ORIGINAL ARTICLE

# Complementary Thyroid Elastography on Conventional Ultrasound in Diagnosis of Malignant Thyroid Nodules

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## ABSTRACT

**INTRODUCTION:** Ultrasound has been widely used to assess thyroid nodules. Although ultrasound elastography has been developed to improve detection of thyroid malignancy, it has received mixed responses. This study aimed to determine the efficacy of ultrasound elastography in detecting malignant thyroid nodules. **MATERIALS AND METHODS**: Patients with thyroid nodules were assessed using conventional ultrasound and elastography followed by fine-needle aspiration and or hemithyroidectomy. The ultrasound findings were compared with the cytology or histopathology for statistical analysis. **RESULTS**: Out of 156 nodules from 92 patients included in the study, 12 (7.7%) were malignant and 144 (88.8%) were benign. The elastography was found to be an independent predictor of malignancy (OR 10.35, 95% CI [1.31, 81.6], p = 0.03). Other independent predictors were taller shape and central Doppler pattern obtained using conventional ultrasound. A combination of the three independent predictors was shown to improve the sensitivity of detecting malignant thyroid nodules up to 100%, 95% CI [73.5,100] with NPV of 100%. A new scoring system incorporating the three variables was developed and an algorithm using the scoring system was proposed. **CONCLUSION**: Thyroid elastography is an independent predictor of thyroid malignancy. Its performance is comparable to conventional ultrasound when used alone and improved when used in combination with conventional ultrasound. It is valuable as screening and risk-stratification tools for patients with thyroid nodules.

**Keywords**
Thyroid nodule, elastography, ultrasound, scoring.

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## INTRODUCTION

Thyroid nodules are common with up to 50% of it being detected by ultrasound.[1] Although more than 90% of the nodules are benign[2], it is important to identify the malignant ones. In the United States, the incidence of thyroid cancer has almost tripled from 4.9% in 1975 to 14.3% in 2009.[3]

Fine-needle aspiration and cytology (FNAC) has been the gold standard of determining benign or malignant nodules. Studies have shown that it has a wide range of sensitivity (54%-95%) and specificity (60%-94%).[4] Although it gives a low false-negative (5%) and false-positive (3%) result, about 10% to 50% of cytology falls under the indeterminate or suspicious category. Usually, a typical cells or cells suggestive of follicular neoplasm is seen, and this carries 10% to 30% risk of malignancy.[5,6] The indeterminate and non-diagnostic categories often cause diagnostic dilemma to surgeons. In addition, non-diagnostic or unsatisfactory cytology also occurs and carries 18% risk of malignancy.[7]

Ultrasound imaging has therefore been used as an important tool for surgeons to decide the status of a thyroid nodule, as it can be easily done during clinic visit. Studies have also shown that ultrasound performed by surgeons are as accurate as those performed by radiologists in detecting thyroid malignancies.[8,9]

Ultrasound characteristics that are associated with malignancy are hypoechogenicity, spiculated margin, microcalcification and taller-than-wide shape.[8] New technology has allowed ultrasound to measure 'elasticity' or 'stiffness' on a tissue or nodule. This 'ultrasound elastography' (USE) is based on the concept that when compression is applied, the degree of deformity on a lesion can be measured, known as 'Elasticity Contrast Index' (ECI). This offers a more objective assessment of 'hardness' of a nodule compared to finger palpation. Three compression methods are currently available; manual free-hand compression, internal compression using carotid artery pulsation (strain elastography), and compression by acoustic pulse generated from the transducer (shear wave elastography).[10,11] Manual compression USE gives qualitative result, whereas strain elastography and shear wave elastography give semi-quantitative and qualitative results. Even though they all have been shown to be an effective and independent predictor of malignancy, this has been disputed by some.[9,12,13]

The main objective of this study is to look at the diagnostic accuracy of USE performed by endocrine surgeons at Hospital Canselor Tuanku Muhriz (HCTM) in detecting benign and malignant thyroid nodules. The secondary objectives of this study are to evaluate the performance of USE in combination with conventional ultrasounds, and to develop a predictive scoring system for thyroid nodules based on the findings.

## MATERIALS AND METHODS

### Study design

This was a prospective study conducted over a two-year period from 1st September 2015 until 30th September 2017. The study obtained approval from the local ethical committee. Patients who presented to Endocrine and Breast Clinic in HCTM with thyroid nodules were screened. Those with previous thyroid surgery or radio-ablative iodine therapy were excluded. Patients later identified as having inconclusive thyroid cytology without histopathological confirmation were also excluded. In total, 92 patients with 156 thyroid nodules were recruited.

### Ultrasound examination

Thyroid nodules were evaluated using the Samsung RS80A ultrasound machine equipped with E-thyroid™ software and L3-12A probe with a 5 to 12 MHz linear transducer. This machine performs strain elastography by using the intrinsic compression of the carotid artery pulse to generate a semi-quantitative result, the Elasticity Contrast Index (ECI). Although intrinsic compression from carotid pulse may vary with individuals' blood pressure and its distance to the target nodule, it is superior to manual compression. It minimizes the performance bias and is reported to improve inter-observer agreement and intra-observer reproducibility.[14]

Two endocrine surgeons with at least three years' experience in thyroid sonography performed the ultrasound. The ultrasound probe was placed on the thyroid and a green indicator on the monitor signalled optimum contact. Patients were instructed to hold their breath for a few seconds to reduce movement. Image of the nodule of interest would then be captured. Subsequently, a Region of Interest (ROI) circle would be positioned within the nodule and the ECI generated (Figure 1). Three readings from three different planes were recorded to get a mean ECI value. Higher ECI value indicates more stiffness or harder nodule and vice versa.

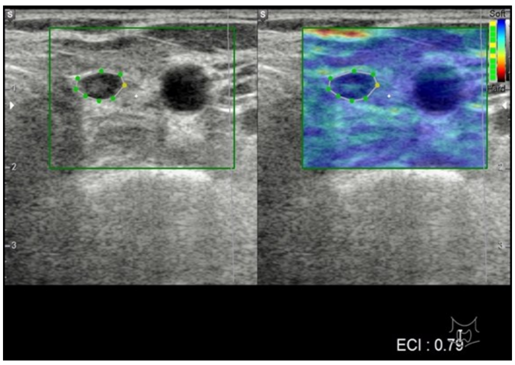


**Figure 1:** Example of ultrasound elastography image showing a thyroid nodule circled within region of interest and it's Elastography Contrast Index of 0.79.

Conventional ultrasound features such as size, consistency, echotexture, echogenicity, doppler pattern, margin, halo sign, spongiform appearance and

### Cytology and histopathology

The majority of FNACs done in HCTM were performed by surgeons or surgical trainees with ultrasound guidance. Occasionally, they were performed by pathology staffs if the nodule is large and obvious. The thyroid cytology results were reported as; C1 for unsatisfactory sample, C2 for benign, C3 for atypical or indeterminate, C4 for suspicious and C5 for malignant. Patients with C1 would be advised for repeat FNAC. Patients with C2 might be observed on follow-ups or undergo thyroidectomy depending on factors such as size of nodule, ultrasound appearance, and patient's choice. While patients with C3, C4 and C5 cytology were generally advised to undergo a lobectomy or thyroidectomy.

### Statistical analysis

All data were analysed using SPSS Statistics Version 22. Descriptive statistics for patient age, sex and standard ultrasound features were performed. This was followed by performing a chi-square ($c^2$) test on each ultrasound features against the cytology or histopathology. Each variable's sensitivity, specificity, PPV, NPV and accuracy were obtained from a two-by-two table.

The association of ECI with malignant thyroid nodules was determined using Spearman's Rho correlation. The ECI values were plotted on a 'receiver operating characteristic' (ROC) curve as sensitivity versus 1-specificity and the 'area under the curve' (AUC) calculated. The optimal cut-off ECI value was determined by calculating the nearest distance of the ECI value to 1 (100% sensitivity) in the ROC curve. This value was then used in a two-by-two table to determine its sensitivity, specificity, PPV & NPV and accuracy. A logistic regression analysis was performed to establish the effects of each ultrasound characteristic on the likelihood of thyroid cancer and to find the independent predictors of malignancy.

## RESULTS

A total of 92 patients with 166 thyroid nodules were initially recruited. There were 74 females and 18 males with a mean age of 52. Ten nodules were excluded due to inconclusive cytology: five C1 cytology did not have repeat FNA and five patients with C3-4 cytology refused surgery. The remaining 156 nodules were included in the study. Total of 144 (88.8%) nodules were benign and 12 (7.7%) nodules were malignant. Of the malignant nodules, 9 out of 12 (75%) were papillary thyroid carcinomas (PTC), 2 (16.7%) were follicular thyroid carcinomas (FTC) and 1 (8.3%) was a medullary thyroid carcinoma.

A chi-square test ($c^2$ test) of independence showed there was significant positive correlation between shape, echogenicity, halo sign, margin, calcification and Doppler signal with thyroid pathology. Taller shape, hypoechogenicity, absence of halo rim, irregular margin, presence of calcification and central Doppler pattern are more likely to be present in malignant thyroid nodules, whereas consistency, echotexture and spongiform appearance showed no significant correlation (Table I).

Table I: Univariate analysis showing correlation of various ultrasound characteristics including elastography represented by ECI value with benign and malignant nodules. *(ECI= Elasticity contrast index)*

| **Ultrasound characters** | | **Benign (Total 144)** | **Malignant (Total 12)** | **Total** | ***p*-value** |
|---|---|---|---|---|---|
| **Shape** | Wider | 120 | 5 | 125 | **0.002** |
| | Taller | 24 | 7 | 31 | |
| Consistency | Cystic | 5 | 0 | 5 | 1 |
| | Solid | 139 | 12 | 151 | |
| Echotexture | Heterogenous | 122 | 11 | 133 | 0.82 |
| | Homogenous | 22 | 1 | 23 | |
| Echogenicity | Iso/ hyperechoic | 115 | 6 | 121 | 0.043 |
| | Hypoechoic | 29 | 6 | 35 | |
| Halo | Complete/ partial | 107 | 5 | 112 | 0.038 |
| | Absent | 37 | 7 | 44 | |
| **Margin** | Regular | 111 | 3 | 114 | **<0.001** |
| | Irregular | 33 | 9 | 42 | |
| **Calcification** | Absent | 106 | 4 | 110 | **<0.001** |
| | Present | 38 | 8 | 46 | |
| Spongiform | Yes | 105 | 8 | 113 | 0.897 |
| | No | 39 | 4 | 43 | |
| **Doppler** | Peripheral/ none | 131 | 5 | 136 | **<0.001** |
| | Central | 13 | 7 | 20 | |
| **ECI value** | <2.04 | 116 | 5 | 121 | **0.006** |
| | ≥2.04 | 28 | 7 | 35 | |

The lowest ECI value was 0.50 and the highest was 4.41. A Spearman's correlation showed a significant positive correlation between the two variables although weak, $r_s = 0.2$, $p < 0.01$. The AUC for the ECI value demonstrated that ECI has fair accuracy with AUC = 0.72, 95% CI [0.56, 0.88] (Figure 2).

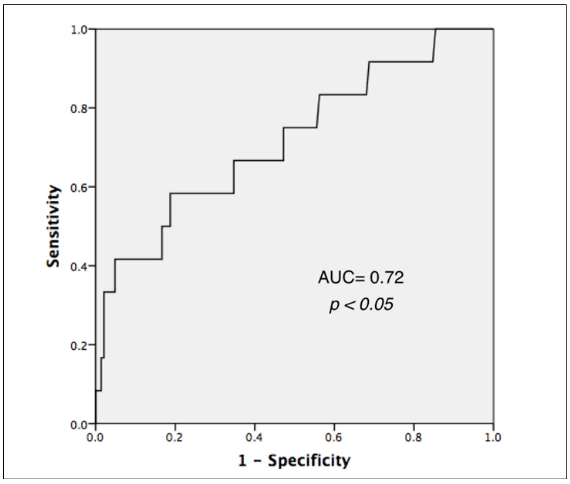


**Figure 2:** Accuracy of thyroid elastography (ECI values) represented by ROC curve (ROC = Receiver operating characteristic, ECI = Elasticity Contrast Index, AUC = area under the curve)

ECI value of ≥ 2.04 was found to be the optimum cut-off point for differentiating benign and malignant thyroid nodules with good specificity (80.6%, 95% CI [73.1, 86.7]), high NPV (95.9%, 95% CI [92.2, 97.85]) and good accuracy (78.85%, 95% CI [71.6, 85.0]). However, it has low sensitivity (58.3%, 95% CI [27.7, 83.8]) and low PPV (20%, 95% CI [12.3, 30]) (Table II).

**Table II**: Sensitivity and specificity, PPV, NPV and accuracy of each ultrasound characters including ECI value and PTM score. *(US= ultrasound, PPV = Positive predictive value, NPV= Negative predictive value, ECI = Elasticity contrast index, PTM = Predictive thyroid model)*

| Ultrasound characteristic | Sensitivity | Specificity | PPV | NPV | Accuracy |
|---|---|---|---|---|---|
| Shape | 58% | 83% | 23% | 96% | 81% |
| Consistency | 100% | 3% | 8% | 100% | 11% |
| Echotexture | 8% | 85% | 4% | 92% | 79% |
| Echogenicity | 50% | 80% | 17% | 95% | 78% |
| Halo | 58% | 74% | 16% | 96% | 73% |
| Margin | 75% | 77% | 21% | 97% | 77% |
| Calcification | 67% | 74% | 17% | 96% | 73% |
| Spongiform | 33% | 73% | 9% | 93% | 70% |
| Doppler | 58% | 91% | 35% | 96% | 88% |
| ECI ≥2.04 | 58% | 81% | 20% | 96% | 79% |
| PTM ≥ 4 | 100% | 75% | 25% | 100% | 77% |

A logistic regression analysis was performed to identify independent ultrasound variables that can predict thyroid cancer. The overall test was statistically significant and indicated that collectively, the ultrasound features could reliably distinguish between benign and malignant thyroid nodules ($c^2 = 47.38$, $p < .001$ with $df = 7$).

There was a fairly strong relationship (Nagelkerke's $R^2$ of 0.63) between the ultrasound features and thyroid cancer with a successful prediction of 94.2% overall (97.2% for benign, 58.3% for malignant). The Wald criterion demonstrated that shape, Doppler pattern and ECI were independent predictors of malignant thyroid nodules ($p$= 0.011, $p$<.003, $p$=0.047) although large confidence interval was noted for 'shape' and 'Doppler pattern'. Exp(B) values indicated that when the ECI value increases by one unit, the risk of malignancy increases by six times (Table III). These findings were in concordance with reports from other authors.[15, 16]

**Table III**: Logistic regression (multivariate) of ultrasound characteristics including elastography (ECI) and their risks of malignancy. *(ECI=Elasticity contrast index)*

| Ultrasound features | Wald | df | *p*-value | Exp(B) | 95% C.I.for EXP(B) | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| **Shape** | 6.50 | 1 | **0.011** | 52.26 | 2.50 | 1094.67 |
| Consistency | 0.00 | 1 | 0.999 | 175612001.4 | 0.00 | . |
| Echotexture | 0.79 | 1 | 0.375 | 4.22 | 0.18 | 101.69 |
| Echogenicity | 3.07 | 1 | 0.080 | 6.83 | 0.80 | 58.50 |
| Halo | 2.16 | 1 | 0.142 | 4.73 | 0.60 | 37.48 |
| Margin | 1.67 | 1 | 0.196 | 4.10 | 0.48 | 34.80 |
| Calcification | 0.08 | 1 | 0.773 | 1.38 | 0.15 | 12.57 |
| Spongiform | 2.29 | 1 | 0.130 | 0.12 | 0.01 | 1.87 |
| **Doppler** | 8.98 | 1 | **0.003** | 98.99 | 4.90 | 1998.81 |
| **ECI** | 3.93 | 1 | **0.047** | 6.13 | 1.02 | 36.85 |
| Constant | 0.00 | 1 | 0.999 | 0.00 | | |

The three independent variables (shape, Doppler pattern and elastography) were each given an estimated score based on the likelihood of malignancy as reported by Anil et al.[15] This scoring system was named the Predictive Thyroid Model (PTM) as shown in Table IV. When the PTM score is plotted against the thyroid cytology or histopathology, the ROC curve showed very good accuracy with an AUC of 93.3%.

**Table IV:** Predictive Thyroid Model (PTM) scoring system using ECI value, shape and doppler characteristics.

| Variables | Character (score) | Character (score) |
|---|---|---|
| ECI value | 2.04 (1) | <2.04 (0) |
| Shape | Taller (3) | Wider (1) |
| Doppler | Central (3) | Peripheral (1) |

## DISCUSSION

Ultrasonography has been an excellent assessment tool for thyroid lesions due to its good sensitivity and specificity in characterizing thyroid malignancy. However, with an increasing number of thyroid nodule detections, a screening tool that allows for more rapid and accurate assessment of thyroid nodules is required for patients to receive prompt treatment. Ultrasound elastography (USE) has been developed to achieve this goal. In this study, ECI is one of the key independent factors that predicts malignancy. Two other independent predictors are 'shape' and Doppler pattern. Elastography alone has high specificity and NPV but lower sensitivity and PPV. Therefore, its performance is at least comparable with conventional ultrasound.

## Predictive Thyroid Model

Based on the ROC curve for the PTM, a cut-off score of 4 was determined. All 108 nodules with scores of <4 were benign. Out of 48 nodules with score $^{3}$4, 36 (75%) were benign and 12 (25%) were malignant (Figure 3).

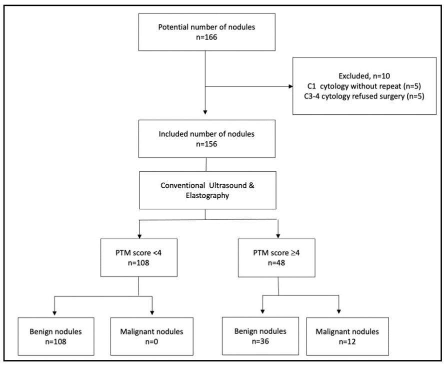


**Figure 3:** Flowchart of patients with thyroid nodules who underwent conventional ultrasound and elastography and subsequently categorized according to PTM score. *(PTM = Predictive thyroid module)*

The detection of malignant thyroid nodules improved with sensitivity of 100%, 95% CI [73.5, 100]. Nonetheless, its specificity and accuracy remained at 75%, 95% CI [67.1, 81.8] and 77%, 95% CI [69.5, 83.3]. This demonstrated that USE and conventional ultrasound features complemented each other. A score of<4 is a good indicator of a benign nodule and patients can be safely observed. Whereas a score of ≥ 4 may be suggestive of malignancy and should therefore have repeat FNAC or undergo thyroidectomy. Based on the PTM, an algorithm for thyroid nodules with C1 to C3 category was developed (Figure 4).

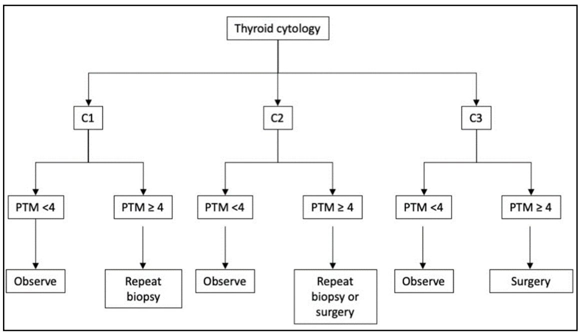


**Figure 4**: Proposed algorithm for patients with cytology C1-3 using PTM score. *(PTM = Predictive thyroid model)*

The PTM serves as a good predictor of a benign thyroid condition. Therefore, it can function as a screening tool to differentiate benign and malignant thyroid nodules. This conforms to the findings of other studies that suggested thyroid elastography, combined with conventional ultrasounds, improved accuracy and that it should not replace but rather complement conventional ultrasound imaging.[17,18] We agree with the 2015 American Thyroid Association Guidelines that USE can be useful in the preoperative risk assessment of patients, but the use of standard ultrasound findings should not be neglected.[2] Few authors have also proposed that the use of thyroid elastography can potentially reduce the number of FNACs.[13,19] Should the PTM be validated in the future, there is a strong possibility that repeated FNAC may be reduced. The algorithm can potentially be applied to patients who are not keen on repeating a biopsy after an indeterminate or inconclusive cytology.

Three ultrasound characteristics that did not have a significant correlation with thyroid pathology were consistency (solid or cystic), spongiform appearance and echotexture (homogenous and heterogenous). This is in contrast with another study that suggests spongiform and cystic appearances are good predictors of benign thyroid pathology and may rule out malignancy.[16] The difference is likely due to inter-observer variability and disparity in definition. We define solid or cystic appearance on a nodule if it contains>50% solid or cystic component. A spongiform appearance is commonly likened to that of a "honeycomb" or "puff pastry" appearance that contains clustered microcystic spaces of similar sizes separated by thin echogenic septa.[20] While these characteristics can be rather subjective, we classified our nodules as spongiform if the spongiform appearance occupied>50% of the nodules. The echotexture of a nodule (heterogenous or homogenous) has received mixed results in terms of its significance towards malignancy. A large retrospective study showed that heterogeneity was not significant in differentiating thyroid malignancy,[21] while other studies concluded otherwise.[9,12]

### Reporting of Elastography

There is currently no standardized international reporting system for thyroid elastography. Results from elastography studies can be qualitative or quantitative depending on the elastography techniques. Free-hand compression elastography gives qualitative results that get translated into scores of one to four.[12] Strain elastography may produce qualitative results reported as "strain ratios". It may also produce semi-quantitative results in the form of an "elasticity contrast index", which is used in this study. Thirdly, shear wave elastography offers a purely quantitative result with the "shear wave velocity" being measured in *m/s*. Currently there are no studies that compare different types of elastography techniques. Moreover, within each elastography technique, variable cut-off values have been reported with different ranges of sensitivity and specificity. This study produced a cut-off value of 2.04 while other studies using similar methods have described higher or lower cut-off values. For example, Dighe et al. used a cut-off ECI value of 3.6 with a sensitivity of 100% and a specificity of 60%, and Luo et al. used a cut-off ECI value of 0.60 which yielded 95% sensitivity and 78.3% specificity.[22,23] This discrepancy could be due to different ultrasound systems and software being used. We believe a standardized unit for stiffness of thyroid nodules will facilitate the clinicians and researchers' work, especially when comparing results.

## LIMITATIONS

Our study is limited by a small sample size, which may impact its significance. The incidence of malignancy was 7.7%, slightly higher than national rate of 2.6-2.8% per 100,000 population as reported in the 2007-2011 Malaysian Cancer Registry.[24] This is likely a reflection of HCTM being a tertiary centre where most referrals are for malignant condition. However, this is comparatively low when compared to data from the United States (14.3% in 2009).[2]

The combination of FNAC and histopathology results for analysis may cause an analytical bias, since we only included thyroid nodules with definite cytology (C2 and C5) and excluded inconclusive ones (C1, C3, C4) if histopathology result not available. However, C2 cytology still carry a small risk of malignancy (0-3%).[25] A heterogenous malignancy group, including papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) and medullary thyroid carcinoma (MTC) was observed in this study. Most cases were PTC and its mean ECI was 2.19. The ECI values of MTC and FTC were lower (1.5 and 1.93). This result concurs with the theory that PTCs tend to have microcalcification and hence higher ECI values compared to other malignancies.[18,26]

The ultrasound elastography machine is limited because it only provides a single two-dimensional plane at one time. Therefore, a given elasticity value may not be representative of the entire nodule. Different planes inevitably have slightly different ECI readings because the ratios of calcification and cystic areas differ in each plane. As such, three measurements were obtained from different planes of a nodule to overcome this issue.

## RECOMMENDATION

From the result of this study, we recommend the inclusion of elastography as part of ultrasound assessment of thyroid nodules, if available. The suggested PTM scoring can be used to risk-stratify patients who have undergone FNAC and decide subsequent management. More studies on elastography and the use of PTM can be explored in the future.

## CONCLUSION

In this study, ultrasound elastography demonstrated high NPV, good specificity and accuracy, moderate sensitivity and low PPV. It also stood out as a strong independent predictor for malignancy. Its performance was comparable to conventional ultrasound features when used alone and improved considerably when combined with conventional ultrasound as shown by the PTM scoring system. Therefore, it is valuable as a screening tool in the assessment of thyroid nodules in conjunction with standard ultrasounds.

### CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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