



CAP Lung Cancer Medical Writers' Circle

Some observations and recommendations on the management of lung cancer patients with more than one tumor.

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In the March 2010 Medical Writer's section of the Caring Ambassadors Lung Cancer Program, Dr. Rodolfo Bordoni provides readers with a concise, well-thought out summary of the recent changes in lung cancer staging guidelines. In the course of doing so he makes a number of comments regarding the implications of staging changes for lung cancer patients who have more than one mass or nodule on CT scans. As an individual who has practiced thoracic surgery for more than 30 years, and who is treated a large number of patients with more than one lung cancer, I believe Dr. Bordoni's recommendations should be reconsidered.

My medical school lecturer on lung cancer, Dr. Oscar Auerbach performed landmark research which showed that individuals who smoke cigarettes typically have multiple separate areas of pathological change in the cells of the lung. Most such areas are premalignant, but some progress to non-invasive carcinoma in situ and invasive lung cancers. These many areas of damaged cells are a logical consequence of smoking, with long-term exposure of cells throughout the lungs to high levels of tobacco carcinogens. Based on Dr. Auerbach's findings, it should come as no surprise that some lung cancer patients will develop more than one primary lung cancer. In my experience and that of other investigators, the risk of a second lung cancer in patients who survive ten years is about 20%. In the past, most second cancers were *metachronous* i.e. they appear following treatment of the original cancer. Other second cancers however are *synchronous*, i.e. they can be seen on the same chest x-ray or CT scan at the time of the original diagnosis of lung cancer. Such second cancers can be either *ipsilateral* (on the same side) in either the same lobe or in a different lobe, or *contralateral* (on the opposite side).

In the era before availability of CT scans, synchronous lung cancers were uncommon, but because of the increased sensitivity of CT scans, an increasing percentage of second lung cancers are now seen synchronously. An important problem that arises when a second nodule is found at the time of first diagnosis of lung cancer is the question of whether the second nodule is a *metastasis* from the larger cancer or a *separate primary cancer*. This is a very important distinction, for if it is a metastasis, implying Stage IV, then treatment with chemotherapy is indicated; but if instead, the two lung tumors represent separate primary tumors, each in a lower, potentially curable stage, then treatment with chemotherapy alone may deny the patient a chance of cure.



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When the appearance under the microscope (pathology) of both nodules is determined by biopsy and shows unequivocally that there are two different lung cancer cell-types, e.g. when one biopsy shows a squamous cancer and the other a small-cell cancer. Such a finding unequivocally shows that the two tumors are separate primary lung cancers.

More commonly, both tumors will be adenocarcinomas -- since adenocarcinomas represent the most common cell-type of lung cancer. In these instances, the appearance of the adenocarcinoma may be sufficiently different under the microscope that the pathologist will be able to confidently diagnose separate primary lung cancers. In other cases special techniques using immunohistochemical staining or molecular marker findings will strongly suggest that the tumors are separate primary cancers rather than primary cancer and metastasis.

But even if the adenocarcinomas look the same under the microscope, I suggest that it is more probable that they represent two separate primary cancers rather than a primary lung cancer together with a solitary lung cancer metastasis. If this supposition is accurate, and if surgical removal of both cancers is possible and safe, then the patient would have a chance for cure following removal of both cancers. Therefore, consultation with an experienced thoracic surgeon should be obtained, rather than treatment with chemotherapy only, which we know will result in only a small chance of long-term survival.

Let's step back a moment and ask on what evidence do I base the assertion that two separate adenocarcinomas more likely represent primary tumors?

First, in almost forty years of experience in treatment of lung cancer patients, I have noted that lung cancer seldom produces multiple bilateral metastases to the lung until late in the course of the disease, after it has proven metastasis to other organs, most commonly bone. This is logical, because metastasis should occur in the first capillary bed of organs through which blood draining from a cancer passes. For example, bone, testicular, breast and kidney cancers all have a high incidence of multiple metastases in the lungs, i.e. the first capillary bed through which metastatic cancer cells circulating in systemic venous blood must traverse. In similar fashion, cancer cells leaving colon, stomach and pancreatic cancers show a predilection for metastases in the liver, because venous drainage passes first through the portal vein into the liver. Considering this principle, one would expect to see a low incidence of multiple lung metastases from lung cancer, since blood leaving the lung must first pass through capillaries in other organs throughout the body before it returns to the lung.

Second, this theoretical model is supported by clinical observation of patients with lung cancer. It predicts that we would not see cases of lung cancer with multiple bilateral pulmonary metastases until the late stages of the disease. This is borne out by clinical practice. Although multiple bilateral pulmonary metastases are seen, this almost always occurs in patients with known distant metastasis.



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Logically, one would then conclude that when a second nodule is found in the same or a different lobe, or the opposite lung in a patient with lung cancer, without evidence of metastasis elsewhere, that the second nodule is more likely to be a primary second primary cancer than a lung metastasis from lung cancer.

Third, these theoretical and observational considerations are supported by the survival of patients following surgical resection of both tumors.

Although Dr. Bordoni describes a 3% long-term survival in patients with synchronous cancers, this does not imply that the synchronous lesions are metastases. This poor survival more likely represents failure to treat potentially curable lung cancers with surgery, instead treating with chemotherapy only, with predictably poor long-term survival. In published series of resected metachronous and synchronous lung cancers, long-term survival is much higher than is expected in Stage IV lung cancer, and roughly approximates the product calculated by multiplying the anticipated survival of the first lung cancer (by stage) multiplied by the anticipated survival of the second cancer (by stage). For example, if both tumors were stage IA, each with an anticipated survival of 80% at five years, bilateral resection should result in five-year survival of approximately 64%. Published results provide such rough quantitative evidence that the second tumors are second primary tumors rather than metastases.

This is well described in the case of metachronous lung cancers. For example, we have previously published our experience at City of Hope National Medical Center. In our retrospective study of annual surveillance CT scans in patients with previous lung cancer, we found a 20% per decade incidence of second lung cancers. In most cases second lung cancers were solitary nodules detected in Stage IA. Survival in patients with detection in early stage by annual CT surveillance was roughly comparable to survival of the first cancers.

Data on surgical resection of synchronous lung cancers is more limited, but two recent reports are pertinent. In the February 2010 issue of the Journal of Thoracic Oncology, investigators from Memorial Sloan-Kettering Cancer Center reported on their experience with 175 patients receiving surgical resection of two synchronous lung cancers. Survival was 64% three years following surgery. The surgeons performed pneumonectomy in only 5 patients and resected only part of a lobe in a high percentage of cases.

A recent update of results at the 22nd the International Conference on Screening for Lung Cancer in Tempe, Arizona showed that patients with synchronous lung cancers detected by CT screening in the International Early Lung Cancer Action Program, who had resection of both cancers, long-term survival was 87%.

Finally, in lung cancers resected in the Memorial series above, genomic and mutational data



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assessment confirmed that two thirds of adenocarcinomas had expression of biomarkers consistent with separate primary cancers.

A few words of caution are required. In some cases, a large lung cancer can obstruct lymphatic drainage channels, and backward flow of tumor cells in lymphatics can result in secondary tumor deposits in the same or an adjacent lobe of the lung. Such second deposits represent local metastasis rather than second primary tumors and prognosis in such cases is not good. Surgical treatment would be inappropriate. Confirmation of cancer stage in such cases can be complex and consultation with experienced thoracic surgeons is an integral part of treatment planning.

When one takes all of this information into consideration, I believe that some revised recommendations are appropriate. We must not assume that a second nodule, whether in the same lobe or another lobe on the same side, or in the opposite lung necessarily represents a metastasis. More likely, the second nodule represents a second primary tumor, and prolonged survival of the patient is contingent upon curative resection of both lesions. The patient should be referred to an experienced thoracic surgeon for careful consideration of surgical resection of both nodules, if feasible and safe. If the second tumor is in the same lobe (a satellite nodule) the surgical operation – lobectomy-- is unchanged. If the second tumor is in a separate lobe on the same side, both can be removed in a single operation, either with a conservative combination of removal of two parts of the lung, or where necessary, by removal of an entire lung. If the second cancer is contralateral, and the higher stage cancer can be removed without resection of the entire lung, a second operation, usually after recovery from the first may offer an opportunity for cure.

If the larger, higher-stage lesion is not suitable for curative resection, then there is no indication for removal of the of the second primary lung cancer. In carefully selected cases, treatment of one or both cancers by radiation therapy may be more appropriate.

In a patient with a tiny (< 5 mm.) contralateral nodule in conjunction with a potentially curable first cancer, the lung cancer should be treated for cure and the tiny nodule should be carefully followed with serial CT scans. If a follow-up CT scan demonstrates growth of the nodule, then consideration of biopsy and/or surgical removal of the second lung nodule is in order.

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