갑상선암의 ^{18}F-Fluorodeoxyglucose PET 섭취 유무에 따른 임상소견, 병리소견 및 초음파 소견의 비교에 대한 고찰

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^{18}F-Fluorodeoxyglucose Positron Emission Tomography for Primary Thyroid Cancer: Correlation with the Clinical, Pathologic and Sonographic Findings

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Purpose: We wanted to investigate the incidence and the clinicopathologic and sonographic characteristics of thyroid cancers that exhibit positive PET scans.

Materials and Methods: From January 2007 to February 2008, 156 patients with thyroid cancer underwent both sonography and FDG-PET for the purpose of staging the cancer. We conducted a retrospective review of their clinical, radiologic and pathologic records and we evaluated the incidence of PET-positive thyroid cancer, as well as the associated clinicopathologic aggressiveness and the sonographic features.

Results: The incidence of PET-positive thyroid carcinoma was 78.2% (122/156). On univariate analysis, PET-positive thyroid cancer was significantly associated with tumor size, extracapsular invasion and central lymph node metastasis, but there was no association between the sonographic features of the thyroid cancer or the sonographic features of the 2 groups of tumor (1. probably benign and 2. suspicious for malignancy) and the FDG uptake. Multivariate logistic regression analysis showed a significant association between PET positivity and both extrathyroidal extension and a higher cancer stage (III/IV) ($p < 0.05$).

Conclusion: The incidence of PET positive thyroid carcinoma is high (78.2%) and PET positivity is significantly associated with tumor size, extracapsular extension and a higher stage. However, there is no significant association between PET positivity and the sonographic features of thyroid carcinoma.

Key words : Thyroid; Positron emission tomography; Thyroid carcinoma

Introduction

Whole body ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is being increasingly used for cancer screening in healthy individuals as well as for the diagnostic work-up and follow-up of patients with a malignancy [1−3].

The role of PET has been emphasized for the postoperative surveillance of thyroid cancer. Several studies have demonstrated that poorly differentiated lesions have a propensity to be highly metabolically active and this causes positive PET scans [4−6], and one recent study has found that most recurrent or metastatic lesions with radioactive iodine-refractory positive PET are of the histologically aggressive type, as compared with the primary thyroid cancer [7]. The importance of the incidentally found PET positive

nodule has recently been reported. In several relatively large sample-size studies, the malignancy rate of thyroid incidentalomas that exhibit FDG uptake has been reported to be 26.7 − 50% [8−12]. Moreover, there was a report that the malignancy rate among PET-positive nodules was related with the sonographic findings, and the malignant rate was significantly lower for the nodules that show no suspicious features on ultrasonography (US) [13]. However, there has been no report about the clinicopathologic and sonographic characteristics of PET uptake in preoperative thyroid cancer.

Therefore, we are interested in studying how the behavior and US features of thyroid cancer are related to PET scans. Accordingly, the purpose of this study was to evaluate the incidence and the clinicopathologic and US characteristics of PET-positive thyroid cancer.

Materials and Methods

Patients

The Institutional Review Board of Yonsei University approved this study and neither patients' approval nor informed consent for review of their images and records was required. From January 2007 to February 2008, 570 patients underwent surgery due to thyroid cancer by a surgeon who specialized in thyroid cancer. During this period, all the patients with thyroid cancer were recommended by the surgeon to undergo FDG-PET and US for staging. Among them, 161 patients with thyroid cancer agreed to undergo a FDG-PET scan and they underwent both US and FDG-PET for the preoperative staging of thyroid cancer due to the patients' preference for these modalities. Five patients were excluded from the study because the uptake status of the thyroid cancer could not be evaluated due to diffuse uptake in both thyroid glands, which was caused by underlying diffuse thyroiditis [14]. Therefore, the study consisted of 156 patients (122 women and 34 men). The interval between PET and operation was less than 90 days for all the patients (range: 0 − 90 days, mean: 22.3 days).

^{18}F-FDG-PET imaging

All patients fasted for at least 4 hours and they had serum glucose levels of less than 140 mg/dl before the intravenous injection of FDG. Scanning was initiated 60 minutes after the administration of FDG. Images from the neck to the proximal thighs were obtained either on a GE advance PET scanner (GE advance, GE Medical Systems, Milwaukee, WI) with a spatial resolution of 5 mm in the center of the field of view (FOV) or on a Philips Allegro PET system (Allegro, Philips-ADAC medical systems, Cleveland, OH, USA) with a spatial resolution of 5.3 mm in the center of the FOV. For the GE advance, approximately 370 MBq of FDG was intravenously injected and the emission scan was 5 min/bed position in a 2 dimensional mode. The Allegro acquired data in a 3 dimensional mode after intravenous administration of 5.18 MBq (0.14 mCi/kg) of FDG. To correct for non-uniform attenuation, transmission scans (3 min/bed position) were obtained using point sources of Ge-68 for the GE advance or Cs-137 for the Allegro. For the Allegro, the transmission scans were then interleaved between the multiple emission scans. Finally, the images were reconstructed using an iterative reconstruction algorithm (the ordered subset expectation maximization (OSEM) for the GE advance, or the low action maximal likelihood algorithm (RAMLA) for the Allegro).

Interpretation and analysis of the ^{18}F-FDG-PET images

An experienced nuclear medicine physician qualitatively interpreted the FDG-PET images by visual inspection on a high-resolution computer screen. At that time, the physician knew both the cytologic and US results of all patients who underwent FDG-PET for the purpose of staging the thyroid cancer. Special attention was paid to the FDG uptake seen on US in the thyroid cancer. FDG uptake was considered positive when the activity was substantially greater than that in the adjacent soft tissue. We did not calculate the standardized uptake value (SUV) for the thyroid cancer with FDG uptake.

High-resolution thyroid US

US images were acquired using a 7- to 15-MHz linear array transducer (HDI 5000; Philips Medical Systems, Bothell, WA), an 8- to 15-MHz linear array transducer (Acuson Sequoia; Siemens Medical Solutions, Mountain View, CA) or a 5- to 12-MHz linear array transducer (iU22; Philips Medical Systems) for evaluation of the thyroid gland and the neck. With the use of the HDI 5000 or iU22 machine, compound imaging was performed for all the cases. Before FNAB, real-time US was performed by 1 of 3 radiologists with 4, 6 or 10 years experience in thyroid imaging, respectively. The thyroid cancers were retrospectively reviewed using the US features, including the internal components, echogenicity, the margin, calcifications and the shape based on the criteria suggested by Kim et al. [15]. The internal component was defined as either solid, mixed or cystic. A mixed component meant the mass had both solid and cystic components, and the US scans for the masses with mixed components were evaluated based on the internal solid component. Malignant US features were defined as marked hypoechogenicity (lower echogenicity than the surrounding strap muscle), microlobulated or irregular margins, microcalcifications and being taller than wide (a greater anteroposterior dimension than the transverse dimension). Thyroid nodules were considered suspicious for malignancy if one of the above findings was present on US. The US results were classified into one of two groups: "suspicious malignancy" or "probably benign". A lymph node was considered pathologic if it exhibited at least one of the following: focal or diffuse hyperechogenicity, internal calcifications, cystic change or a round shape [16, 17].

Histopathologic Analysis

Using the pathologic reports, we evaluated the multifocality, extracapsular extension and presence of central and lateral LNM. The pathologic staging was performed using the 6th edition AJCC/UICC TNM Classification system [18], Thyroid microcarcinoma was defined as a cancer of 1.0 cm or less in diameter on pathologic examination.

Statistical Analysis

The categorical data is presented as frequencies and percents. The chi-square test or Fisher's exact test were used to compare PET-positive thyroid cancer with the categorical variables. We also evaluated the association of PET-positive thyroid cancer with the continuous variables using independent two-sample t tests. Nonparametric statistics were used to compare the continuous variables. Comparisons of two groups were performed using the Wilcoxon rank sum test. Because thyroid microcarcinoma was about half of the tumor in this study, we also evaluated the association between PET-positive thyroid microcarcinoma and both the categorical and continuous variables. All the reported p-values are two-sided, and p values less than 0.05 were deemed statistically significant. Logistic regression analysis was performed to assess the odds ratios (ORs) of the significant predictive factors found in the univariate analysis.

Multivariate logistic regression analysis was performed to assess the independent associations between PET-positive thyroid cancer and all the factors found to be significant by univariate analysis after

Table 1. The Patients' Demographics and Clinical Characteristics

Variable	Number of Patients
N (Total)	156
Age	
Age at diagnosis (yr)	52.9±12.3 (22-83)*
Groups (< 45 vs. ≥45, yr)	43/113
Gender	
Female	122 (78.2%)
Male	34 (21.8%)
Primary tumor	
Size (mm)	14.4±10.3 (3-60)*
Multifocality	44 (28.2%)
Extracapsular invasion	96 (61.5%)
Capsule (T3)	90 (57.7%)
Strap muscle (T4a)	6 (3.8%)
Nodal involvement	
Central compartment	77 (49.4%)
Lateral compartment	41 (26.3%)

* Mean±standard deviation (SD), range

controlling for various established clinicopathological prognostic factors. The ORs with relative 95% confidence intervals (CIs) were also calculated to assess the relevance of all the potential predictors of the outcomes. All the analyses were performed using SAS software (version 9.1.3; SAS Institute, Cary, NC).

Results

Patient and Cancer Characteristics

Table 1 shows the demographic and clinical data of the 156 patients. One hundred forty-one patients (90.4%) underwent total, near total or subtotal thyroidectomy, while the remaining 15 underwent hemithyroidectomy due to the small size of the cancer and there was no evidence of lymph node metastasis (LNM). All the patients received central neck node dissection. Lateral neck node dissection was performed in 55 out of 156 patients (35.3%) whose preoperative US and clinical findings were suspicious for lateral LNM. Among them, 17 patients underwent bilateral neck dissection. Lateral LNM was found in 41 of the 156 patients (26.3%) and bilateral lateral LNM was found in 12 of the 41 patients with LNM (29.3%).

The thyroid cancers observed were divided into the following pathologic types: 142 conventional papillary carcinomas, 7 medullary carcinomas, 3 follicular carcinomas (2 widely aggressive, 1 minimally invasive), 2 follicular variant papillary carcinomas, 1 diffuse sclerosing variant of papillary carcinoma and 1 poorly differentiated carcinoma.

The Association of PET-Positive Thyroid Cancer with Various Clinical, Sonographic and Pathologic Features

The incidence of PET-positive thyroid carcinoma was 78.2% (122/156). On univariate analysis, PET-

Table 2. Correlation Between the Clinical and Histopathological Parameters and the Thyroid Carcinoma's FDG Uptake Status

	PET+	PET−	OR	95% CI	P value
N (Total)	122	34			
Age at diagnosis (yr)			0.4	0.2−1.1	0.058
< 45	38 (31.1%)	5 (14.7%)			
≥45	84 (68.9%)	29 (85.3%)			
Gender			1.4	0.5−3.7	0.508
Male	28 (23%)	6 (17.6%)			
Female	94 (77%)	28 (82.4%)			
Tumor size (mm)	13 (4−60)*	8 (3−30)*	1.2	1.1−1.3	< .001
Multifocality	35 (28.7%)	9 (26.5%)	1.1	0.5−2.6	0.8
Pathologic extracapsular invasion	85 (70%)	11 (32.4%)	1.8	2.1−10.9	< .001
Pathologic type			0.6	0.1−2.7	0.736
Conventional papillary carcinoma	110 (90.2%)	32 (94.1%)			
Other thyroid carcinoma†	12 (9.8%)	2 (5.9%)			
Central LNM	66 (54.1%)	11 (32.4%)	2.5	1.1−5.5	0.025
Lateral LNM	35 (28.7%)	6 (17.7%)	1.9	0.7−4.9	0.196
Stage			2.1	1−4.5	0.064
I/II	50 (41%)	20 (58.8%)			
III/IV	72 (59%)	14 (41.2%)			

PET+, thyroid cancer with FDG uptake; PET−, thyroid cancer without FDG uptake; OR, odds ratio; CI, confidence interval; LNM, lymph node metastasis

*Median (minimum-maximum)

†Other thyroid carcinomas included the follicular variant of papillary carcinoma, the diffuse sclerosing variant of papillary carcinoma, follicular carcinoma, medullary carcinoma and poorly differentiated carcinoma.

positive thyroid cancer was significantly associated with the tumor size, extracapsular invasion and central LNM (Table 2). However, PET positivity showed no association with the different pathologic types of cancer (p=0.941) (Table 3), nor was there any association when we divided the type of cancer into "conventional papillary thyroid carcinoma" and "other thyroid carcinoma". Although a higher PET-positive rate was observed for the thyroid cancers with multifocality, lateral LNM and higher (III/IV) stages, these results were not statistically significant.

Table 3. Correlation Between the Histopathological Types of Thyroid Carcinoma and the FDG Uptake Status

	PET+	PET−
N (Total)	122	34
Conventional papillary carcinoma	110	32
Medullary carcinoma	5	2
Follicular carcinoma	3	0
Follicular variant of papillary carcinoma	2	0
Diffuse sclerosing variant of papillary carcinoma	1	0
Poorly differentiated carcinoma	1	0

PET+, thyroid cancer with FDG uptake; PET−, thyroid cancer without FDG uptake

When we evaluated the association of PET positivity with several clinicopathologic factors of the 79 PET positive microcarcinomas (79 of the 156 total, 50.6%), the univariate analysis revealed a significant association with age, the tumor size and extracapsular invasion (Table 4). We also evaluated the association between the US features and FDG uptake, but we found no association between any of the US features/groupings ("probably benign," "suspicious malignancy") and FDG uptake (Table 5).

Multivariate logistic regression analysis was performed to assess the independent associations of PET-positive thyroid carcinoma and microcarcinoma with the various clinicopathological factors after controlling for other, known prognostic factors (age at the time of diagnosis, gender, multifocality and tumor size) [19-22]. There was a significant association between PET positivity and both extrathyroidal

Table 4. Correlation Between the Clinical and Histopathological Parameters and Thyroid Microcarcinoma's FDG Uptake Status

	PET+	PET−	OR	95% CI	P value
N (Total)	51	28			
Age at diagnosis (yr)			0.3	0.1-0.9	0.034
< 45	16 (31.4%)	3 (10.7%)			
≥45	35 (68.6%)	25 (89.3%)			
Gender			1.7	0.5-5.8	0.43
Male	11 (21.6%)	4 (14.3%)			
Female	40 (78.4%)	24 (85.7%)			
Tumor size (mm)	8 (4-10)*	7 (3-10)*	1.4	1.1-1.8	0.014
Multifocality	12 (23.5%)	7 (25%)	0.9	0.3-2.7	0.9
Pathologic extracapsular invasion	35 (68.6%)	7 (25%)	6.6	2.3-18.6	< .001
Pathologic type			0.9	0.1-10.5	1.000
Conventional papillary carcinoma	49 (96.1%)	27 (96.4%)			
Other thyroid carcinoma†	2 (3.9%)	1 (3.6%)			
Central LNM	22 (43.1%)	9 (32.1%)	1.6	0.6-4.2	0.34
Lateral LNM	9 (17.7%)	2 (7.1%)	2.8	0.6-13.9	0.212
Stage			2.4	0.9-6.2	0.07
I/II	20 (39.2%)	17 (60.7%)			
III/IV	31 (60.8%)	11 (39.3%)			

PET+, thyroid cancer with FDG uptake; PET−, thyroid cancer without FDG uptake; OR, odds ratio; CI, confidence interval; LNM, lymph node metastasis

*Median (minimum-maximum)

†Other thyroid carcinomas included the follicular variant of papillary carcinoma and medullary carcinoma.

extension and a higher cancer stage (III/IV) for all the thyroid cancers and the microcarcinomas ($p < 0.05$) (Table 6).

Discussion

^{18}F-FDG-PET has been used for primary staging, evaluating the treatment response and to detect recurrence of many malignancies [23]. For the evaluation of thyroid disease, ^{18}F-FDG-PET is usually used to detect a metastatic lesion after operation [24, 25] and to differentiate between benign and malignant tumors [11, 12, 26−28], although this is somewhat controversial [13, 29]. Recent studies have demonstrated that a thyroid nodule showing ^{18}F-FDG uptake may be malignant if it gives an indeterminate cytologic reading [27]. The relationship between the FDG avidity and tumor aggressiveness/differentiation appears to be in line with the limited sensitivity of preoperative FDG PET for ruling our malignancy in patients with thyroid nodules because the majority of thyroid nodules are well differentiated. Visually discernible FDG uptake is associated with a significantly higher prevalence of extrathyroidal extension and central lymph node involvement compared with that of the FDG-negative group [28]. Due to the flip-flop phenomenon (uptake of ^{131}Iodine with no FDG uptake and vice versa), FDG-PET can improve the detection of metastatic lesions when the iodine scan is negative and the serum thyroglobulin is elevated [24, 25]. Loss of the ability to concentrate radioactive ^{131}Iodine is associated with poor differentiation, resulting in a tumor that is refractory to ^{131}Iodine treatment. Metastatic thyroid lesions with negative ^{131}Iodine whole body scans and positive PET scans are associated with more aggressive clinical progression [30−32]. Some authors have reported that a high maximum SUV at the metastatic lesions from thyroid cancer is associated with an aggressive histologic type of cancer [7] and poor survival [33]. Yet there have been no reports on the association between PET-positive primary thyroid cancer and clinicopathologic aggressiveness.

Table 5. Correlation Between the Sonographic Parameters and Thyroid Carcinoma's FDG Uptake Status

	PET+	PET−	P value
N (Total)	122	34	
Echogenicity			0.891
Hyperechogenicity	0	0	
Isoechogenicity	13 (10.7%)	3 (8.8%)	
Hypoechogenicity	94 (77%)	26 (76.5%)	
Marked hypoechogenicity	15 (12.3%)	5 (14.7%)	
Margin			0.305
Well-circumscribed	23 (18.9%)	4 (11.8%)	
Microlobulated	44 (36.1%)	17 (50%)	
Irregular	55 (45%)	13 (38.2%)	
Calcifications			0.347
Microcalcifications	47 (38.5%)	12 (35.3%)	
Macrocalcifications	7 (5.7%)	4 (11.8%)	
Mix calcifications	35 (28.7%)	6 (17.6)	
Absent	33 (27.1%)	12 (35.3%)	
Shape			0.637
Wider than tall	63 (51.6%)	16 (47.1%)	
Taller than wide	59 (48.4%)	18 (52.9%)	
Sonographic grouping			0.455
Probably benign	7 (5.7%)	3 (8.8%)	
Suspicious for malignancy	115 (94.3%)	31 (91.2%)	

PET+, thyroid cancer with FDG uptake; PET−, thyroid cancer without FDG uptake

Table 6. Multivariate Analysis of the Association Between Thyroid Carcinoma's and Thyroid Microcarcinoma's FDG Uptake Status and the Clinicopathologic Outcome

	All Carcinoma			Microcalcinoma		
	OR	95% CI	P value	OR	95% CI	P value
Pathologic extracapsular invasion*	3.5	1.5−8.5	0.005	5.5	1.8−16.9	0.003
Central LNM*	2.1	0.8−5.2	0.12	1.9	0.6−6	0.249
Lateral LNM*	0.8	0.2−2.4	0.636	2.5	0.4−14.1	0.307
Higher stage (III/IV) *	5.1	1.8−14.5	0.002	8.3	2.1−32.4	0.003

LNM, lymph node metastasis; OR, odds ratio; CI, confidence interval
*Adjusted for age at diagnosis, gender, multifocality and tumor size.

In this study, we evaluated the association between clinical aggressiveness and PET-positive primary thyroid cancer, and we found that 78.2% (122/156) of the thyroid cancers were PET positive. Univariate analysis revealed that PET positivity was significantly associated with tumor size, extracapsular invasion and central lymph node metastasis (Table 2). When we evaluated the association between PET positivity and several clinicopathologic factors in 79 microcarcinomas, univariate analysis revealed that PET positivity was significantly associated with age, tumor size and extracapsular invasion (Table 4).

Many reports have found that poor clinical outcomes of thyroid cancer are associated with the patient age at diagnosis, gender, tumor size and multifocality [19-22], which led us to perform a multivariate analysis with adjusting for these known factors to identify the independent correlations between PET-positive thyroid cancer and several other clinicopathologic factors (Table 6). We found a significant association between PET-positive thyroid cancer and both extracapsular extension and a higher cancer stage ($p < 0.05$), and this was irrespective of size ($\leq$1 cm or >1 cm). Also we found FDG positivity of thyroid cancer showed no significant association with the known clinicopathological poor prognostic factors (age at diagnosis, gender, multifocality and tumor size).

Ito et al reported that thyroid microcarcinoma with poor edge definition (i.e., an ill defined margin) on US shows worse disease-free survival, and thyroid microcarcinoma with fine strong echoes (i.e., microcalcification) shows frequent recurrence [34]. So, they suggested that an ill-defined tumor edge is an important US feature of biologically aggressive papillary microcarcinoma. However, in our study, any sonographic feature was not associated with the PET positivity (Table 5). This may be explained by the interobserver variability in analyzing the US features of a nodule [35, 36] and the possibility that there is no relationship between the morphologic features on US and the metabolic and functional features on PET.

Dramatic advances in understanding the tumorogenesis of papillary thyroid carcinoma have been made over the past several years. Several reports have demonstrated that BRAF mutation [37-39], a S100A4 expression [40], an increased expression of transketolase-like-1 [41], the overexpression of cyclin D1 [42] and the underexpression of p27 [42] can be associated with the aggressiveness of thyroid carcinoma. Therefore, further studies will be needed to elucidate the association between PET-positive thyroid cancer and the known molecular factors related to the aggressiveness of thyroid cancer.

In our study, the incidence of PET-positive thyroid carcinoma was 78.2% (122/156). Yun et all reported that 53% (46/87) of the papillary thyroid microcarcinomas showed discernible FDG uptake. [28] Despite of the high incidence of PET positivity of thyroid carcinoma and the usefulness of PET scanning to detect the presence to detect the presence of malignancy, there is no consensus on the benefit and efficacy of PET in the setting of thyroid cancer. Therefore, it would be interesting to carry out further studies about the clinical significance of PET scanning in thyroid cancer patients.

There were several limitations to our study. First, we included only the thyroid cancer patients (28.2%, 161/570) who underwent both US and FDG-PET, which was performed at the patients' preference, meaning a selection bias could not be avoided. In the currently reported studies, the role of PET has been emphasized for the postoperative surveillance of thyroid cancer. But we did not include long-term follow-up result in our study. Therefore, further studies are required to evaluate the association between PET-positive thyroid cancer and recurrence and the survival rates.

In conclusion, the incidence of PET-positive thyroid carcinoma is high (78.2%). PET positivity of thyroid carcinoma is significantly associated with size, extracapsular extension and a higher cancer stage, but there is no significant association with the US features in our study.

요 약

목적 : 갑상선암 환자를 대상으로 FDG-PET 스캔상 섭취를 보이는 경우와 보이지 않는 경우의 임상 소견 및 병리학적, 초음파 소견에 대한 비교 연구.

대상 및 방법 : 2007년 1월부터 2008년 2월까지 수술 전 병기 결정을 위해 초음파와 FDG-PET 스캔을 모두 시행한 156명의 갑상선암 환자를 대상으로, 임상소견, 초음파 소견 및 병리학적 결과를 후향적으로 검토하였다. 또한 FDG 섭취를 보이는 갑상선암의 빈도, 임상병리학적 침윤성과 초음파 소견간의 상관성을 분석하였다.

결과 : FDG 섭취를 보이는 갑상선암의 빈도는 78.2% (122/156)이었다. 단일변량분석을 이용한 분석에서 FDG 섭취는 종양의 크기, 피막 외 침범 및 중심 림프절 전이와 유의한 상관관계가 있었다. 그러나 양성 (probably benign) 또는 악성 (suspicious malignant)을 시사하는 초음파 소견과 FDG 섭취 사이에는 유의한 상관 관계가 관찰되지 않았다. 다중 로지스틱 회귀분석을 이용한 분석에서 FDG 섭취를 보이는 갑상선암은 갑상선 바깥으로의 침범(extrathyroidal extension) 여부와 높은 병기(stage III/IV)에서 유의한 상관 관계를 보였다 ($p < 0.05$).

결론 : FDG 섭취를 보이는 갑상선암의 발병률은 높게 관찰되었으며 (78.2%), FDG 섭취는 종양의 크기, 피막 외 침범, 높은 병기와 유의한 상관관계가 있었다. 그러나 초음파 소견과의 유의한 상관관계는 나타나지 않았다.

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