

LUNG TUMORS

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Most of the common ones are the things we generally call “lung cancer”. They arise from the bronchial mucosa and are more correctly termed “bronchogenic carcinoma”. These usually occur in large bronchi and are therefore proximal, near the hilum. Bronchogenic carcinomas account for about 85 % of all lung cancers.

Some lung cancers arise from the small airways (bronchioles) and from the alveolar lining cells and are called “bronchioloalveolar carcinomas” (BAC). These are usually peripheral. They account for about 10% of lung cancers.

About 90% of bronchogenic carcinomas are caused by tobacco smoke. Some of the peripheral bronchioloalveolar carcinomas are caused by cigarettes, but many are not.

Two somewhat unusual bronchial tumors are the bronchial carcinoid and the bronchial adenoid cystic carcinoma.

The carcinoid is a neuroendocrine tumor that is mostly outside the bronchus with a little bit inside (like an iceberg). Carcinoids may be “typical” or “atypical”. The former are relatively benign. The latter, while not so aggressive as ordinary bronchogenic carcinomas, are more malignant and metastasize to nodes and other places in about half the cases. Histologically, the difference between typical and atypical carcinoids is the presence of necrosis and/or mitoses found in the atypical ones. Carcinoids are not caused by smoking. Neuroendocrine cells may be identified by immunostains or by EM showing neurosecretory granules. Carcinoids of the appendix and colon are more common than are those of the bronchus, and they occur in other locations too. If the bulk of carcinoid tumor is sufficiently great, the secretions can cause carcinoid syndrome (facial flushing, diarrhea, and various other symptoms / signs).

Another bronchial tumor which occurs often enough so you should know about it is the adenoid cystic carcinoma. These look like the more common adenoid cystic carcinomas of salivary glands. They arise from bronchial mucous glands, which are close relatives of salivary glands. They are worse than carcinoids, burrowing under the mucosa and being more difficult to resect. Again, not caused by smoking.

When surgeons ask the pathologist for frozen section or for fine needle aspiration interpretation of a lung tumor, the main things they want to know are: Is it cancer? Then, Is it Oat Cell? Reason being that “oat cell” cancer is not a surgical disease. It’s a medical disease. Don’t try to take it out. It has already metastasized, so treat it with chemo - rad. The other name for oat cell cancer is small cell carcinoma. It is of neuroendocrine derivation, just like the carcinoid, but far more malignant, and it is caused by smoking. The small cell type makes up just under 20 % of lung cancers. They cause large hilar masses with large lymph nodes. They respond quickly to chemo-rad, but come back. With apparently limited disease on initial presentation, about 10% survive 5 years. With distant metastases at presentation, most die in less than 2 years and virtually all by 5 years. Radiation treatment of the brain is routine, since cerebral metastases are assumed in this tumor. Of all the lung tumors, this one which most often causes “paraneoplastic” syndromes. These are the results of secretions of these neuroendocrine tumors that are much like normal hormones such as ACTH and ADH and gastrin releasing peptide and calcitonin. Lung cancers like to

metastasize to adrenals, but if there's bilateral adrenal enlargement and evidence of Cushing's disease, the enlargement may be the result of ACTH-like peptide production by the tumor rather than metastasis to the adrenal. The other lung tumor that is not small cell that causes a paraneoplastic syndrome is squamous cell carcinoma which occasionally secretes parathormone and causes hypercalcemia.

The tumors that are not small cell type are usually of 3 other main histologic sorts: squamous cell, undifferentiated large cell ("large cell"), and adenocarcinomas. If you're a pathologist looking at a lung tumor, you say, "Hmm." (We say that a lot.) You say, "Hmm, cells aren't small, so it's not small cell." Often we stop right there and just call it "non-small cell carcinoma". But if we have pretty good biopsy material, we usually go further and say, "Hmm, cells don't have keratin whorls and pearls and prickles (intercellular bridges), so it's not squamous cell. Cells don't make glands and intracellular mucin, so it's not adenocarcinoma. Must be large cell."

And those are the types:

1. Small cell ~ 20%
2. Large cell ~ 10%
3. Adeno ~ 35%
4. Squamous ~25%

The last 3, large cell, adeno, squamous make up the category called "non-small cell lung cancer".

Surgeons take them out if they haven't metastasized too far. If they have gone too far for surgical treatment, chemo-rad works pretty well for a while. There is a lot to offer these patients, even though the eventual outcome is dismal. For instance, if a bone metastasis is causing pain, it can be treated with local radiation.

There are already identifiable distant mets when the patients are first seen in about half the cases of non-small cell lung cancer. Five year survival among these people is rare. With non-small cell cancer apparently confined to the lung at first presentation, the 5 year survival is about 50%.

With bigger tumors or nearby node involvement but no distant mets at first presentation, 5 year survival is about 30%.

The non-small cell lung tumors sometimes arise in the apex of the lung and may invade the brachial or cervical plexus. Arm pain from neural invasion may be present. Horner syndrome may occur (enophthalmos, ptosis of the eyelid, meiosis, anhidrosis). Such apical tumors were first described by the pioneering American radiologist Pancoast and bear his name: Pancoast tumor. Pancoast syndrome.

Bronchioloalveolar carcinomas (BAC) arise from alveolar or bronchiolar epithelium (or both) and are peripheral rather than hilar. They begin as a focus of atypical alveolar hyperplasia (AAH). At first, they grow along pre-existing alveolar walls without invading. This "lepidic" growth pattern is their hallmark. Growth may be slow, nodules sometimes slowly growing for years before suddenly spreading throughout the lungs or metastasizing like any other adenocarcinoma of lung. (At that point, they are termed "adenocarcinoma with bronchioloalveolar features".) They are a type of adenocarcinoma, but differ from the usual bronchogenic adenocarcinoma in important ways. For one thing, many of them occur in non-smokers. Often younger people. For example, a 28 yo WF becomes short of breath, has a persistent productive cough, has a coin lesion as well as multiple small nodules on chest x-ray. (Coin lesions are rounded lung nodules about the size a coin.) Needle biopsy shows well-differentiated tumor cells growing along alveolar walls....

Morphologically, there are 2 types of BAC: mucinous (less common) and non-mucinous (more common). Sometimes combined.

There aren't very many things that we know cause lung cancer. Cigarette smoke is number 1. It's dose related. The more and longer you smoke, the more likely you are to get lung cancer. Lung cancer is the commonest deadly cancer in the Western world. It is not more common than breast or prostate cancer, but it kills more people since it is so hard to cure. If you are a never-smoker, your chance of getting lung cancer is perhaps 1 / 500. If you are a smoker, about a pack a day, for about 40 or 50 years, your chances are about 1 / 20. Add asbestos to smoking, and the rate rises to 1 / 7. With heavy smoke and a lot of asbestos, it may be 1 out of 2. Cigarette smoke combined with asbestos causes a great increase in lung cancer. Asbestos alone may cause a small increase. Cigarette smoke combined with radioactive dust (radon daughters inhaled by uranium miners) causes a great increase. Uranium dust alone causes a small increase.

Environmental radon in basements etc. may cause lung cancer, but probably almost solely in smokers. Arsenic, nickel, chromium, vinyl chloride all behave the same way. But of all of these, the big one is tobacco smoke in primary smokers. After noting that 90% of lung cancers occur in smokers, with or without other co-carcinogens, you wonder what causes the other 10%. Well, a good many of those are probably caused by second-hand tobacco smoke (environmental tobacco smoke - ETS). Perhaps in conjunction with other low-dose carcinogens. And a good many of the 10% are cancers not associated with tobacco smoke, such as bronchial carcinoids, adenoid cystic carcinomas, and certain of the bronchioloalveolar carcinomas. We don't know what causes most of these tumors. Genes. Hormones. Viruses. (There is a form of BAC that occurs in sheep which is caused by a transmissible virus. The disease goes by the wonderful Boer name "jaagziekte," which means "driving sickness".)

Much of lung cancer is in the genes. Cancer is a genetic disease. In the case of bronchogenic carcinomas, P450 metabolism of certain carcinogens is necessary for their activation. Some people can activate a lot more than others because they have more active P450 metabolic potential. 3p tumor suppressor gene deletions occur in most people with lung cancer and MYC oncogene overexpression is found in most people with lung cancer. Interestingly, K-RAS shows mutations in many of the non-small cell cancers, but not in small cell.

Morphology: the following are what you might expect. These are cancers, however, and they can do what they want to.

	location	size	cavitation	nodes	mitoses	big bad cells
small cell	hilar	big	+/-	BIG	yes	no
squamous	hilar	big	often	big	yes	yes
adeno	hilar / peripheral	medium/ small	+/-	biggish	yes	Yes
large cell	like adeno	like adeno	like adeno	like adeno	like adeno	like adeno
BAC	peripheral	small	0	late	not prominent	no
carcinoid	hilar	medium	0	not often if typical	no (typical)	no

Small cell cancers are highly invasive. Cells are not all that small, about 2 or 3 times bigger than a lymphocyte. Not much cytoplasm compared with the non-small cell ones. Crush artifact is common in biopsies. Nucleoli are inconspicuous.

Squames have big cells, often making whorls, sometimes depositing keratin centrally to form a keratin pearl. If the tumor is well-differentiated, intercellular bridges are often found. Atypical changes in bronchial epithelium preceding formation of a cancer are much as they are in the cervix, proceeding over the course of about 10 years from mild changes to intraepithelial neoplasia and finally to invasive cancer.

Adenocarcinomas are quite variable and display a number of patterns. The cells are usually large, nuclei may be huge, nucleoli are usually big and prominent. They may make papillary formations or glands. They may be solid but still produce intracellular mucin. (Same as a large cell cancer but with mucin.)

Large cell cancers are like adenos, but with none of the specific features that let you call them adenocarcinoma – no glands and mucin.

Tumor giant cells and / or spindle cells may occur in adeno's, large cell cancers, and squames.

If they are a dominant feature, the tumor may be called "giant cell carcinoma" or "spindle cell carcinoma" (or just pleomorphic carcinoma).

BAC's, by definition, grow along alveolar walls. The term lepidic applies to this. Like lepidoptera (butterflies) perching on the alveolar walls. (Or like scales covering the wall.)

There may be a central scar, as there often is in other peripheral adenocarcinomas. When the tumor invades structures or metastasizes, no more butterfly, it is best just to call it "adenocarcinoma" and let it go at that. Tumor cells are well-differentiated. Mitoses are few. Nucleoli are not very big. In the mucinous type, the cells contain mucin, and secreted mucin fills alveoli. (Patients with BAC may produce such copious secretions as to make them lose substantial amounts of protein. The secretions may taste salty. The tumor may spread throughout the lungs to the point that the patient suffocates.)

Other lung cancers don't usually suffocate the patient. Death is caused by a variety of complications such as brain metastasis, infection, hemorrhage, etc. Mediastinal tumor masses may occlude the vena cava (superior vena cava syndrome: swollen arms, neck, head). Patients may just waste away (cachexia associated with TNF), develop fluid and electrolyte abnormalities, and die of cardiac arrhythmia.

All modes of treatment for lung cancer – surgery, radiation, chemo, and others continue to improve. The growing understanding of cancer genetics offers improvements in diagnosis and therapy. But by far the most important opportunity to help with the scourge of lung cancer is that of helping with prevention. Don't let kids start smoking. Grownups? Too late. Quitting helps somewhat. Never starting virtually prevents the disease.