Correlation of Regional Emphysema and Lung Cancer
A Lung Tissue Research Consortium-Based Study

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Background: Chronic obstructive pulmonary disease and lung cancer are linked because both airflow obstruction and emphysema, on computer tomography, are independent risk factors for lung cancer. However, the local risk of malignancy relative to development of regional emphysema has not yet been defined. Specifically, it is not known if primary lung cancers are associated with regions of worse emphysema within individual patients.

Methods: We performed a database analysis evaluating the association between the degree of regional emphysema as scored on computer tomography and development of primary lung cancer. We also studied the association between regional emphysema and benign lung nodules. We assembled two distinct cohorts using the National Heart, Lung, and Blood Institute’s Lung Tissue Research Consortium database, hypothesizing that lung malignancy will preferentially locate in the regions of the most severe emphysema.

Results: In the Lung Tissue Research Consortium database, 624 cases met criteria for the malignant nodule cohort and 64 were included in the benign nodule cohort. When comparing location of a malignant nodule to other lung regions within the same person, the odds of having a more severe emphysema score in the location of lung cancer was 1.342 (95% confidence interval 1.112–1.620; p = 0.0022). When comparing location of a benign nodule to other lung regions within the same person, the odds of having a more severe emphysema score in the location of the benign nodule was 1.118 (95% confidence interval 0.725–1.725; p = 0.6137).

Conclusions: Primary lung cancers are associated with areas of worse regional emphysema.

Key Words: Emphysema, COPD, Lung cancer, Computerized tomography.

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Lung cancer is the leading cause of cancer death in the United States, and the overall 5-year survival rate remains a dismal 16%. Despite an overwhelming need for better detection and treatment of lung cancer, an effective screening method has remained elusive. Recently, computer tomography (CT) has shown promise as an effective means of screening for cancer. The National Lung Cancer Screening Trial demonstrated a 20% reduction in mortality of a high-risk population in those that received screening by low-dose CT. However, this method was found to be fraught with an unacceptably high level of false-positive findings (95%), resulting in a very high burden of cost and exposure to imaging and procedures for those with benign disease. Nonetheless, the National Lung Cancer Screening Trial serves as a strong reminder of the need to better understand the risk factors for the development of lung cancer, so that individuals at risk can be more precisely stratified.

Chronic obstructive pulmonary disease (COPD) is one of the most well-established risk factors for the development of lung cancer. COPD itself accounts for approximately one in 20 deaths in the United States, and its mortality rate has continued to rise over the past decade. Tobacco use was long believed to be the only link between the two diseases. However, since the 1980s, studies have shown COPD itself to be an independent risk factor for lung cancer. This data showed a connection between airflow obstruction, as measured by pulmonary function tests (% predicted forced expiratory volume in 1 second), and the risk of lung cancer. These first studies showed that, even when tobacco exposure was accounted for, those with airflow obstruction were up to four times more likely to develop and die of lung cancer. Subsequently, we have also learned that this relationship is severity dependent, indicating that as airflow obstruction worsens, the risk of lung cancer increases.

The relationship between airflow obstruction and lung cancer has been well defined, but the clinical entity of COPD encompasses more than simply airflow obstruction. COPD...
includes a spectrum of clinical phenotypes. These phenotypes are characterized by varying degrees of airflow limitation, chronic bronchitis, and emphysema. Until recently, the relationship between emphysema and lung cancer was unclear. However, with the technological advancement of imaging techniques, CT has become the standard procedure for non-invasively diagnosing and quantifying emphysema. Recent studies, using semiquantitative emphysema scores based on visual assessment of CTs, have shown that the presence of emphysema is an independent risk factor for lung cancer. These large population-based studies have shown that individuals with visible emphysema on CT were approximately three times as likely to develop lung cancer than those without emphysema. This relationship held true even in the absence of airflow obstruction.

These recent CT studies have explored the presence of emphysema related to overall risk of malignancy, but did not evaluate the relationship of the presence or magnitude of regional emphysematous changes to the location of the lung cancer. In fact, emphysema is a heterogeneous process throughout the lungs, with some regions, often the apices, being affected more than others. In addition, it is a chronic, inflammatory process characterized by up-regulation of various cytokines, including tumor necrosis factor-α, interleukin (IL)-1β, and IL-6. This may engender a pro-oncogenic milieu. However, it remains unknown whether lung cancers are more likely to be found in areas of the lung with worse emphysema within the same person. We hypothesized that primary lung cancers will be preferentially associated with the areas of the lung with the greatest amount of regional emphysema. In addition, we hypothesized that benign lung nodules would not preferentially be localized to areas of the lung with the greatest degrees of regional emphysema.

To test these hypotheses, we conducted a database review using the National Heart, Lung, and Blood Institute (NHLBI) Lung Tissue Research consortium (LTRC) database. From the available cases, we sought to correlate the location of both primary lung cancers and benign lung nodules with CT regional emphysema scores (RES).

MATERIALS AND METHODS

Participants

Participants for this study were identified in the NHLBI LTRC database. This database’s primary goal was to collect lung tissue and blood from patients who were referred for lung resection. Patients enrolled included (1) individuals with COPD scheduled to have lung volume reduction surgery, lung transplant, or resection of suspected malignancy, (2) patients with interstitial lung disease scheduled to undergo video-assisted thorascopic surgery or lung transplant, and (3) control subject without a primary diagnosis of COPD or interstitial lung disease scheduled for resection of suspected malignancy. A secondary goal of the LTRC database was to collect clinical, physiological, and CT scan data. From this group, 1215 patients were available for review for the current study. Selection of cases of lung malignancy and benign nodules was determined based on the “final clinical diagnosis” for each patient as assigned by the site investigator, 2 months after surgery. “Final clinical diagnosis” for the LTRC study was made using histopathologic diagnosis from resected lung specimens, in addition to supplemental radiographic and clinical data. Primary lung cancers included non–small-cell lung cancer or small-cell lung cancer. Resected metastatic lesions and lymphoma were not included. This project has received approval from the Mayo Clinic IRB (IRB number 1640-04) last reviewed on February 5, 2013. Informed consent for this study was covered under the initial enrollment into the LTRC database.

CT Analysis

All CT images were obtained according to the procedures outlined in the LTRC protocol. These studies included a variety of acquisition techniques depending on whether the images were obtained for clinical purposes before LTRC enrollment or whether the studies were obtained prospectively according to the high-resolution CT techniques specifically designed by the LTRC radiology core laboratory. All prospective scans using the LTRC protocol were obtained using either General Electric or Siemens scanners with 16 or more detectors, and imaging parameters were standardized as much as possible among the enrollment centers (with slice thickness 1.25 mm or less with 50% overlapping reconstruction in a high-spatial, frequency-preserving algorithm). For viewing and analysis of both retrospective clinical scans and LTRC protocol scans, the acquisition with the thinnest slice reconstruction obtained during supine inspiration was used for evaluation of emphysema and other parenchymal abnormalities.

Regional emphysema was scored in a semiquantitative fashion by an experienced thoracic radiologist as part of the LTRC radiology core laboratory evaluation of the images according to a scale modified from the National Emphysema Treatment Trial guidelines. Emphysema involvement was classified as follows: 0, none; 1, mild = 1 to 25%; 2, moderate = 26 to 50%; 3, marked = 51 to 75%; and 4, severe greater than 75%. A regional emphysema score was given to each of 12 lung zones: right and left lungs; upper, middle (or lingua), lower lobes; and central versus peripheral regions based on a distance less or more than 5 cm from the hilar structures. The interpreting radiologist was blinded to all clinical data except for patient age. Specifically, the presumed preoperative diagnosis, the smoking status, presence or absence of malignancy on pathological specimens, and all physiologic data were unknown at the time of visual regional emphysema estimation. Benign and malignant nodule location was not available in the LTRC database but was confirmed by visual review of the CT scan data and available surgical site data based on a final clinical diagnosis of primary lung cancer; 624 CT scans were again reviewed using Osirix Imaging Software DICOM Viewer (version 5.6, http://www.osirix-viewer.com) on a 5-megapixel LCD display. Location of the nodule was documented as being in one of 12 lung regions as described previously with regional emphysema scoring. The same process was carried out on 64 CT scans of those with a final clinical diagnosis consistent with benign nodules. The nodule location was determined by...
the first author with review by B.J.B., an experienced chest radiologist and principal radiologist of the NHLBI LTRC database. At the time of visual review for nodule localization, both were unblinded to the characteristic of the nodule (malignant versus benign) because of the structure of the study. This visual review primarily served to confirm nodule location already registered with the pathology specimens found within the LTRC database.

Pulmonary Function Testing

Spirometric data were obtained using standards set forth by American Thoracic Society (ATS) recommendations for accuracy and precision. Reference equations by Hankinson et al. were used. Diffusion capacities were obtained using standard techniques according to ATS recommendations. Reference equations by Crapo and Morris were used. Diffusing capacity for carbon monoxide (DLCO) measurements were corrected for hemoglobin as available in the LTRC database; however, both corrected and uncorrected measurements were reported. Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages were assigned as described in the 2007 Global Executive Summary.

Statistical Analysis

Baseline characteristics were summarized with continuous variables being reported as means and standard deviations or medians and interquartile ranges (if not normally distributed). Categorical values were reported as counts and frequencies. Conditional logistic regression analysis was used on both the malignant \( n = 624 \) and benign \( n = 64 \) cohorts of participants to assess whether a higher regional emphysema score was a predictor of the presence of either a malignant or benign lung nodule. These parameters were stratified for each individual, using each subject in the LTRC database as one case (one lung region with nodule) and 11 comparator control regions (i.e., 11 lung regions without nodule) for that given individual.

RESULTS

We had postulated that primary lung malignancies would be more likely to be associated with anatomic areas of worst radiographic emphysema, whereas benign lung nodules would not. To address this question, two cohorts of subjects were identified within the NHLBI LTRC database. The first was a cohort of patients with primary lung malignancies. As show in Figure 1, 624 patients were initially selected based...
on a “final clinical diagnosis” of lung cancer, presence of adequate CT images for review, and presence of a solitary nodule. Final analysis was conducted on 615 of these. Of the 624 initial cases, in one case we were unable to localize the tumor by CT because of small size and incidental removal during lung surgery for other indications. Of the 623 remaining cases, eight lacked reliable emphysema scores around the tumor usually because of architectural distortion of the lung, and thus they were also excluded, leaving a total of 615 cases for analysis. The second cohort was a cohort of subjects with benign lung nodules. Again, as shown in Figure 1, 64 subjects were selected based on a clinical diagnosis of a nodule that was proven to be benign.

The baseline characteristics of the patients in each cohort were analyzed and are summarized in Table 1. The malignant lung nodule cohort was evenly split between genders (men, 50.8%; women, 49.2%). The mean age was 67.1 ± 9.9 years, and the mean pack-year tobacco smoking history was 47.9 ± 32.5 years (one pack-year is defined as smoking one package of cigarettes per day for 1 year, whereas smoking one package per day for day years equates to 10 pack-years). The most frequent GOLD stage was 0 (40.8%). Among the type of primary cancers, 98% (n = 613) were non–small-cell lung cancer (NSCLC) with the rest being small cell. Further characterization into adenoacarcinoma or squamous cell was not available in the LTRC database. The benign cohort was also equally split between genders (men, 50%; women, 50%). The average age was 61.4 years and mean pack-year tobacco smoking history was 53.9 ± 31.5 years. Most frequent GOLD stage was four (51.6%). Granulomatous disease was the most common etiology of the benign nodules representing 85% of these cases (n = 52).

The distribution of the emphysema severity differed between the two cohorts. Figure 2A, B describes the distribution of emphysema severity between the case regions (anatomic regions with a malignant nodule) compared with all control regions (lung regions without a nodule) in the malignant nodule cohort. For both cases and controls, the most frequent regional emphysema score was 0 (no visible emphysema; 52.7% and 60% in the two cohorts, respectively). There was a trend toward the case regions (those regions with a nodule) having a higher emphysema score. Specifically, across all degrees of emphysema (1 through 4), there was a greater percentage in the case group compared with the control group.

Figure 3A, B shows the distribution of emphysema severity in the benign nodule cohort. The distribution of the severity of emphysema is more even across both case (containing nodules) and control regions (not containing nodules) of the lung. The most frequent regional emphysema scores for both case and control regions were 0 (29.7% and 30.5%, respectively). The most severe degree of emphysema (4) was more frequently noted in the case regions (26.6% versus 14.8%), but all other degrees of less severe emphysema were more often found in the control regions.

The above distributions do not take into account that our study had been stratified for each individual subject. Therefore, conditional logistic regression was next used to analyze the location of either malignant or benign lung nodule with respect to severity of regional emphysema, as quantified by a regional emphysema scores, within individual subjects. A higher regional emphysema score was associated with the presence of a malignant lung nodule [OR 1.342, 95% confidence interval (CI) 1.112–1.620, p = 0.0022], as shown in Table 2. A malignant nodule was also more likely to be found on the right side (versus left, p < 0.001), in the upper lobe (versus middle or lower, p = 0.0093), and in the peripheral region of the lobe (versus central, p < 0.001). This is consistent with a previously described series of non–small-cell carcinomas. The most common location of a malignant nodule was found to be in the right upper peripheral region (27%).

In contrast, when analyzing the benign nodule cohort, a higher regional emphysema score was not associated with the presence of a benign lung nodule (OR 1.118, 95% CI 0.725–1.725, p = 0.614), as shown in Table 3. A benign nodule was less likely to be found in the middle lobe (p = 0.006). Benign nodules were also more likely to be found in the peripheral region of the lobe when compared with the central (p < 0.001), but otherwise did not show preference for laterality (R versus L) or upper lobe versus lower lobe location.

**DISCUSSION**

In this LTRC database review, we found that higher regional emphysema scores were associated with the presence of a primary lung cancer, but not a benign pulmonary nodule. Our study was setup in such a way in that each subject acted as his/her own internal control, using regional analysis criteria to differentiate between the region with a nodule and those regions without. This provided us the unique opportunity to control for all known and unknown confounders, including age, gender, and cigarette exposure. Interestingly, we found that the degree of regional emphysema, and GOLD class, in the benign nodule cohort was of greater severity than in the

<table>
<thead>
<tr>
<th>TABLE 1. Patient Demographics</th>
<th>Malignant Nodule Cohort (n = 624)</th>
<th>Benign Nodule Cohort (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, No (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>317 (50.8)</td>
<td>32 (50)</td>
</tr>
<tr>
<td>Female</td>
<td>307 (49.2)</td>
<td>32 (50)</td>
</tr>
<tr>
<td><strong>Age, yr</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>67.1 (9.93)</td>
<td>61.4 (8.63)</td>
</tr>
<tr>
<td><strong>Pack-years of smoking</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mean (SD)</td>
<td>47.9 (32.5)</td>
<td>53.9 (31.5)</td>
</tr>
<tr>
<td><strong>DLCO</strong></td>
<td></td>
<td></td>
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<tr>
<td>Median (IQR)</td>
<td>72 (58–88)</td>
<td>34.5 (26–63)</td>
</tr>
<tr>
<td><strong>GOLD stage, No (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>255 (40.8)</td>
<td>15 (23.4)</td>
</tr>
<tr>
<td>1</td>
<td>97 (15.5)</td>
<td>5 (7.8)</td>
</tr>
<tr>
<td>2</td>
<td>215 (34.5)</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>3</td>
<td>49 (7.9)</td>
<td>7 (10.9)</td>
</tr>
<tr>
<td>4</td>
<td>8 (1.3)</td>
<td>33 (51.6)</td>
</tr>
</tbody>
</table>

*p = 563 for analysis of DLCO only. Sex, age, pack-years, and Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage all represent n = 624 and n = 64 for the malignant and benign groups, respectively.

SD, standard deviation; IQR, interquartile ranges.
malignant nodule cohort. This is likely a result of the approach for recruitment into the LTRC database. Those subjects who were enrolled for concern of lung malignancy and preceded to lung resection for removal of a presumptive malignant nodule were more likely to have less severe emphysema. And if the nodule was indeed found to be histopathologically malignant after resection, these were the subjects who were categorized into our malignant nodule cohort. This is because those individuals with less severe degrees of emphysema would more likely have been the ones to qualify as surgical candidates, and in fact, severe emphysema would have precluded individuals from being surgical candidates. In addition, in the LTRC study, only patients with severe emphysema would be considered for LVRS or lung transplant and may have had incidentally benign nodules found on surgical resection, therefore, ultimately being categorized into our benign nodule cohort.

**TABLE 2.** Malignant Nodule Cohort

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emphysema score severity</td>
<td>1.342 (1.112–1.620)</td>
<td>0.0022</td>
</tr>
<tr>
<td>Side: right n = 369 vs. left n = 254</td>
<td>1.469 (1.250–1.726)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lobe: upper n = 344 vs. lower n = 232</td>
<td>0.776 (0.641–0.939)</td>
<td>0.0093</td>
</tr>
<tr>
<td>Lobe: upper n = 344 vs. middle n = 47</td>
<td>0.160 (0.116–0.220)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Region: peripheral n = 491 vs. central n = 132</td>
<td>3.716 (3.061–4.510)</td>
<td>&lt;0.001</td>
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**TABLE 3.** Benign Nodule Cohort

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emphysema score severity</td>
<td>1.118 (0.725–1.725)</td>
<td>0.6137</td>
</tr>
<tr>
<td>Side: right n = 37 vs. left n = 27</td>
<td>1.339 (0.814–2.203)</td>
<td>0.2502</td>
</tr>
<tr>
<td>Lobe: upper n = 36 vs. lower n = 21</td>
<td>0.636 (0.331–1.222)</td>
<td>0.1745</td>
</tr>
<tr>
<td>Lobe: upper n = 36 vs. middle n = 7</td>
<td>0.214 (0.089–0.517)</td>
<td>0.006</td>
</tr>
<tr>
<td>Region: peripheral n = 53 vs. central n = 11</td>
<td>4.858 (2.536–9.309)</td>
<td>&lt;0.001</td>
</tr>
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</table>
Although our study is the first to semiquantitatively investigate the localization of the lung cancer to the anatomic area of emphysema, previous studies have linked emphysema and lung cancer. The connection was first described in 2007 on the basis of clinical diagnosis of emphysema (as diagnosed by a treating physician). That methodology for the diagnosis of emphysema was less than ideal with inherent bias. The strongest evidence linking emphysema and lung cancer is found in a series of studies that have used semiquantitative methodology of grading radiographic emphysema by experienced radiologists. All three studies show an increase risk in lung cancer with emphysema, but both Wilson et al. and Li et al. describe the risk in a severity dependent relationship between emphysema and lung cancer, with exception of the groups with the most severe emphysema. This suggests that there may be a threshold of lung parenchymal damage beyond which there is no longer a risk for cancer development because the tissue has been nearly entirely replaced by air space. The connection between emphysema and lung cancer, however, remains controversial, as there are conflicting data in the literature. Two studies have failed to show that emphysema is a risk factor for lung cancer. Both studies used a case-control design, which used computerized quantitative analysis of radiographic emphysema. Both found increased risk for lung cancer with airflow obstruction, as is consistent with previous studies, indicating that the methodological approaches of these studies were likely sound. They did not, however, demonstrate an association with emphysema. Both were relatively small studies (lung cancer cases: n = 24 in Kishi et al. and n = 64 in Maldonado et al.), with greater percentage of women (Kishi et al. n = 58% women and Maldonado et al. n = 61%), and were based on low-dose CT scanning techniques. Using low-dose CT scanning, it is often more difficult to detect subtle emphysematous disease, particularly by quantitative methods, because those scans can have a great deal of noise and other imaging artifacts. The image noise in low-dose and thin slice CT limits threshold-based emphysema quantitative measure, and thus yielding potentially false-positive or false-negative pixel counts. This pattern has also been noted in a recently published meta-analysis. There is an increased risk of lung cancer when emphysema is semiquantitatively assessed but this does not persist when emphysema is quantitatively assessed. It should also be noted that, although the data did not reach statistical significance, Maldonado et al. did show that there was a trend toward increased risk of lung cancer in the presence of greater emphysema presence until overall severe emphysema was present. This is essentially the same finding as described by both Wilson et al. and Li et al. as above.

Our study represents the first investigation into the role of regional emphysema and the localization of lung cancer. Given the unique study design of subjects acting as their own controls, comparing regions with malignancy to regions without tumors in each individual subject, we were able to eliminate the bias and confounders that regularly accompany case-control studies. However, we were unfortunately not able to evaluate the distribution of regional emphysema in subjects without pulmonary nodules; as such, individuals were not routinely enrolled in the LTRC database. Instead, we chose to look at those who had developed a benign nodule. Unfortunately, this group was much smaller (n = 64) than the malignant nodule cohort group, which limits our interpretation. This group may have been underpowered to adequately detect correlation of lung nodule location with regional emphysema scoring.

We further have no means to account for missing data in the LTRC database. For instance, we cannot rule out the possibility of bias in the calculation of the summary statistic of the DLCO within the malignant nodule cohort. Only 563 data points were available for specifically the DLCO analysis. Those with greater obstructive disease may have had difficulty performing the maneuver and therefore these values would be missing within the database. A final limitation to the study was the review of the CT imaging in a semiquantitative manner. The regional emphysema scores were scored by experienced chest radiologists involved with the LTRC, but these remain subjective estimates and could potentially have been biased by the presumed presence of malignancy in the image data.

Despite these limitations, this study furthers our understanding of the role that emphysema may play in the development of lung cancer. By gaining a better understanding of the clinical phenotype of those with COPD who develop lung cancer, further work can be done to better understand the mechanism at a cellular level. There are presently several theories regarding how these two diseases are linked at the pathogenic level. The first relates to the potential role of neutrophil elastase. Neutrophil elastase (NE) is a neutrophil-derived protease capable of degrading elastin. α1-antitrypsin is a naturally occurring antiprotease that binds and neutralizes NE. When NE is allowed to act unopposed, such as in the setting of clinical α1-antitrypsin deficiency, emphysema results. Those with α1-antitrypsin have also been shown to be at increased risk of lung cancer as well. Another theory revolves around the activity of a family of enzymes termed matrix metalloproteinases (MMPs). These enzymes are responsible for the degradation of collagen and other proteins that make up the cellular matrix. Two members of the family in particular, MMP1 and MMP9, have been not only implicated in alveolar destruction leading to emphysema but also in promoting tumor growth, leading to metastasis and invasiveness. Neutrophils and macrophages have been shown to release increased amounts of MMPs as a result of increased levels of cytokines such as tumor necrosis factor-α and IL-1β resulting from activation of the nuclear factor-κB pathway. Tumor necrosis factor-α and IL-1β are well-known be upregulated in the sputum of patients with COPD. It is possible this inflammatory milieu could further support carcinogenesis.

In conclusion, this study demonstrates that a higher regional emphysema score, as a marker of emphysema severity, is associated with the presence of a malignant nodule. A number of questions remain regarding the role of regional emphysema and the development of lung cancer, and these questions require further study. Analysis of radiographic emphysema using quantitative methods has yet to conclusively link emphysema and lung cancer, but certainly deserves additional study.
ACKNOWLEDGMENTS

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