24.1%)
pCR-positive	17 (19.5%)

Except for age, data are number of patients.

($P = 0.038$), and ΔSUV_{max} ($P = 0.014$) (Table 2). Although the Kaplan–Meier overall survival estimation showed a statistical difference according to RCB index ($P = 0.034$), the prognostic value of RCB index was not retained in the multivariate analysis because of statistical insignificance found on univariate Cox analysis ($P = 0.120$). In multivariate analysis, ΔSUV_{max} and clinical N stage were significant independent prognostic factors for overall survival ($P = 0.015$ and 0.05, respectively), and the concordance index of this model was 0.87 (Table 3).

Using the method of Contal and O'Quigley, we selected 66.4% as the optimal cutoff to maximize the difference between recurrence-free and overall survival for ΔSUV_{max}. Patients were categorized as metabolic responders if ΔSUV_{max} was greater than 66.4% and as metabolic nonresponders if 66.4% or less. There were 55 metabolic responders and 32 nonresponders, and they significantly differed in recurrence-free and overall survival (Fig. 2). In our current data, the smallest SUV_{max} reduction required to achieve a pathologic response (RCB-0 or RCB-1) was 39.3%. When we used this value as a cutoff for ΔSUV_{max} in the current study, similar results were observed. We further investigated whether there was any survival difference according to ΔSUV_{max} among the molecular subtypes of breast cancer. There was a statistically significant difference in recurrence-free survival and a tendency toward a difference in overall survival between metabolic responders and nonresponders for the luminal subtype ($P = 0.005$ and 0.061, respectively, Supplemental Fig. 1; available at http://jnm.snmjournals.org), and there was a statistically significant difference in recurrence-free survival between metabolic responders and nonresponders for the nonluminal (triple-negative and HER2) subtypes ($P = 0.042$).

Comparison of ΔSUV_{max} and RCB Index

We investigated whether there were any survival differences according to metabolic response between patients with a good pathologic response (RCB index ≤ 1) and those with a poor pathologic response (RCB index ≥ 2). Patients were categorized into 4 groups according to RCB index and ΔSUV_{max}: group 1 comprised pathologic responders and metabolic responders; group 2, pathologic responders and metabolic nonresponders; group 3, pathologic nonresponders and metabolic responders; and group 4, pathologic nonresponders and metabolic nonresponders. Within the groups that included pathologic nonresponders, the Kaplan–Meier recurrence-free and overall survival estimates differed significantly according to ΔSUV_{max} ($P = 0.007$ and $P = 0.017$,

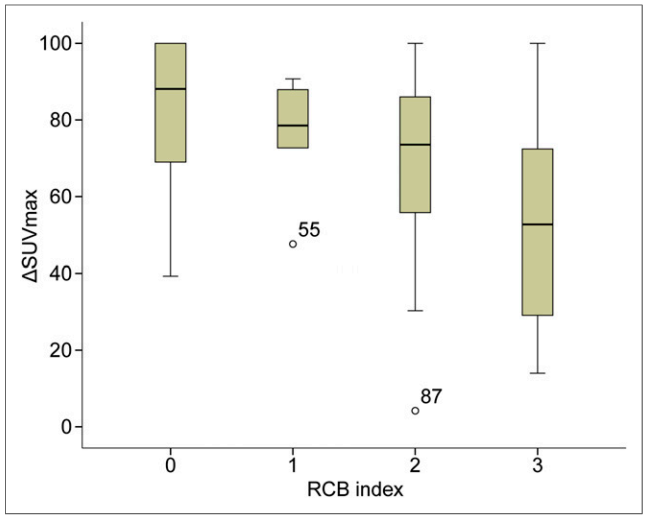

FIGURE 1. Comparison of ΔSUV_{max} according to RCB index.

TABLE 2
Univariate Analysis of Recurrence-Free and Overall Survival

Variable	Recurrence-free survival			Overall survival		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Age	1.12	0.48–2.61	0.797	1.09	0.37–3.19	0.877
HG			0.480			0.555
I	Reference			Reference		
II	0.97	0.26–3.67	0.968	0.51	0.11–2.29	0.381
II	1.72	0.46–6.50	0.422	0.99	0.24–4.16	0.993
RCB index			0.058			0.120
RCB-0	Reference			Reference		
RCB-1	0.00	0.00	0.982	0.00	0.00	0.987
RCB-2	1.47	0.40–5.34	0.560	2.44	0.29–20.28	0.410
RCB-3	4.04	1.12–14.50	0.033	6.96	0.87–55.72	0.067
Clinical T stage			0.113			0.045
I	Reference			Reference		
II	1.71	0.39–7.46	0.478	2.14	0.27–16.90	0.472
III	3.45	0.63–18.90	0.153	4.23	0.38–47.28	0.242
IV	5.97	1.00–35.87	0.051	11.97	1.23–116.06	0.032
Clinical N stage			<0.001			0.005
0 or I	Reference			Reference		
II	1.93	0.51–7.27	0.333	5.02	1.01–24.91	0.049
III	5.97	2.46–14.46	<0.001	8.80	2.38–32.55	0.001
Subtype			0.003			0.038
Luminal A	Reference			Reference		
Luminal B	1.03	0.23–4.61	0.967	1.48	0.21–10.58	0.695
HER2	1.11	0.30–4.12	0.882	1.39	0.24–8.35	0.716
Triple-negative	4.95	1.59–15.44	0.006	5.72	1.21–26.99	0.028
ΔSUV_{max}*	0.97	0.95–0.98	<0.001	0.98	0.96–0.99	0.014

*Continuous variable.
CI = confidence interval.

respectively, Fig. 3). Conversely, within the groups that included metabolic responders, there was no difference in either recurrence-free or overall survival according to RCB index ($P = 0.185$ and 0.523, respectively). When we used pCR and non-pCR to discriminate pathologic response, similar results were observed (Supplemental Fig. 2).

DISCUSSION

A potential advantage of neoadjuvant chemotherapy is the ability to monitor the degree of response. A previous randomized phase III study in which patients were randomly assigned to a regimen that would be maintained, versus one that would be prolonged or switched according to the early response to neoadjuvant chemotherapy, showed that response-guided neoadjuvant chemotherapy might improve survival in patients with early breast cancer (*21*). Thus, it is important to monitor early response in patients receiving neoadjuvant chemotherapy, and a wide variety of imaging and pathologic measurements have been used to assess the response so far.

Because ^{18}F-FDG PET can reflect the biologic characteristics of tumors, it is an attractive method for assessing the response to neoadjuvant chemotherapy (*12,13*). Prospective clinical studies showed that an early change in ^{18}F-FDG uptake is a surrogate marker of survival in patients with triple-negative breast cancer and even in patients with luminal HER2-negative breast cancer (*22,23*). The results of the present study also support these findings, and we additionally demonstrated that ΔSUV_{max} is a significant independent predictive and prognostic factor. Moreover, ΔSUV_{max} provided additional prognostic information in patients with pathologic nonresponse (high RCB index). Although pathologic response in metabolic responders failed to show a survival difference, ΔSUV_{max} was able to demonstrate the difference in recurrence-free and overall survival in pathologic nonresponders. Furthermore, we found that the smallest reduction in SUV_{max} required to achieve pathologic response was 39.3%, indicating that pathologic response becomes relevant only after a certain amount of metabolic response has occurred. Thus, metabolic response to neoadjuvant chemotherapy is more sensitive than pathologic

TABLE 3
Multivariate Analysis of Recurrence-Free and Overall Survival

Variable	Recurrence-free survival			Overall survival		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
RCB index			0.924			
RCB-0	Reference					
RCB-1	0.00	0.00	0.981			
RCB-2	1.62	0.41–6.42	0.490			
RCB-3	1.49	0.33–6.64	0.605			
Clinical T stage						0.265
I				Reference		
II				0.56	0.05–6.53	0.645
III				0.62	0.04–9.87	0.735
IV				2.82	0.18–44.20	0.461
Clinical N stage			0.015			0.05
I	Reference			Reference		
II	1.05	0.23–4.66	0.954	5.15	0.91–29.09	0.064
III	3.90	1.35–11.22	0.012	6.35	1.39–29.01	0.017
Subtype			0.002			0.111
Luminal A	Reference			Reference		
Luminal B	1.54	0.34–7.04	0.579	2.20	0.31–20.46	0.456
HER2	1.15	0.30–4.38	0.840	2.18	0.30–15.46	0.436
Triple-negative	6.93	2.05–23.35	0.002	6.55	1.15–32.14	0.024
ΔSUV_{max}*	0.97	0.95–0.99	<0.001	0.97	0.95–0.99	0.015

*Continuous variable.
CI = confidence interval.

response. Our previous study showed that in the adjuvant setting, prognosis correlates more significantly with the tumor-metabolism information provided by ^{18}F-FDG PET than with tumor burden (*24*). These findings suggest that tumor biology significantly affects not only prognosis but also response to neoadjuvant chemotherapy.

There have been efforts to advance the assessment of response to neoadjuvant chemotherapy by combining pathologic response and biologic factors. To assess prognosis after neoadjuvant chemotherapy, M.D. Anderson Cancer Center has described a new staging system based on pretreatment clinical stage, estrogen receptor status, grade, and posttreatment pathologic stage (*25*). Another group has provided proof of principle that the addition of posttreatment Ki-67, grade, and estrogen receptor to RCB improves the prediction of long-term outcome (*26*). However, all such systems essentially need postoperative pathologic findings. ^{18}F-FDG PET can provide prognostic information without pathologic findings and the surgery required to obtain them.

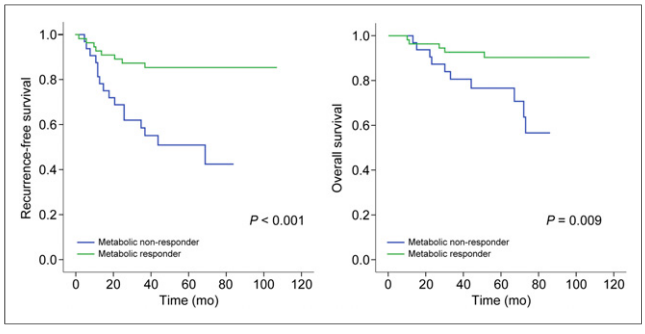

FIGURE 2. Kaplan–Meier survival curves according to cutoff of 64.4% for ΔSUV_{max}.

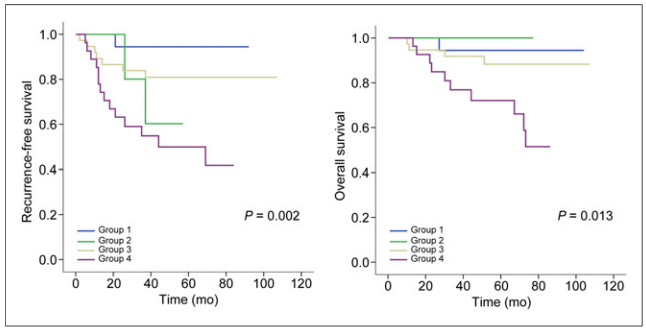

FIGURE 3. Kaplan–Meier survival estimates. *P* values for log-rank results for recurrence-free survival were 0.054 for groups 1 and 2, 0.185 for groups 1 and 3, 0.394 for groups 2 and 3, and 0.007 for groups 3 and group 4. *P* values for log-rank results for overall survival were 0.598 for groups 1 and 2, 0.523 for groups 1 and 3, 0.464 for groups 2 and 3, and 0.017 for groups 3 and 4.

Our study had some limitations related mostly to its retrospective nature. Because of differences in study populations, methods of evaluation, and types of treatment, as well as the limited number of patients in each study, there currently is no standard optimal cutoff for categorizing patients as metabolic responders or nonresponders according to survival outcome. The cutoff we selected, 66.4%, differs from that of previous studies (*22,23*). However, this study did not aim to define the standard optimal cutoff but to determine whether metabolic response as assessed by ^{18}F-FDG uptake can add information to pathologic response. Further prospective studies are required to determine the optimal cutoff.

CONCLUSION

We have highlighted the biologic and prognostic impact of an early change in ^{18}F-FDG uptake in patients with locally advanced breast cancer who received neoadjuvant chemotherapy. The reduction in ^{18}F-FDG PET SUV_{max} after the third cycle of neoadjuvant chemotherapy is an independent and good prognostic marker beyond pathologic response. We suggest that in these patients, the use of ΔSUV_{max} should be considered not only for the assessment of tumor response but for the prediction of posttreatment outcome.

DISCLOSURE

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