Pulmonary Nodules: When to worry, when to ‘chill’

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Disclosure

- MDCH Grant Funds to improve tobacco cessation service in the Michigan Medicine Health System
- Past paid service Consultant/Advisory panel member for Nucleix, a company developing lung cancer biomarkers
- I will not be discussing any specific products or medications relevant to either of these financial relationships
Objectives

• Recognize features of the patient and the nodule that predict a likelihood of malignancy

• Understand the indications for (and limitations of) lung nodule biopsy
Let’s start with an exercise

- Each of the next few slides has two nodules found on CT scans
- There are some differences between the nodules
- Select which one you think is more likely to be malignant (A or B), and (in your head) think of one or two words why you chose your answer
Which of these is more likely malignant?
Which of these is more likely malignant?
Which of these is more likely malignant?

- 65 year old man
- 32 year old man
Which of these is more likely malignant?

- 65 year old heavy smoker
- 64 year old non-smoker
What features did you use to guess which one was more likely to be cancer?

- **Features about the nodule?**
  - Size
  - Edge characteristics?

- **Features about the patient?**
  - Age
  - Social history
This method of determining the malignancy of a solitary pulmonary nodule (SPN) was derived from multivariate logistic regression in 629 patients (65% benign, 23% malignant, 12% indeterminate). The equation is based on 3 clinical and 3 radiographic variables.

Note: this equation is not applicable to patients with a diagnosis of cancer that has been made within the previous 5 years or to patients with previous lung cancer.

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
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<tr>
<td><strong>Age (yrs)</strong></td>
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<tr>
<td><strong>Smoking</strong></td>
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<td><strong>Hx Prev Malig</strong></td>
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<table>
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<th>Radiographic Characteristics</th>
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<tr>
<td><strong>SPN Diameter (mm)</strong></td>
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<tr>
<td><strong>Location</strong></td>
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<tr>
<td><strong>Edge</strong></td>
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**Calculate the Probability of Malignancy**

The Probability of Malignancy is: 

Probability of Malignancy = \(e^x(1 + e^x)\)
where \(x = -6.8272 + (0.0391 \times \text{Age}) + (0.7917 \times \text{Cigarettes}) + (1.3388 \times \text{Cancer}) + (0.1274 \times \text{Diameter}) + (1.0407 \times \text{Spiculation}) + (0.7838 \times \text{Upper})\).


Google “Swensen SPN calculator”
Approach to the patient with a nodule

- Definitely Benign
  - Younger age
  - Small
  - Smooth borders
  - Fat or calcium
  - Non-smoker
  - Lower lobe
  - Negative PET

- Low probability

- Intermediate Probability

- High probability

- Definitely Malignant
  - Older age
  - Large
  - Spiculated borders
  - Heavy smoker
  - Upper lobe
  - FDG-avid on PET
What do we do with this “probability”? 

Fleischner Zone

PET scan zone

“Is this more or less likely to be cancer?”

PET scan zone

“This is cancer. What stage is it?”

Definitely Benign

Definitely Malignant

Low probability

Intermediate probability

High probability
PET scan:
Correlates anatomic and metabolic data

~95% sensitivity for malignancy

False negatives
Ground glass
Small lesions (<8-10 mm) lesions close to the diaphragm

False + (15-20%) ANYTHING inflammatory
Don’t get PET in patients with recent symptoms of infection
63 yo former smoker otherwise healthy with a 3.5 cm RML mass...what would you do next?

A. Biopsy the mass
B. PET scan
C. Refer for surgical resection
D. Mediastinoscopy
E. Trick question...take a history
63 yo former smoker otherwise healthy with a 3.5 cm RML mass…what would you do next?

E. Trick question…take a history

He presented with abrupt onset chest pain, fever, diaphoresis and productive cough

How soon would you repeat the CT?
You’ve determined a pre-test probability of lung cancer
Now what?

Younger age
Small
Smooth borders
Fat or calcium
Non-smoker
Lower lobe
Negative PET

Older age
Large
Spiculated borders
Heavy smoker
Upper lobe
FDG-avid on PET

Goal:
Definitely
Benign

Goal:
Definitely
Malignant

Low probability
~5-15% or less

Intermediate Probability

High Probability >60%
You’ve determined a pre-test probability of lung cancer
Now what?

Goal: Definitely Benign

Proof of benign:
Take it out
Time (radiographic observation)

Goal: Definitely Malignant

Proof of Malignancy:
Any tissue under the microscope (Biopsy or resection)

<table>
<thead>
<tr>
<th>Low probability</th>
<th>Intermediate Probability</th>
<th>High Probability &gt;60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>~5-15% or less</td>
<td></td>
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#1. ANY TIME YOU NEED TO PROVE ITS CANCER

Corollary: Biopsy cannot prove you don’t have cancer. Absence of evidence is not evidence of absence

WHEN IS BIOPSY INDICATED?
When is it appropriate to biopsy a patient with a lung nodule?

- Biopsy is of no use in patients with a high risk of cancer who are good surgical candidates
  - For this group, the “biopsy” is a surgical procedure
- Biopsy people who need a diagnosis to facilitate treatment
  - Medically or anatomically unresectable
  - Make sure biopsy yields an unequivocal stage
- Suspicion of Small cell lung cancer or metastasis
When do we biopsy?
What is a biopsy?

Surgical "biopsy"
- Clinical stage I-II
- High probability of lung cancer
- Good pulmonary function
- Minimal co-morbid illness

Bronchoscopic biopsy
- Clinical stage I-III
- Central location
- Suspicious mediastinal nodes
- "Airway sign"
- Multiple nodule biopsies indicated

CT guided biopsy
- Clinical stage I
- Peripheral location
- No enlarged or suspicious lymph nodes
- Navigational bronchoscopy expertise unavailable
Don’t let this happen to you...

FINDINGS: The scans again demonstrate a spiculated mass in the right apex. Maximum measurement is about 2.3 cm compared to the previous exam of 6/18/10 where it maximally measured about 1.7 cm. No other lesion is seen. There is no definite evidence of adenopathy. There is no effusion. No infiltrate is seen. The scans extend into the abdomen and the liver appears essentially normal and the adrenals appear normal. The patient is noted to have a gallstone.

IMPRESSION: There is a spiculated mass in the right apex that maximally measures 2.3 cm today. It has increased in size since 6/18/10 and undoubtedly represents a neoplastic lesion. I would suggest a CT guided needle biopsy of the lesion for further evaluation.

FEV₁ 2.40 (73% of predicted), FVC 3.88 (93% of predicted)
DLCO 14.5 (72% of predicted)

The right upper lobe spiculated mass lesion is metabolically active and has an SUV maximum of the least 11.2. Biopsy is now suggested to exclude malignancy. Malignancy is favored given its configuration and activity. No other areas of metabolic activity in the chest or mediastinum are observed. Atherosclerotic disease is noted. No abnormal activity in the neck or axilla is appreciated.

Impression:

1. The spiculated abnormal right upper lobe mass lesion is metabolically active and needle biopsies now suggested.
IMPRESSIO:N:

1. Masslike abnormality in the left upper lobe apical posterior segment measuring 66 x 49 mm with postobstructive atelectasis and complete occlusion of the left upper lobe apical posterior segmental bronchus concerning for lung neoplasm. An aggressive infection is in the differential diagnosis. Bronchoscopy with biopsy is suggested for further evaluation.

2. Nodular thickening as well as solid nodules as detailed above are indeterminate.

3. Small to moderate layering left pleural effusion with adjacent atelectasis.

4. Mildly enlarged AP window lymph nodes and left hilar lymph node enlargement.

5. Thickening of the left adrenal gland and indeterminate peripherally enhancing lesion in the left hepatic lobe.
What do we do with this “probability”? Is there a single answer?

- Biomarkers with high NPV
- Benign imaging features
  - High patient anxiety, safer biopsy techniques, Positive PET
  - Safer surgery/Better outcomes?
  - Higher surgical risk, or poorer outcomes

Serial CT Observation | Diagnostic testing (PET) or biopsy | Surgery or invasive staging
When to chill? When there is evidence of benignity**

- **Characteristics of benign nodules**
  - CT is more sensitive for detection of Ca++
  - Detection of fat suggests a benign cause
  - Important for non-radiologists to recall patterns that are NOT predictive of benign behavior

**How to you pronounce this?**
How do you prove a nodule is benign?

What tools do we have?

- Calcium or fat
- Time
- Cold hard steel
Characteristics of benign nodules:
Perifissural nodules

de Hoop B et al. Radiology 2012;265:611-616
Pulmonary Perifissural Nodules on CT Scans: Rapid Growth Is Not a Predictor of Malignancy.

©2012 by Radiological Society of North America
Not all GGOs are created equally

How good are we at identifying solid components?

How long should these be followed?
How Long Should Small Lung Lesions of Ground-Glass Opacity be Followed?

108 total non-solid lesions from 61 subjects followed for a median period of 4.2 years.

82 of the followed lesions were recorded as “pure GGO”.

Of these 82, 18 grew during observation.

Journal of Thoracic Oncology 2013 8, 309-314
‘Disarming’ language

• Nodules are common
• The VAST majority, even in people at very high risk for cancer, are benign
• “Lung freckles”
• Patient education materials…
What is a Lung Nodule?

Commonly called a “spot on the lung” or a “shadow,” a nodule is a round area that is more solid than normal lung tissue. It shows up as a white spot on a CT scan. Lung nodules are usually caused by scar tissue, a healed infection that may never have made you sick, or some irritant in the air. Sometimes, a nodule can be an early lung cancer.

Why have I been given this handout?
One or more lung nodules were seen on your recent chest x-ray or CT (“CAT”) scan.

How common are lung nodules?
Nodules are found in up to half of adults who get a chest x-ray or CT scan.

Do nodules cause any symptoms?
In general, small nodules don’t cause any noticeable problems. They’re too small to cause pain or breathing problems.

How big is the nodule?
Your healthcare team can tell you the exact size of your nodule. Most nodules are less than 10 millimeters (about a ½ inch).

Here are the sizes of some common fruits & vegetables for comparison.

- LIME
- APRICOT
- PEA
- CHERRY

5 mm 10 mm 1.5 cm 4.1 cm

Should I worry that I have a nodule?

- are older
- have a larger nodule
- smoked or still smoke cigarettes
- have other cancer risks, such as lung cancer in your family or handling asbestos in the past.

For example, a small nodule in a young person who never smoked is less likely to be cancer than a larger nodule in an older person who recently quit smoking. **However, even in the person with a high risk of lung cancer, most small nodules are not lung cancer.**

Some patients would like an estimate of how likely their nodule is lung cancer. If knowing that number would help you, please contact your provider.

What if my nodule is lung cancer?
Even if a nodule turns out to be lung cancer, it is likely to be an **early stage lung cancer. People with early stage lung cancer that is treated are less likely to die of lung cancer than people who are diagnosed at a later stage when the cancer has started to cause symptoms.**

*Your healthcare team will be with you every step of the way.* Please discuss any concerns you have about lung cancer with your healthcare team.

What will happen next?
Your healthcare team will probably recommend getting more CT scans to keep a close eye on the nodule to see if it changes. We call this “active surveillance.”

http://www.thoracic.org/patients/patient-resources/resources/lung-nodules-online.pdf
Take Home Points

- Nodule and patient features can be used to estimate the probability of malignancy.
- This probability can determine the next step(s):
  - Long term follow up, PET scan, Surgery, etc.,
- The PET scan has a very high NPV in the right scenario.
- Benign features of nodules should allow conservative management.