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Risk factors and distribution pattern of lateral lymph node recurrence after central neck dissection for cN1a papillary thyroid carcinoma

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Abstract

Background The indication and extent of selective lateral neck dissection (LND) for cN1a papillary thyroid carcinoma (PTC) remain uncertain. The present study aimed to identify potential predictors and distribution pattern of lateral lymph node recurrence (LLNR) after central neck dissection in cN1a PTC patients.

Methods The cN1a PTC patients who underwent initial central neck dissection at our centre were retrospectively reviewed, and the median follow-up period was 6.8 years. Reoperation with LND was performed when LLNR was confirmed. Risk factors for LLNR were identified, and the metastatic status of each lateral level was recorded.

Results Of the 310 patients enrolled in the present study, fifty-eight patients (18.7%) presented with LLNR. Six independent factors, including tumour diameter, pathological T4 stage, number of involved central lymph nodes, pTNM stage, extrathyroidal extension, and I^{131} treatment (*P* values < 0.05) were identified via multivariate analysis. LLNR was found at level II in 26 patients (44.8%), level III in 38 patients (65.5%), level IV in 30 patients (51.7%), and level V in 8 patients (13.8%). The number of positive lateral lymph nodes at levels II, III, IV and V was 44 (22.9%), 76 (39.6%), 63 (32.8%), and 9 (4.9%), respectively.

Conclusions For cN1a PTC patients who underwent central neck dissection, tumour diameter ≥ 2 cm, pathological T4 stage, number of involved central lymph nodes ≥ 3, pTNM stage III-IV, extrathyroidal extension, and failure to receive I^{131} treatment were independent predictors of LLNR, which was more likely to occur at levels III and IV.

Keywords cN1a, papillary thyroid carcinoma, Lateral lymph node recurrence, Central neck dissection, Lateral neck dissection, Risk factors

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Background

Thyroid cancer is an endocrine malignancy with an increasing incidence and tendency in younger individuals [1]. As the most common pathological type of thyroid carcinoma, papillary thyroid carcinoma (PTC) is characterized by low malignancy, slow progression, and good prognosis, but patients with PTC are vulnerable to early cervical nodal metastasis [2, 3], which is closely associated with tumour persistence, recurrence, and a relatively poor prognosis [4].

At present, the indications and extent of lateral neck dissection (LND) for cN1a PTC patients are controversial. It has been reported that nearly 20% of PTC patients are accompanied by lateral lymph node metastasis once diagnosed [5, 6], but routine prophylactic LND is not generally recommended because of the higher frequency of complications due to greater surgical invasiveness [7, 8]. The accuracy of preoperative imaging (such as Doppler ultrasound and computed tomography) for evaluating cervical nodal metastasis is only 67.6% [9], thus, the neglect of early metastatic lymph nodes easily causes unradical dissection and increases locoregional lymph node recurrence. As a result, selective LND for cN1a patients with high-risk factors is recommended in the latest guidelines from China (medium-quality evidence) [10]. However, a consensus on the identification of these risk factors has not been reached. Therefore, knowledge of predictors of lateral lymph node recurrence (LLNR) facilitates the identification of cN1a PTC patients who should receive LND.

The occurrence and number of lateral lymph node metastases differ with levels II-V. The latest American Thyroid Association (ATA) guidelines recommend that patients with lateral lymph node metastasis should undergo LND at levels IIa, III, IV, and Vb [11]. Spinal accessory nerve injury is not uncommon after dissection at levels IIa or Vb, and the value of selective LND at these two levels remains controversial. There is still no evidence to determine the most appropriate extent for selective LND, but most scholars favour anatomic neck dissection instead of berry-picking surgery [12, 13]. To date, few studies have summarized the risk factors for LLNR after central neck dissection in cN1a PTC patients to identify potentially valuable participants for selective LND. The present aimed to investigate the indications and optimal surgical extent of selective LND by retrospectively analysing all the records of LLNR in cN1a PTC patients who underwent central neck dissection from 2013 to 2017 at Taihe Hospital Affiliated to Hubei University of Medicine.

Materials and methods

Patients

The clinical information of cN1a PTC patients admitted to the Department of Thyroid Surgery at Taihe Hospital Affiliated to Hubei University of Medicine from January 2013 to December 2017 who underwent central neck dissection was retrospectively collected. Postoperative pathological staging was performed according to the American Joint Committee on Cancer (AJCC) 8th edition staging system [14]. The majority of the Doppler ultrasounds were completed in our centre, except for 10% of the PTC patients whose preoperative Doppler ultrasounds were completed at the county hospital. the diagnostic criteria for cervical lymph node metastasis were based on the US-guided fine needle aspiration for cytology for positive signs of cervical lymph nodes via a colour ultrasonic scanner. The positive sonographic features of abnormal metastatic lymph nodes included lymph node enlargement, calcification, cystic change, hypoechogenicity, a rounded rather than oval shape, loss of the fatty hilus, and peripheral vascularity [15]. The inclusion criteria were as follows: 1) the preoperative lymph node stage was limited to cN1a on the basis of puncture biopsy pathology for positive signs of central lymph nodes, and no abnormal signs for lateral lymph nodes were found on Doppler ultrasound; (2) the initial intervention was limited to therapeutic central neck dissection; and (3) the LND reoperation was performed once the postoperative LLNR was determined by pathology after needle biopsy when lateral nodal abnormity was detected by imaging. The exclusion criteria were as follows: (1) other types or mixed types of thyroid malignancies were pathologically diagnosed; (2) PTC patients with distant metastasis; and (3) the clinicopathological data were not intact. The present study was conducted with the informed consent of the PTC participants.

Data collection and follow-up

After the establishment of the database, sex (male vs. female), BMI (≥25 kg/m^2 vs. <25 kg/m^2), ECOG physical status score (1 point vs. 0 points), anaesthetic risk ASA score (1 point vs. 2 points vs. 3 points), surgical method (total incision vs. subtotal resection), tumour location (upper pole vs. middle pole vs. lower pole), tumour diameter (≥2 cm vs. <2 cm), pT stage (T4 vs. T1-3), number of positive lymph nodes in the central region (≥3 vs. <3), TNM stage (III-IV vs. I-II), vessel carcinoma embolus (yes vs. no), perineural invasion (yes vs. no), multifocal lesions (yes vs. no), extrathyroidal extension (yes vs. no), Hashimoto thyroiditis (yes vs. no), preoperative hyperthyroglobulin (level of thyroglobulin in serum≥40 μg/L according to the chemiluminescence method) (yes vs. no), and postoperative I^{131} treatment (yes vs. no) were analysed to identify the risk factors for LLNR. Both the

number of LLNRs for patient-based data and node-based data at different levels were collected. All patients were followed up for more than 5 years until December 31, 2022.

Treatment methods

Total or subtotal thyroidectomy was performed according to the tumour diameter and location, and initial central neck dissection was performed according to Chinese guidelines [16]. First, therapeutic central neck dissection was routinely performed, and LND was conducted only if lateral nodal metastases were revealed by preoperative ultrasonography and further confirmed by puncture biopsy pathology. Second, postoperative thyroglobulin levels and lymph node metastasis were monitored to determine whether patients should receive I^{131} adjuvant therapy. After total resection, patients were prescribed levothyroxine tablets to suppress thyroid function and prevent tumour recurrence. Thyroglobulin and cervical ultrasound were performed every 6 months to monitor for recurrence in PTC patients. Third, lymph node metastasis was diagnosed based on B-ultrasound or computed tomography signs of cervical lymph node metastasis, which was further confirmed by puncture biopsy pathology. Finally, a secondary operation for lateral neck dissection was performed in those who did not complete total thyroidectomy during the previous operation, in which complete excision of the residual thyroid was performed. For suspicious lymph nodes in the central region, supplementary dissection was performed. Lateral lymph nodes at levels *II*, *III*, *IV*, and *V* were dissected.

Statistical methods

The data were analysed with STATA 14.0. Quantitative data with a normal distribution are represented by $x \pm s$, and qualitative data are expressed as frequencies and percentages. The $\chi 2$ test or Fisher's exact probability method was used for comparisons between groups, and statistically significant factors were introduced into the logistic regression model for multivariate analysis. $P<0.05$ was considered statistically significant.

Results

Patient characteristics

According to the inclusion and exclusion criteria, A total of 310 cN1a PTC patients who underwent central neck dissection were included. The median follow-up period was 6.8 years. The characteristics of the patients and tumours are listed in Table 1. There were 58 patients with LLNR (18.7%, recurrent group) and 252 patients without postoperative LLNR (81.3%, nonrecurrent group).

Correlation between pathological characteristics and LLNR

As shown in Table 1, comparison of the pathological characteristics of the two groups indicated that sex, age, BMI, ECOG score, ASA score, tumour location, vessel carcinoma embolus, perineural invasion, Hashimoto's thyroiditis, resection extent, and elevated thyroglobulin were not associated with postoperative LLNR (all *P* values > 0.05). However, tumour diameter, pathological T4 stage, TNM stage, number of positive central lymph nodes, extrathyroidal extension, multifocal lesions, and postoperative I^{131} treatment were correlated with postoperative cervical LLNR (all *P* values < 0.05).

The above seven statistically significant influencing factors were introduced into a logistic regression model for multivariate analysis. A tumour diameter ≥ 2 cm, pathological T4 stage, number of positive central lymph nodes ≥ 3, pTNM III-IV stage, and extrathyroidal extension were determined to be independent risk factors for LLNR (all P values < 0.05). Postoperative I^{131} treatment (OR = 0.43, $P=0.044$) was an independent protective factor for LLNR (Table 2).

Distribution of LLNR for patient-based data

Among the 58 PTC cases with LLNR, 16 cases (27.6%) were located in the upper pole, 20 cases (34.5%) were located in the middle pole, and 22 cases (37.9%) were located in the lower pole. Among them, 22 patients (37.9%) had one-level metastasis, 28 patients (48.3%) had two-level metastasis, and 8 patients (13.8%) had three-level metastasis. Thirty-six patients (62.1%) had multiple-level metastasis. As shown in Table 3, the percentages of LLNR patients with levels II, III, IV, and V were 44.8%, 65.5%, 51.7%, and 13.8%, respectively.

Distribution of LLNR for lymph node-based data

As shown in Table 4, the number of positive lymph nodes was distributed at each level across the different tumour sites. A total of 192 lymph nodes metastasized in 58 patients. The percentages of positive lymph nodes at levels II, III, IV, and V were 22.9% (44/192), 39.6% (76/192), 32.8% (63/192), and 4.7% (9/192), respectively. The percentages of involved lymph nodes were 25% (48/192), 33.3% (64/192), and 41.7% (80/192) when the primary lesions were located in the upper, middle, and lower poles of the glandular lobe, respectively.

Discussion

In the present study, the preoperative lateral lymph nodes were negative in all the participants, but the incidence of LLNR after central neck dissection was as high as 18.7%. In 2014, an American study has reported that 21 (3.4%) of 610 cN0 PTC patients who partially underwent CND experienced lateral lymph node recurrence after a mean of 35.9 months. However, in the present study,

Table 1 Univariate analysis for LLNR in cN1a PTC patients undergoing central neck dissection

Variables	Nonrecurrent group($n=252$)	Recurrent group($n=58$)	X^2/t	*P*
Sex				
Female	99	24	0.09	0.769
Male	153	34		
Age				
< 55	116	22	1.25	0.263
≥ 55	136	36		
BMI				
< 25 kg/m^2	154	33	0.35	0.554
≥ 25 kg/m^2	98	25		
ECOG performance status				
0	217	54	2.10	0.148
1	35	4		
ASA score				
1	189	46	0.96	0.608
2	53	9		
3	10	3		
Resection extent				
Subtotal thyroidectomy	120	30	0.32	0.573
Total thyroidectomy	132	28		
Tumour location				
Upper pole	80	16	1.97	0.373
Middle pole	108	20		
Lower pole	64	22		
Tumour diameter				
< 2 cm	160	27	5.65	0.020
≥ 2 cm	92	31		
pT stage				
T_{1-3}	228	42	13.68	0.001
T_4	24	16		
No. of CLNM				
< 3	153	23	8.52	0.004
≥ 3	99	35		
pTNM stage				
I-II	228	42	13.68	0.001
III-IV	24	16		
Vessel carcinoma embolus				
No	140	25	2.94	0.087
Yes	112	33		
Perineural invasion				
No	141	26	2.35	0.125
Yes	111	32		
Multifocal lesions				
No	212	41	5.67	0.017
Yes	40	17		
Extrathyroidal extension				
No	196	37	4.94	0.026
Yes	56	21		
Hashimoto thyroiditis				
No	228	50	0.13	0.719
Yes	24	8		
Preoperative hyperthyroglobulin				
No	142	26	2.52	0.112
Yes	110	32		

Table 1 (continued)

Variables	Nonrecurrent group($n=252$)	Recurrent group($n=58$)	X^2/t	*P*
I^{131} treatment				
No	180	49	4.16	0.046
Yes	72	9		

Note: LLNR: lateral lymph node recurrence; PTC: thyroid papillary carcinoma; CLNM, central lymph node metastasis; ECOG, Eastern Cooperative Oncology Group; ASA score, American Society of Anaesthesiologists' physical status classification system

Table 2 Multivariate analysis of LLNR in cN1a PTC patients undergoing central neck dissection

Variables	Multivariate analysis		
	OR	95% CI	*P*
Tumour diameter (≥ 2 cm vs.<2 cm)	1.79	1.00-3.18	0.043
pT stage (T_4 vs. T_{1-3})	2.67	1.31–5.45	0.018
No. of CLNM (≥ 3 vs.<3)	1.87	1.04–3.35	0.035
pTNM stage (III-IV vs. I-II)	2.67	1.31–5.45	0.018
Multifocal lesions (yes vs. no)	1.68	0.87–3.24	0.077
Extrathyroidal extension (yes vs. no)	1.84	1.05–3.67	0.039
I^{131} treatment (yes vs. no)	0.43	0.20–0.92	0.044

Note: LLNR: lateral lymph node recurrence; PTC: thyroid papillary carcinoma; CLNM, central lymph node metastasis

Table 3 Distribution of LLNR for patient-based data with different primary tumour locations

Tumour location	Patients with LLNR, (%) *n/N*			
	Level II	Level III	Level IV	Level V
Upper pole	17.2(10/58)	17.2(10/58)	10.3(6/58)	0(0/58)
Middle pole	13.8(8/58)	24.1(14/58)	17.2(10/58)	3.5(2/58)
Lower pole	13.8(8/58)	24.1(14/58)	24.1(14/58)	10.3(6/58)
Total	44.8(26/58)	65.5(38/58)	51.7(30/58)	13.8(8/58)

Note: LLNR, lateral lymph node recurrence. Of the 58 patients, 22 had single-level metastasis, 28 had two-level metastasis, and 8 had three-level metastasis

the enrolled subjects were cN1a PTC patients who had a relatively high N stage and were relatively prone to lateral neck recurrence [17]. In addition, the preoperative Doppler ultrasound examinations of 10% of the patients with papillary thyroid carcinoma (PTC) were completed in county hospitals, which to a certain extent affected the accuracy of the present results. Besides, the high incidence of LLNR may be explained by the inconsistency of diagnostic criteria, as no single sonographic feature was adequately sensitive for the detection of lymph nodes with metastatic thyroid cancer. In PTC patients, a meta-analysis [18] has revealed that the pooled region-based or node-based sensitivity for preoperative ultrasonography was 0.63 (95% CI, 0.47–0.76) and that the specificity was 0.93 (95% CI, 0.73–0.99). Initial preoperative understaging leads to inadequate lymph node dissection. Therefore, identification of the variables associated with LLNR helps to strengthen the preoperative assessment in high-risk patients. The promising imaging techniques of contrast-enhanced ultrasound, ultrasonic elastography, and PET-CT [19–21] may be selectively applied to avoid underestimation and inadequate treatment.

The indications for and the extent of selective LND in PTC patients with cN1a disease remain uncertain. Simultaneous prophylactic dissection can ensure radical dissection and prevent lateral lymph node recurrence, but unnecessary complications, such as cervical adhesion, paresthesia, cervical lymphatic leakage, and nerve damage, can cause adverse effects in pN0 patients [22, 23]. As a result, exploring the risk factors for LLNR in patients with cN1a PTC after surgery is essential for providing individualized therapy for each patient, reducing hazards, and optimizing benefits. The present study determined six independent influencing factors, namely, tumour size, pathological T4 stage, number of involved central lymph nodes, pTNM stage, extrathyroidal extension, and postoperative I^{131} treatment. Among them, tumour diameter is considered one of the key predictors of recurrence [17, 24, 25]. Patients with larger tumour diameters often have a greater probability of LLNR. Xu et al. [26] reported that the number of CLNMs (>3) combined with the primary tumour size (>2 cm) effectively stratify the lateral neck recurrence risk for patients with pN1a PTC after a median follow-up of 62 months. Ito et al. [27] reported that both the incidence and number of metastatic lateral lymph nodes are positively correlated with the tumour diameter; consequently, prophylactic lateral node dissection is recommended for patients who meet two of four significant risk factors, including tumour diameter≥3 cm and other factors. Another

Table 4 Distribution of LLNR for node-based data in different primary tumour locations

Tumour location	Involved lateral lymph nodes, (%) *n/N*				Total
	Level II	Level III	Level IV	Level V	
Upper pole	10.9(21/192)	7.8(15/192)	6.3(12/192)	0(0/192)	25.0(48/192)
Middle pole	7.3(14/192)	17.7(34/192)	7.3(14/192)	1.0(2/192)	33.3(64/192)
Lower pole	4.7(9/192)	14.1(27/192)	19.2(37/192)	3.6(7/192)	41.7(80/192)
Total	22.9(44/192)	39.6(76/192)	32.8(63/192)	4.7(9/192)	100(192/192)

Note: LLNR, lateral lymph node recurrence

Japanese study [28] has suggested that PTC patients with tumour diameter ≥ 4 cm should receive preventive modified radical lateral neck dissection to reduce the risk of postoperative LLNR. Close surveillance may be necessary for the early detection of LLNR in PTC patients with tumour size ≥ 1 cm and central LN metastasis with extranodal extension [25].

Owing to the thyroid lymphatic drainage pathway, patients with central lymph node metastasis are more likely to present with lateral lymph node metastasis [29, 30]. The number of metastatic central lymph nodes or the lymph node ratio is positively correlated with the risk of LLNR [17, 31, 32]. In general, skip metastasis (negative central lymph node and positive lateral lymph node) in PTC patients is rare [33]; however, the risk of lateral lymph node metastasis can reach as high as 60-75% when there are 3 or more involved central lymph nodes [34, 35], and prophylactic LND can be considered when there are ≥ 5 involved central lymph nodes [30, 36]. The incidence of lateral lymph node metastasis can increase by 12.6% for every additional central lymph node metastasis [31]. The present study revealed that ≥ 3 positive central lymph nodes significantly increased the risk of LLNR (OR = 1.87, $P = 0.035$), whereas Wu et al. [29] reported that patients with positive central lymph nodes are 11.8 times more likely to have simultaneous homolateral lateral lymph node metastases than those without positive central lymph nodes. N1a PTC patients with a lymph node ratio ≥ 0.75 are recommended for comprehensive evaluation of lateral neck lymphadenopathy and consideration for lateral neck dissection and radioactive iodine treatment [24].

Extrathyroidal extension, i.e., tumour extension outside the thyroid capsule with infiltration into surrounding tissues, was identified as an independent predictor of LLNR in the present study. According to the ATA guidelines (2015 edition), the presence of extrathyroidal extension is considered a useful predictive factor of tumour recurrence [11] and an auxiliary indication for prophylactic cervical lymph node dissection [37]. Studies have shown that all levels of extrathyroidal extension, including microscopic extension, are related to increased risk for nodal metastasis, recurrence, and unfavourable prognosis, which potentially affects the clinical decision-making for PTC patients [38, 39]. Randolph et al. [40] regarded that the specific characteristics of the clinically apparent size, number of positive nodes, and extranodal extension of nodal metastases can be used to stratify the risk of recurrence in pN1 PTC patients. The implications of N1 stratification for PTC suggest potential modifications to the AJCC TNM and ATA risk-recurrence staging systems.

Compared with solitary lesions, multifocal papillary thyroid carcinoma is more malignant and highly differentiated. A systematic review has revealed that multifocality is significantly associated with an increased risk of recurrence in patients with PTC, whereas cancer-specific survival does not differ [40]. Multifocal lesions are also considered risk factors for LLNR and poor prognosis in PTC patients [41, 42]; thus, comprehensive selective LND is recommended in multifocal PTC patients with lymph node metastasis or capsular invasion [42, 43]. However, multifocal lesions and vascular invasion were not correlated with LLNR in the present study, which may be explained by the small sample size. Therefore, more multicentric large-sample studies are warranted.

The present study revealed that I^{131} treatment may reduce the risk of LLNR by 52% (OR = 0.48), which was consistent with the findings reported by Wu [44]. For the indication of I^{131} after thyroid cancer surgery, the Chinese guidelines for thyroid cancer diagnosis and treatment [45] recommend I^{131} treatment for PTC patients in the high recurrence and intermediate recurrence risk groups based on various parameters, such as lesion residual degree, tumour diameter, capsule invasion, and postoperative thyroglobulin level after TSH stimulation. Most scholars have reported that upper pole tumours were more likely to present with cervical lateral lymph node metastasis [29, 31, 32], which was not consistent with the conclusions of the present study.

The distribution of lymph node recurrence at each lateral level of the neck was analysed to guide precise treatment of the lateral area. The presence of lateral lymph node metastasis in PTC patients is more common at levels III and IV than at levels II and V [46], with incidences of 82.8% at level III, 65.6% at level IV [47], and 41.1% at multiple levels [46, 47]. A meta-analysis [48] of 18 studies indicated that level II were involved in 53.4%, level III were involved in 70.5%, level IV were involved in 66.3%, and level V were involved in 25.3% of PTC patients. In the present study, 62.1% of the recurrent patients experienced multiple-level recurrence. In terms of both the number of recurrent patients and the number of recurrent lymph nodes, levels III and IV were the most common sites, whereas level V was the rarest site, which conforms to the cervical lymphatic reflux route [49]. Therefore, levels III and IV should be particularly highlighted to ensure adequate dissection in the process of LND.

The present study had several limitations, including factors related to the single-centre design, retrospective study design, follow-up, and surveillance. Therefore, future multi-centre studies are needed to conduct a more comprehensive assessment of clinical markers, survival analysis, and metabolic comorbidities to improve the management and reduce LLNR in cN1a PTC patients.

In conclusion, the present study demonstrated that tumour diameter ≥ 2 cm, pT4 stage, number of positive

central lymph nodes≥3, pTNM III-IV, and extrathyroidal extension are independent risk factors for LLNR, whereas postoperative I^{131} treatment is an independent protective factor for LLNR after central neck dissection in cN1a PTC patients. For patients with these risk features, meticulously detailed preoperative imaging evaluation and selective LND should be considered, and postoperative I^{131} treatment can be performed to avoid LLNR. With respect to the distribution of postoperative LLNR in cN1a PTC patients, a significant proportion of patients have multilevel metastases. Both the node-based and patient-based analyses indicated that LLNR commonly occurs at levels III and IV, which may represent key sites in selective LND.

Abbreviations

PTC	Thyroid papillary carcinoma
LLNR	Lateral lymph node recurrence
CLNM	Central lymph node metastasis
LND	Lateral neck dissection
ATA	American thyroid association
ECOG	Eastern cooperative oncology group
ASA	American Society of Anaesthesiologists

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Author contributions
BL, ML and KZ contributed to the data curation, analysis, investigation and writing of the manuscript. BL and WL performed the operation of the patients. WL and TZ also reviewed, edited the writing and validated the whole analysis process. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This research was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Taihe Hospital Affiliated to Hubei University of Medicine. Written informed consent for publication was obtained from the patients and/or their legal guardians for publication. The patients' clinical information and imaging materials are private data, which are protected by Chinese laws. Therefore, the data and materials cannot be uploaded and shared with the public.

Consent for publication
The manuscript has been approved for publication by all the authors.

Competing interests
The authors declare no competing interests.

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