

Isthmic Papillary Thyroid Carcinoma Presents a Unique Pattern of Central Lymph Node Metastasis

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Purpose: Treatment protocols for occult central lymph node metastasis (LNM) associated with papillary thyroid cancer (PTC) located in the isthmus are debatable. We aimed to analyze the pattern of occult central LNM in isthmic PTC, including risk factors for bilateral paratracheal LNM.

Patients and Methods: Consecutive patients with PTC were recruited to this study. All patients underwent total thyroidectomy and prophylactic bilateral central neck dissection. The clinicopathologic features and distribution of central LNM were compared between the two groups, and risk factors for bilateral paratracheal LNM were analyzed.

Results: A total of 174 patients with PTC were enrolled in this study, of whom 87 patients had isthmic PTC (study group) and 87 patients had lobe-originating PTC (control group). The two groups had comparable demographics and tumor features. There were higher frequencies of pretracheal LNM ($P = 0.001$) and bilateral paratracheal LNM ($P = 0.002$) in the isthmic PTC group. Bilateral paratracheal LNM was significantly associated with age < 55 years ($P = 0.037$), capsular invasion ($P = 0.034$), tumor location (isthmus) ($P < 0.001$), *BRAF* gene mutation ($P = 0.013$), and pretracheal LNM ($P < 0.001$). Isthmus location (odds ratio [OR]: 4.116, 95% confidence interval [CI]: 1.264–13.433, $P = 0.019$) and pretracheal LNM (OR: 3.422, 95% CI: 1.214–9.642, $P = 0.020$) were independent risk factors for bilateral paratracheal LNM.

Conclusion: Because of its unique anatomic location, isthmic PTC differs from PTC in the lobe with respect to pretracheal and bilateral paratracheal LNM, even in patients of comparable age, sex, tumor size, extrathyroidal extension, *BRAF* mutation, and pathologic TNM staging. The isthmus location was found to be an independent risk factor for bilateral paratracheal LNM. This information may contribute to the development of an appropriate surgical protocol for isthmic PTC.

Keywords: tumor location, bilateral paratracheal sub-compartments, risk factors

Introduction

Papillary thyroid cancer (PTC), which accounts for $>90\%$ of all thyroid malignancies, is a differentiated carcinoma with a relatively good prognosis and low mortality rate.¹ However, PTC is prone to central lymph node metastasis (LNM), which is associated with a high prevalence of locoregional recurrence.² In many patients, central LNM is undetected by preoperative imaging and intraoperative palpation, accounting for a clinically node-negative (cN0) group.³ The role and extent of prophylactic central neck dissection (CND) in patients with PTC remains controversial because of a lack of substantial evidence for benefit and the potential morbidity associated with the procedure.⁴

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Although the isthmus makes up only a small proportion of the thyroid, PTC located in the isthmus is not uncommon, with a prevalence of 12.3% reported by Lim et al⁵ and 10.2% by Chang et al.⁶ Isthmic PTC has a unique anatomic location, and its blood supply and lymphatic drainage differ from those of lobe-originating PTC.⁷ Sometimes, the isthmus presents with the fibers of Soemmerring's muscle. This is a small strap of muscle arising from the hyoid bone and inserting partly on the thyroid cartilage and partly on the isthmus. Such presentation can lead to a reliable diagnosis of extrathyroidal extension (ETE) in lobe-originating PTC, but not in isthmic PTC.^{8,9} In addition, some authors have reported that isthmic PTC has a higher central LNM rate compared with tumors in the lobe.^{10,11} Despite this evidence, the American Thyroid Association has not provided specific guidelines for managing isthmic PTC.³ Indeed, little is currently known about the pattern and predictors of occult central LNM in isthmic PTC. Therefore, various groups have applied different treatment protocols for occult central LNM, including isthmectomy alone or with limited CND,^{7,10} unilateral CND,^{5,12,13} and bilateral CND.¹⁴ Lymph node dissection in bilateral paratracheal sub-compartments is more complicated and hazardous than in unilateral central compartment owing to the risk of bilateral recurrent laryngeal nerve injury and damage to the parathyroid glands.

The goals of this study were: 1) to explore the pattern of occult central LNM in isthmic PTC versus lobe-originating PTC; and 2) to determine whether the isthmus location represents an additional risk factor for bilateral paratracheal LNM, which would help to inform appropriate treatment for occult central LNM in patients with isthmic PTC.

Patients and Methods

Patients

Consecutive patients with PTC being treated at our hospital between November 2016 and October 2019 were considered to the analysis. Approval for this study was obtained from the ethics committee of Qilu Hospital of Shandong University which compliance with the Declaration of Helsinki and a statement of written informed consent from all participants is required. All patients were diagnosed on high-resolution ultrasonography and in most cases, disease was confirmed by fine-needle aspiration. Computed tomography was performed in each patient for a detailed preoperative evaluation of

nodules and the central lymph nodes. All patients underwent total thyroidectomy and bilateral CND, with all procedures performed by the same surgeon. Exclusion criteria included multiple malignant carcinomas, cN1 PTC, other pathologic types of thyroid cancer, recurrent disease, previous neck surgery or a history of irradiation involving the neck region, and thyroid lobectomy or unilateral CND.

Patient data were extracted from medical records and analyzed for various clinicopathologic factors, including demographics, tumor features, and postoperative pathologic details.

Surgical Procedures

Operations were performed according to the method described by Koo et al.¹⁵ We divided the central compartment into the prelaryngeal (Delphian), pretracheal, and right and left paratracheal sub-compartments following recommendations previously reported by Orloff and Koppersmith.¹⁶ Prelaryngeal lymph nodes were bounded superiorly by the inferior border of the hyoid bone and inferiorly by the cricoid cartilage. Pretracheal lymph nodes were bounded superiorly by the inferior border of the gland, inferiorly by the innominate artery, and posteriorly by the trachea. Ipsilateral/contralateral paratracheal lymph nodes were demarcated laterally by the carotid artery and medially by the trachea.

Pathology Examination of Lymph Nodes in Sub-Compartments

We submitted lymph nodes to histology examination according to the protocol described by Haglund and colleagues.¹⁷ Upon removal, the thyroid and CND specimens (including fat tissue in sub-compartments) were sent directly to the Pathology Department of our hospital for gross diagnostic evaluation. First, macroscopically identified lymph nodes were dissected out of the fat, then bisected if they were ≥ 5 mm in greatest dimension. The only difference was that we selected patients with CN0 in the present study. The lymph nodes in each sub-compartment were not too large, so multiple-level sectioning (which can improve the diagnostic accuracy of larger lymph nodes¹⁷) was not adopted.

BRAF Mutation Analysis

Analyses of BRAF mutations were done in the Pathology Department of our hospital. DNA samples for molecular analyses were extracted from postoperative surgical

specimens using the QIAamp™ DNA FFPE Tissue kit (Qiagen, Stanford, VA, USA) following manufacturer instructions.

Definitions

PTC Located in the Isthmus

We defined PTC located in the isthmus according to Lim et al.⁵ Briefly, we first drew virtual lines perpendicularly from the most lateral point of the trachea to the surface of the skin on both sides. Next, we designated the center point of the tumor as the intersection of its longest and shortest diameters. If the center point of the tumor was located between the two virtual lines, it was deemed to be located in the isthmus (Figure 1).

Extrathyroidal Extension and Capsular Invasion

Extrathyroidal extension (ETE) is defined as tumor extension into the adjacent tissues, and subdivided into minimal and extensive ETE.⁹ Capsular invasion, which is a type of minimal ETE, is defined as microscopic invasion into the

immediate perithyroidal soft tissues without attachment to the surrounding muscular components.¹⁸ In this study, ETE specifically refers to macroscopic invasion into the sternothyroid muscle (T3 tumors) and extensive invasion into the subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve (T4a tumors).

TNM Staging

Pathologic tumor staging was determined in accordance with the American Joint Committee on Cancer staging system (8th edition).¹⁹

Statistical Analysis

SPSS Statistics 20.0 (SPSS, Inc., Chicago, IL) was used for data analysis and statistical significance was defined as $P < 0.05$. Continuous variables are shown as means \pm standard deviation, and were analyzed using *t*-tests. Categorical variables were compared using the χ^2 test or Fisher's exact test. Logistic regression was used for multivariate analysis.

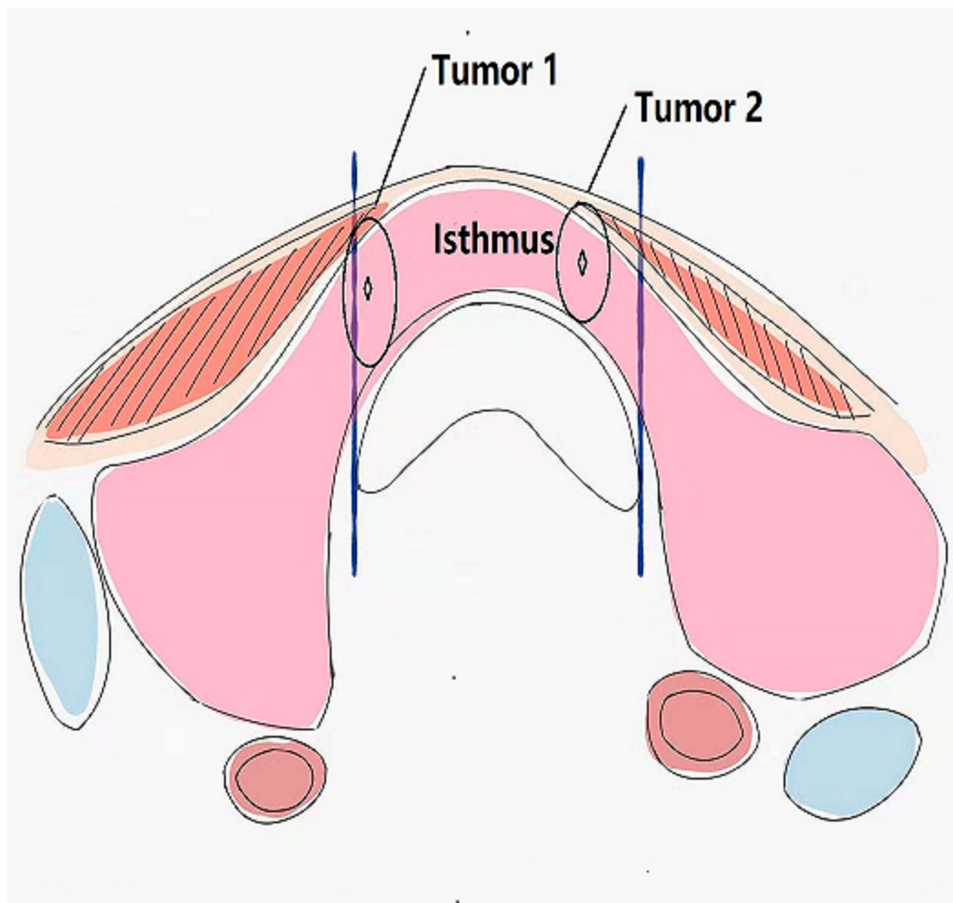


Figure 1 Papillary thyroid cancer located in the isthmus. Papillary thyroid cancer was defined as being located in the isthmus if the center point of the tumor was located between two virtual lines (both Tumor 1 and 2 were regarded as isthmus tumors).

Results

Demographic and Pathologic Features

A total of 174 patients with PTC were enrolled in this study and successfully underwent total thyroidectomy and bilateral CND, of whom 32 were men and 142 were women. Patient age ranged from 19 to 75 years, with a median of 49 years. A total of 87 patients had isthmus PTC, while 87 patients with PTC located in the right or left lobe formed the non-isthmus control group. The demographics and tumor features of the two groups are shown in Table 1. There were no significant differences between two groups in terms of sex, age, body mass index, tumor size, ETE, concomitant thyroiditis, pathologic subtype, *BRAF* gene mutation, or pathologic (p)TNM staging (all $P > 0.05$). However, capsular invasion was more frequent in the isthmus group than in the control group ($P < 0.001$).

Pattern of Central LNM

The overall central LNM rate was 63.2% (55/87) in the isthmus group and 49.4% (43/87) in the control group. Despite this numeric difference between the two groups, the difference was not statistically significant ($P = 0.067$). Regarding the distribution of central LNM, pretracheal LNM was significantly more frequent in the isthmus group compared with the control group (35.6% vs 13.8%, $P = 0.001$). Prelaryngeal LNM trended toward a higher rate in the isthmus PTC group, but the difference was not significant (20.7% vs 13.8%, $P = 0.229$). The overall rate of paratracheal LNM was comparable between the two groups (32.2% vs 31.0%, $P = 0.870$). However, bilateral paratracheal LNM was more significantly more frequent in the isthmus group compared with the control group (24.1% vs 6.9%, $P = 0.002$). In contrast, the control group had a significantly higher frequency of unilateral paratracheal LNM (24.1 vs 8.0%, $P = 0.004$) (Table 2).

Risk Factors for Bilateral Paratracheal LNM in PTC

On univariate analysis, bilateral paratracheal LNM was significantly associated with age < 55 years ($P = 0.037$), capsule invasion ($P = 0.034$), tumor location (isthmus) ($P < 0.001$), *BRAF* gene mutation ($P = 0.013$), and pretracheal LNM ($P < 0.001$), while sex, tumor size, ETE, pathology subtype, Hashimoto's thyroiditis, pTNM staging, and prelaryngeal LNM were comparable between the two groups (all $P > 0.05$) (Table 3). Isthmus location (odds ratio [OR]: 4.116, 95% confidence interval [CI]: 1.264–13.433, $P = 0.019$) and pretracheal LNM (OR: 3.422, 95% CI: 1.214–9.642, $P =$

Table 1 Comparison of the Baseline Demographics and Pathologic Features Between the Isthmus and Control Groups

Variable	Isthmus Group (n = 87)	Control Group (n = 87)	P value
Sex			
Male	14	18	0.434
Female	73	69	
Age			
< 55 years	58	53	0.430
≥ 55 years	29	34	
Body mass index, kg/m ²	25.4 \pm 4.1	25.1 \pm 3.8	0.617
Tumor size			
≤ 10 mm	31	29	0.750
> 10 mm	56	58	
Capsular invasion, yes/no	49/38	22/65	< 0.001
Extrathyroidal extension, yes/no	19/68	11/76	0.108
Intraglandular dissemination, yes/no	11/76	6/81	0.202
Concomitant thyroiditis, yes/no	22/65	29/58	0.244
Pathologic subtype			
Classical	59	54	0.427
Non-classical	28	33	
<i>BRAF</i> gene mutation, yes/no	65/22	61/26	0.497
pTNM stage, I/II/III/IV	65/4/12/6	59/3/21/4	0.349

Notes: Values are n or mean \pm standard deviation. Significant values are shown in bold. **Abbreviation:** pTNM stage, pathologic TNM stage.

0.020) were independent risk factors for bilateral paratracheal LNM on multivariate logistic regression analysis (Table 4).

Discussion

In this study, most clinicopathologic factors such as sex, age, body mass index, tumor size, ETE, concomitant thyroiditis, pathologic subtype, *BRAF* gene mutation, and pTNM staging were comparable between patients with isthmus PTC and those with non-isthmus, lobe-originating PTC. This is partly because the patients enrolled in this study were required to have surgical indications for total thyroidectomy and bilateral CND, which excluded patients with noninvasive, small PTC in a unilateral lobe who needed only a lobectomy and unilateral CND.

However, previous studies have reported a higher central LNM rate in isthmus compared with lobe-originating PTC.^{10,11,20} In these studies, patients with isthmus PTC

Table 2 Distribution of Cervical Lymph Node Metastasis in the Isthmus and Control Groups

Distribution, n (%)	Isthmus Group (n = 87)	Control Group (n = 87)	P value
Central LNM	55 (63.2)	43(49.4)	0.067
Pretracheal LNM	31 (35.6)	12 (13.8)	0.001
Prelaryngeal LNM	18 (20.7)	12 (13.8)	0.229
Paratracheal LNM	28 (32.2)	27 (31.0)	0.870
Unilateral	7 (8.0)	21 (24.1)	0.004
Bilateral	21 (24.1)	6 (6.9)	0.002

Note: Significant values are shown in bold.

Abbreviation: LNM, lymph node metastasis.

had a higher frequency of ETE and multifocality, which were predictors of central LNM and also associated with contralateral paratracheal LNM^{10,11,20,21} Therefore, we cannot know whether the higher central LNM rate in isthmus PTC is due to a higher frequency of ETE and multifocality or to the unique anatomic location of isthmus PTC. To determine this, we have explored the pattern of LNM in isthmus PTC in two groups with similar basic data, which seems likely to give more meaningful results.

In our study, the isthmus group had a higher frequency of capsular invasion than the control group (56.3% vs 25.3%, $P < 0.001$), which is consistent with previous results.^{10,22} A high frequency of capsular invasion may be attributable to the thin shape of the isthmus,¹⁸ and appears to be independent of tumor size because it has also been reported to be common in isthmus microcarcinomas.²⁰ According to our study, only the higher frequency of capsular invasion may have little effect on central LNM. Recently, Li et al also reported no difference in central LNM between PTC patients with and without capsular invasion.²³

This study found an occult central LNM rate of 63.2% in the isthmus group, which is within the reported range from previous series (29.6–71.1%).^{12,14,22,24,25} Although isthmus PTC was more prone to central LNM than the control group, there was no significant difference between the two groups (63.2% vs 49.4%, $P = 0.067$). Similar findings have been reported in a previous study, in which the isthmus PTC group trended toward having a higher rate of central LNM ($P = 0.09$), but a significant difference was not shown because of comparable multifocal disease ($P = 0.08$) and ETE ($P = 0.09$) between the isthmus and non-isthmus groups.²⁴

Table 3 Univariate Analysis of the Clinical Pathologic Factors Associated with Bilateral Paratracheal LNM in Papillary Thyroid Cancer

Variable	Number and Percentage of Patients with Bilateral Paratracheal LNM			χ^2	P value
	Yes	No	M rate		
Age					
<55 years	22	89	19.8%	4.329	0.037
≥55 years	5	58	7.9%		
Sex				1.209	0.272
Female	20	122	14.1%		
Male	7	25	21.9%		
Tumor size				0.019	0.891
≤10 mm	9	51	15.0%		
>10 mm	18	96	15.8%		
Capsule invasion				4.506	0.034
Yes	16	55	22.5%		
No	11	92	10.7%		
Extrathyroidal extension				3.437	0.064
Yes	8	22	26.67%		
No	19	125	13.19%		
Tumor location				17.955	<0.001
Isthmus	22	55	28.6%		
Lobe	5	92	5.2%		
Pathologic subtype				0.453	0.501
Classical	16	97	14.16%		
Non-classical	11	50	18.03%		
Hashimoto's thyroiditis				0.177	0.674
Yes	7	44	13.73%		
No	20	103	16.26%		
BRAF gene mutation				6.230	0.013
Yes	25	102	19.7%		
No	2	45	4.3%		
TNM staging				0.025	0.874
I + II	20	111	15.3%		
III + IV	7	36	16.3%		
Pretracheal LNM				22.454	<0.001
Yes	18	32	36.0%		
No	9	115	7.3%		
Prelaryngeal LNM				0.556	0.456
Yes	6	24	20.00%		
No	21	123	14.6%		

Note: Significant values are shown in bold.

Abbreviation: LNM, lymph node metastasis.

Table 4 Multivariate Analysis of the Clinical Pathologic Factors Associated with Bilateral Paratracheal LNM in Papillary Thyroid Cancer

Variable	β	SE	Wald	P	Exp(β)	95% CI
Age <55 years	0.282	0.516	0.300	0.584	1.326	0.483–3.644
Capsule invasion	0.872	0.476	3.355	0.067	2.392	0.941–6.081
Isthmic tumor	1.415	0.604	5.496	0.019	4.116	1.264–13.433
<i>BRAF</i> gene mutation	1.178	0.677	3.029	0.082	3.248	0.861–12.244
Pretracheal LNM	1.230	0.529	5.415	0.020	3.422	1.214–9.642
Constant	–5.313	1.546	11.808	0.001	0.005	1.214–9.642

Note: Significant values are shown in bold.

Abbreviations: β , regression coefficient; CI, confidence interval; Exp(β), odds ratio; LNM, lymph node metastasis; SE, standard error.

Although there was no significant difference in the overall central LNM rate in the current study, both pretracheal LNM and bilateral paratracheal LNM were significantly more frequent in the isthmus group compared with the control group (pretracheal LNM: 35.6% vs 13.8%, $P = 0.001$; bilateral paratracheal LNM: 24.1% vs 6.9%, $P = 0.002$), and only unilateral paratracheal LNM was more involved in the control group (24.1% vs 8.0%, $P = 0.004$). Song et al also reported that pretracheal and bilateral paratracheal lymph nodes were more likely to be affected in patients with isthmus PTC, with involvement rates of 26.0% and 38.4%, respectively.²⁵ A limitation, however, was that the participants enrolled in their study included not only patients with cN0 but also those with cN1. The homogeneity of the patients in our study might contribute to a more reliable result. The exact pathophysiologic mechanism explaining the distribution and incidence of LNM in sub-compartments is unclear. A possible explanation is that the lymphatics from the isthmus drain more easily into the inferior pretracheal sub-compartment, and subsequently into the bilateral paratracheal sub-compartment.²⁰ As to prelaryngeal LNM, Lee et al previously reported it was significantly associated with isthmus PTC.²⁶ In this study, the isthmus group trended toward a higher rate of prelaryngeal LNM, but there was no significant difference between two groups (20.7% vs 13.8%, $P = 0.229$), perhaps because the prelaryngeal sub-compartment simultaneously receives afferent lymphatic drainage from the isthmus and thyroid lobes.¹³

To the best of our knowledge, little is currently known about whether an isthmus location of PTC is an independent risk factor for bilateral paratracheal LNM. Isthmus location has previously been reported to be predictor of central LNM, which was not found to contribute to the extent of CND for patients with cN0 disease.^{14,25,27,28} The same was true for the relationship between isthmus PTC

and prelaryngeal LNM, as reported by Lee et al.²⁶ And, as mentioned above, the data from most of these studies have been heterogeneous in terms of ETE, multifocality, and nodal status in the central compartment,^{14,25} which will have affected the accuracy of the results. In the current study, bilateral paratracheal LNM involvement was associated with age (<55 years), capsular invasion, *BRAF* gene mutation, pretracheal LNM, and tumor location in the isthmus. Isthmic location represented an independent risk factor for bilateral paratracheal LNM on multivariate analysis.

Our findings indicate that bilateral CND is an appropriate surgical procedure for occult central LNM of isthmus PTC. Surgical protocols including limited or ipsilateral CND can reduce the risks of bilateral recurrent laryngeal nerve injury and damage to the parathyroid glands, but their disadvantages are obvious from treatment effectiveness evaluations. In a large retrospective study that included data from 1810 patients with isthmus PTC over a 20-year period, isthmusectomy alone was suitable for just 19 patients (1%) with small, noninvasive, and well-differentiated PTC in the isthmus.⁷ In addition, limited or ipsilateral CND for patients with isthmus PTC is more often associated with short-term recurrence in the contralateral central compartment,¹³ and approximately a third of patients (32%) have a serum thyroglobulin concentration of more than 2.0 U/mL after postoperative iodine-131 remnant ablation.¹²

Strengths of this study include the prospective design, the homogeneity of the participants, and its high practical value because of the involvement of bilateral paratracheal LNM. Limitations are the short follow-up time to assess outcomes and the lack of investigations into mechanisms that might explain findings. As reported by Conzo et al,²⁹ the effect of CND in PTC on survival and recurrence is controversial. Additional long-term perspective studies are

therefore needed to further analyze outcomes and clarify the LNM mechanism of isthmic PTC, which may involve epithelial–mesenchymal transition related to the unique anatomy and blood supply of the isthmus location within the thyroid.

Conclusions

Because of its unique anatomic location, isthmic PTC differs from PTC in the thyroid lobes with respect to pretracheal and bilateral paratracheal LNM, even in patients of comparable age, sex, tumor size, ETE, *BRAF* mutation, and pTNM staging. The isthmus location was found to be an independent risk factor for bilateral paratracheal LNM. This information may contribute to the development of an appropriate surgical protocol for isthmic PTC.

Abbreviations

CND, Central neck dissection; ETE, Extrathyroidal extension; LNM, Lymph node metastasis; PTC, Papillary thyroid cancer; pTNM, Pathologic TNM; cN0, Clinically node-negative; cN1, Clinically node-positive.

Disclosure

The authors report no conflicts of interest in this work.

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