Cardiothoracic Imaging

Clinical significance of perifissural nodules in the oncologic population

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ARTICLE INFO	ABSTRACT
	Purpose: To evaluate for stability of perifissural nodules (PFNs) in a dedicated oncologic population. *Methods:* A retrospective review of 500 computed tomography (CT) chests from oncologic patients at our tertiary care cancer center with at least a three year follow up yielded 76 patients with PFNs. Patients with metastases on baseline CT chest were excluded (*n* = 14) as the presence of a PFN would not be clinically relevant, thus our final patient cohort was 62 patients with a total of 112 PFNs. PFN features, clinical features, and ancillary information was recorded from the CT and the electronic medical record for all patients. The two patient cohorts—stable or decreased PFN vs. increased PFN—were then compared. *Results:* 112 PFNs were examined in 62 patients with a median follow up interval of 5.7 years. Of 62 patients, 59 (95.2%, 95% CI: 86.5, 99.0) had decreased/stable PFNs on follow up scan (median follow up 5.6 years) and 3 (4.8%, 95% CI: 1.0, 13.5%) had enlarged PFNs (median follow up 6.3 years). None of the PFN features, clinical features, nor ancillary information from the CT proved to be statistically significant. *Conclusions:* Despite the lack of statistically significant distinguishing features to predict growth, our results are reassuring, since the majority of PFNs in our oncology patients were decreased or unchanged in size which is comparable to previously published data on PFNs in non-oncologic patients. Thus, we can similarly presume these nodules are most likely benign and can provide reassurance to our oncologic colleagues and our patients. Larger studies are warranted to further evaluate PFNs in the oncologic population which also examines the nodules by cancer type.

1. Introduction

Perifissural nodules (PFNs) have been described in the radiology literature since 1964 [1]. They were initially considered a rare entity but have been more commonly encountered in routine practice due to the widespread use of computed tomography (CT) [2–5]. PFNs, when identified, have been described as benign when they demonstrate no or minimal growth over a two-year period with characteristic appearance of noncalcified, homogeneous solid nodules with sharp margins and either round, oval, or lentiform shape within 15 mm of the pleural surface [6–9]. Recently, several studies conducted in high-risk screening populations have suggested that PFNs have a very low likelihood of malignancy [10], even when they display interval growth [11], and that most of these nodules represent intrapulmonary lymph nodes which do not require follow up due to their benign nature [12,13]. In 2012, de Hoop et al. published a study evaluating growth of PFNs in a screening population with no known malignancy. Their results showed that PFNs can grow rapidly, with growth rates in the range of malignant nodules, but none of the PFNs in their study turned out to be malignant. They concluded that recognition of these nodules can reduce the number of follow up examinations [14].

To our knowledge, no published study has evaluated whether PFNs can be confidently classified as benign lesions in patients with cancer. PFNs have previously been reported in patients who also have multiple pulmonary metastases, but no mention was made to any distinction in CT appearance between the metastatic nodule and the PFN [15].

Our primary aim was to evaluate for stability of PFNs in oncologic patients over a 3 year follow up period or longer. Our purpose was to determine whether these generally benign lesions found in the general population could also be regarded as benign in the oncologic population, negating the need for follow up.

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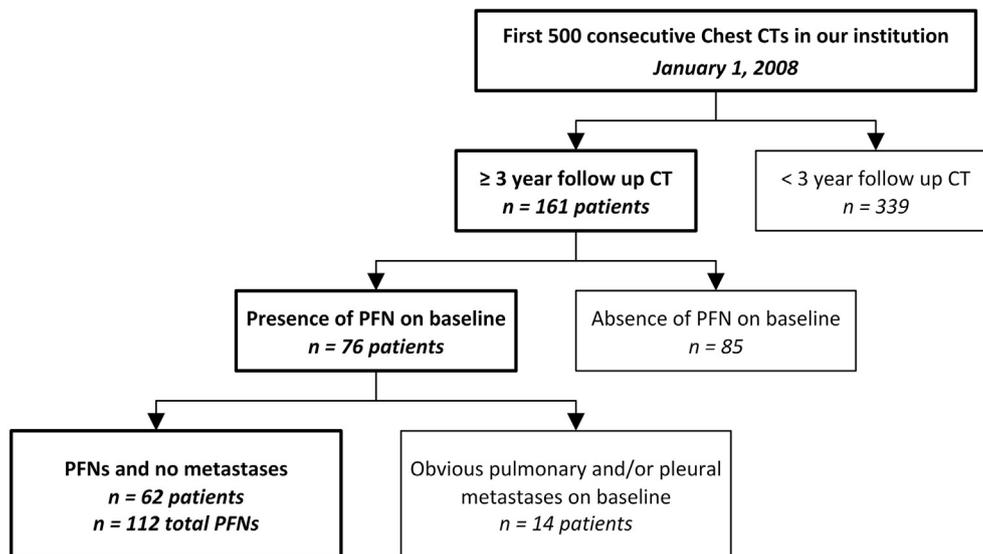 *E-mail address:* goliapej@mskcc.org (J.S. Golia Pernicka).

Fig. 1. Flow chart of study population.

2. Materials and methods

2.1. Patient cohort

Institutional Review Board approval was obtained for this retrospective study. We reviewed the first 500 consecutive chest CT scans performed starting January 1, 2008 at our tertiary referral oncology center. We included all patients with at least a 3 year follow up chest CT and compared the baseline to the most recent exam (Fig. 1). All participants were oncologic patients with one or more primary malignancies.

For all included patients, the initial CT chest in 2008 and the most recent follow up CT at the time of review were evaluated for the presence of PFNs by three radiologists in consensus (all oncologic imaging fellows). Where differences arose, they were resolved by an attending thoracic radiologist with 19 years of experience. The demographic and clinical information for each patient with a PFN was obtained from the medical records. Patients' age, gender, smoking history, primary malignancy, and whether any chemotherapy was administered during the study period were recorded (Table 1). Additionally, the electronic medical charts of all patients were examined to determine if any nodules were resected for pathologic proof.

2.2. Acquisition and evaluation of CT scans

All CT scans (GE) were obtained with a 16×1.25 detector row configuration using a pitch/table speed of 1.375/27.50 mm with a 2.5×2.5 mm collimation. Axial images were reconstructed at 5 mm thickness.

The images were reviewed on a picture archiving and communications system (GE PACS; Waukesha, WI) in the axial plane using lung windows. Maximum intensity projection images were used to improve the detection of nodules.

2.3. Definition of PFNs

Nodules were reported if their characteristics met the criteria for a PFN. CT descriptors of pathologically proven intrapulmonary lymph nodes in the literature include: size up to 12 mm, within 10 mm from the pleural surface [16,17], and location in the lower lobes and right middle lobe [10]. Using these descriptors as our guide for characterizing PFNs, we documented any fissural-attached and perifissural/subpleural ($\leq$ 10 mm from the pleural surface) nodules, which were noncalcified, homogeneous and solid in attenuation with smooth margins. The lung apices were excluded due to possibility of apical scarring as a potential confounder.

2.4. PFN features

The largest size in two perpendicular dimensions was recorded for all PFNs on both the initial baseline and most recent follow up CT. Change in the long and short axes dimensions were then calculated independently of one another. We recorded the size and pertinent morphologic characteristics for each PFN, including shape (triangular, oval, round, rectangular, dumb-belled), presence or absence of a septal connection, and nodule location, including both lobe and whether they were above or below the carina (Table 2).

2.5. Clinical and ancillary CT features

Imaging features from the thoracic CTs were recorded including the presence of mediastinal/hilar adenopathy, emphysema, and the CT scan interval between baseline and most recent follow up.

Table 1
Patient characteristics.

	N (%)
Age, median (range), years	67 (8, 85)
Sex	
Female	33 (53.2%)
Male	29 (46.8%)
Smoking history	
No	28 (45.2%)
Yes	34 (54.8%)
Primary malignancy site	
GI/Hepatobiliary	22 (35.5%)
Lung	10 (16.1%)
Leukemia/Lymphoma	10 (16.1%)
Breast	5 (8.1%)
GYN	5 (8.1%)
GU	3 (4.8%)
Prostate	2 (3.2%)
Other	5 (8.1%)
Chemotherapy during study period:	
Yes	30
No	32
CT scan interval, median (range), years	5.7 (3–7.1)

Table 2
Imaging features of PFNs at baseline.

		N (%)
Shape	Triangle	79 (71%)
	Oval/round	25 (22%)
	Rectangular/dumbbelled	8 (7%)
Septal connection	No	94 (84%)
	Yes	18 (16%)
Relationship to carina	Above	27 (24%)
	Below	85 (76%)

2.6. Statistical analysis

To test whether growing PFNs had different baseline CT features than stable/decreased PFNs, we performed generalized estimating equation methods with a robust covariance matrix and an independent correlation structure assuming binomial distribution with a logit link function, considering multiple nodules per patient. Fisher's exact test or the Wilcoxon rank-sum test was used to examine if patients with at least one growing PFN differed from other patients in clinical characteristics. The 95% confidence interval (CI) for the percent of increased, stable, or decreased PFNs was estimated based on Taylor series variance.

A test with p-value < 0.05 was considered statistically significant. Statistical analyses were performed in software packages SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

Review of the CT chest examinations with at least a 3 year follow up or longer resulted in 161 patients with a baseline exam date ranging from January 1–January 4, 2008. Of the 161 patients with the minimum three-year interval follow up CT at time of data collection, 76 patients had PFNs. Patients with obvious pulmonary or pleural metastases on baseline were excluded as the presence of additional PFNs would not be of clinical relevance in this patient group (*n* = 14, Fig. 1).

Our study group thus consisted of a total of 62 patients with at least one PFN. Among them, 31 patients had one PFN, 17 patients had two PFNs, eleven patients had three PFNs, one patient had four PFNs, and two patients had 5–20 PFNs. For one of the patients with three PFNs at baseline, only one of their PFNs was included for evaluation, as the other two nodules were obscured by pleural thickening on the follow up scan. In total, 112 PFNs were examined in 62 patients with the median follow interval of 5.7 years (range: 3.0–7.1 years) between the initial scan in January 2008 and the most recent follow up scan.

Of the 62 patients, 59 patients (95.2%, 95% CI: 86.5, 99.0) had decreased/stable PFNs at the follow up scan (median follow up 5.6 years; range 3.0–7.1 years) and 3 patients (4.8%, 95% CI: 1.0, 13.5%) had enlarged PFNs (median follow up 6.3 years; range 4.9–6.9 years). On baseline, the mean long and short axis diameter of all PFNs was 3 mm and 2 mm, respectively. At follow up, the mean long and short axis diameters of the stable/decreased PFNs was 3 mm and 2 mm and for the increased PFNs was 5 mm and 3 mm. For the three PFNs that increased, the median change was 5 mm for both the long and short axis.

Of the total 112 PFNs we followed, 86 (76.8%, 95% CI: 65.9%, 85.0%) had decreased size in at least one dimension, 23 (20.5%, 95% CI: 13.0%, 30.9%) were stable, and 3 (2.7%, 95% CI: 0.8%, 8.3%) had increased in size in at least one dimension. We then tested if the nodules that were decreased/stable in size on follow up (*n* = 109, 97.3%) differed from the enlarged nodules (*n* = 3, 2.7%) in their baseline size and imaging characteristics, with results in Table 3.

None of the patients had their PFNs resected during the study period.

Table 3
Comparison of imaging features between stable/decreased PFNs and increased PFNs

		Decreased/ Stable PFN (n = 109)	Increased PFN (n = 3)	p value
		N (%)	N (%)	
Shape[a]	Triangle	77 (76.2%)	2 (66.7%)	0.707
	Oval/round	24 (23.8%)	1 (33.3%)	
	Rectangular/ dumbbelled	8	0	
Septal connection	No	92 (84.4%)	2 (66.7%)	0.425
	Yes	17 (15.6%)	1 (33.3%)	
Above/below Carina	Above	26 (24.1%)	1 (33.3%)	0.713
	Below	82 (75.9%)	2 (66.7%)	

[a] Rectangular and dumbbelled shape nodules were not included in the test due to low incidence.

4. Discussion

Our results showed that, even in an oncology population, almost all (97.3%) of the PFNs studied were stable or decreased in size on follow up (Fig. 2). Only 3 PFNs out of 112 showed any increase in size over a three-year minimum follow up period. Perhaps because of small sample size, none of the patient/clinical characteristics nor PFN characteristics we examined proved to be statistically significant. Nonetheless, we believe our results offer reassurance that even in an exclusively onco-logic population, PFNs with classical imaging features seen on baseline/staging imaging can still be presumed to be benign.

A main limitation is that the prevalence of PFNs in our study was lower than that reported in other studies of PFNs [11,14,18]. This may have been because, compared to other studies, ours was an oncologic population, many of whom were acutely unwell, and many of the patients had other pulmonary findings which may have obscured the PFNs. For a future study with a larger cohort of patients, it may be beneficial to focus purely on an outpatient oncologic population as that population would likely yield a larger number of PFNs yet remain relevant for the purpose of baseline staging of these patients. A possible limitation for low numbers of PFNS is that, for the benefit of establishing a lengthy follow up, the initial scans from January 2008 were available only with 5 mm slice thickness on axial plane, as routine coronal and sagittal reformatted images were not being performed at that time, thus potentially lowering the sensitivity for detection of PFNs on the baseline exam.

An additional limitation is the lack of pathologic proof of benign etiology as none of the PFNs were surgically resected during the study period. We can only infer based on interval growth and the subsequent presence of metastatic disease whether these PFNs were likely to be benign/malignant. Our assumption was that any PFN unchanged or decreased in size over at least the three-year period is likely to be benign [17,19–21]. However, past studies have shown that even interval growth is not a predictor of malignancy [14] so even the 3 PFNs which had increased in size may also be benign. Additionally, almost half the patients were on chemotherapy at one point or another during the time interval of the scans reviewed so there is also the possibility that the decreased/stable PFNs could represent stable or improved metastatic disease. A further consideration is the possibility that PFNs may harbor metastatic disease [22], the same as lymph nodes in other locations.

Another additional limitation to our study is the lack of follow up of the PFNs on interval CTs during the study period. While we may have missed interval changes within some of the nodules, we believe the overall impact would have been minor as small changes in size without pathologic proof of malignancy would not have contributed significantly to our results.
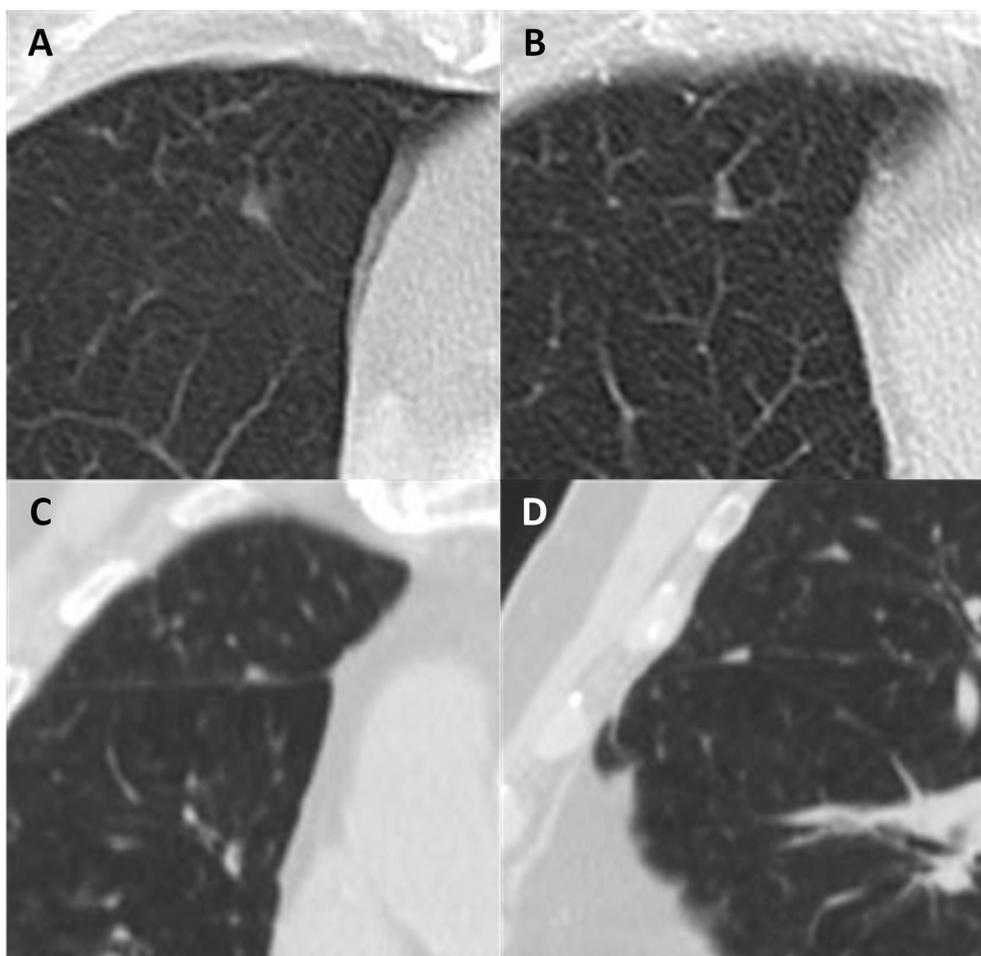
Fig. 2. Example of stable PFN in a non-small cell lung cancer patient who underwent surgical resection of a left upper lobe tumor. (A) Axial image from baseline CT showing 4 mm PFN in the minor fissure of the right upper lobe. (B) Axial image from follow up scan 6 years later demonstrating stable 4 mm PFN with associated (C) coronal and (D) sagittal reformatted images.

An important element to consider is the wide spectrum of malignancies in our patient group, which have differing predilections for the development of pulmonary and pleural metastases. For example, a small lung nodule, perifissural or otherwise, would be regarded with more suspicion in a rectal cancer patient than a prostate cancer or lymphoma patient. Due to low numbers, we did not stratify our results according to cancer type.

Despite the lack of statistically significant distinguishing features to predict growth, our results are reassuring, since the majority of PFNs in our oncology patients had decreased or were unchanged in size on a lengthy follow up period. When correlated with prior published data on these nodules, we can presume that they are most likely to be benign although larger studies are needed which also examines the nodules by cancer type. Given the small sample size of our study and the high-risk population, the presence of a PFN will still necessitate follow up for oncologic patients. The practical relevance of this study is that we, as radiologists, can reassure our oncological colleagues, and thus the patients, that most of these nodules are indeed benign nodules rather than metastases.

Declarations of interest

None.

Funding source

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