Basics of Bronchioloalveolar Carcinoma (BAC)

Bronchioloalveolar carcinoma, or BAC, is a unique subtype of non-small cell lung cancer (NSCLC) that has unique features in terms of the demographics of who gets it, how it appears on scans, how it often behaves, and potentially in how it responds to treatment. It is a subset of lung cancer for which most of what we know emerged in the last 10 years, with our understanding of this entity, and even the definition of BAC, still evolving.

What is BAC?

BAC was first identified and defined as a separate subtype of lung cancer by Dr. Averill Liebow in 1960. At that time, he highlighted it as a form of well differentiated adenocarcinoma of the lung that appeared to not be able to invade the surrounding lung scaffolding and spread within the lung(s), presumably aerogenously and/or through lymphatic channels.

Under the microscope, an image such as that on the left shows thickened walls of the gas-exchanging sacs in the lungs called alveoli. The classic description of this pattern is lepidic, meaning “scale-like.” X-rays and other imaging shows a picture that looks remarkably like pneumonia, as shown on the right, and probably more than any other kind of lung cancer, patients with BAC are routinely diagnosed as having pneumonia for weeks or months before a diagnosis of cancer is actually established.

The diagnosis has undergone some revisions over the past 50 years, and the most widely used system is still the 1999 definition by the World Health Organization that defines “pure BAC” as a subtype of adenocarcinoma that has no invasive component. Under this strict definition, BAC accounts for only about 2-4% of NSCLC cases, but up to 15-20% of NSCLC tumors have a combination of invasive adenocarcinoma with some component of BAC.

There is actually a continuum from pure BAC to BAC with focal invasion, to adenocarcinoma with BAC features, and then invasive adenocarcinoma with no BAC component:
Although pathologists have sometimes been rigid in their use of the term “BAC” to describe the pure form, many clinicians have observed that the distinctive features of BAC in terms of natural history and behavior can be seen not only with pure BAC but in the more common situation of a combination of BAC with some component of invasive adenocarcinoma. Accordingly, clinicians have generally considered the eligibility for a clinical trial on BAC to depend on having an adenocarcinoma with at least *BAC features*, rather than restrict to a much smaller population of patients with pure BAC.

There are two main subtypes of BAC. The non-mucinous (NM-BAC) subtype is more common, comprising about 50-60% of cases, while the mucinous (M-BAC) subtype accounts for 30-40%, with the remainder designated as mixed subtype.

Although nearly all work in the field of BAC had not historically made a distinction between the two main subtypes, early work is suggesting that the NM-BAC subtype is far more likely to have an EGFR mutation and respond well to oral epidermal growth factor...
receptor (EGFR) tyrosine kinase inhibitors (TKIs) like Tarceva (erlotinib) and Iressa (gefitinib). In contrast, it appears that K-RAS mutations are more common in patients with M-BAC, in whom it appears that EGFR TKIs may be much less effective overall. However, this work remains very preliminary.

The BAC Population, and BAC symptoms

Although there is some controversy about this, BAC is generally felt to be rising in incidence, or at least being recognized and diagnosed more commonly. This is difficult to measure accurately, because much depends on how strictly or liberally BAC is defined (pure vs. any component of BAC). The demographics of BAC are also unique, in that about 1/3 of patients with BAC are never-smokers, far more than are seen for lung cancer in general, and more women are affected than men, which is a reversal of the trend for other forms of lung cancer.

A little more than half of patients with BAC present with no symptoms but are detected after an incidental finding is noted on chest imaging. The classic imaging finding on CT is a “ground-glass opacity”, which is a non-solid lattice of increased density. In contrast, a semi-solid appearance has been associated with an invasive adenocarcinoma with BAC features, and specifically with the solid component of a lung lesion generally felt to represent the solid component on a CT scan. More advanced cases typically have multiple tiny lung nodules (sometimes described as a “miliary pattern”) or larger hazy lung infiltrates, which are sometimes diffuse and extensive throughout one or both lungs.

When people have symptoms, it is most commonly a cough, seen in about 30-40% of patients; this is sometimes productive of a frothy sputum, known as bronchorrhea, and this can be very copious, even a liter or more per day. This is generally felt to be a manifestation of the mucinous subtype. Shortness of breath is also a common symptom seen in about a third of patients.

Clinical progression of BAC, and Early BAC

Another important and distinct aspect of BAC is that the rate of progression can be extremely variable. More than any other type of lung cancer, BAC can be so slow that it doesn’t clearly need any treatment for years, growing at a barely perceptible rate from one year to the next. Other BAC tumors can progress rapidly and lead to declines in a patient’s lung capacity and activity level over a matter of just weeks.

The more favorable survival with BAC has been demonstrated for stage I BAC compared with other adenocarcinomas, as shown in a retrospective review out of Massachusetts General Hospital. In some recent series from Asia, the smaller, pure BAC tumors have been associated with a five-year survival actually approaching 100%. Because of this, several Asian studies have demonstrated that surgical outcomes can be excellent even doing a surgery less extensive than a lobectomy for BAC. In some parts of Asia, a wedge resection or segmentectomy are the standard surgical approach for small BAC lesions, and there is increasing interest in and acceptance of this approach in North America for the right case settings. This topic and other special considerations about surgery for BAC are covered in this
This has also led to a planned revision by the pathology community, and actually an elimination of the diagnosis of BAC in favor of it being considered “adenocarcinoma *in situ*” (*in situ* meaning that it doesn’t invade into the tissues of the lung), technically a non-malignant condition. This reflects the fact that prognosis is *extremely* good for patients with small, non-invasive lung lesions. The proposal specifies that for people with a mixture of invasive and non-invasive adenocarcinoma, only the non-BAC component be included in the measurement of the tumor when determining stage and estimating prognosis accordingly. The non-invasive component is felt to contribute negligibly to risk of poor outcomes compared with the invasive adenocarcinoma component.

**Advanced BAC**

*Other work from the same group out of Mass General* has shown that the median overall survival of patients with advanced BAC is also significantly longer than that of patients with other subtypes of non-small cell lung cancer.

It generally hasn’t been felt that this more prolonged survival has been due to greater responsiveness to chemotherapy. BAC historically hasn’t been very well studied, given that it represents such a small proportion of non-small cell lung cancer cases. They have generally been pooled with other subtypes or sometimes excluded from trials, but in neither situation has it been possible to properly assess how BAC patients do with standard chemotherapy. Limited retrospective reviews have generated far-ranging conclusions.

As shown in the table on the bottom of this slide above, a careful look has shown that the benefit may be comparable between BAC and non-BAC lung cancer, but many oncologists have historically perceived that BAC is resistant to chemotherapy. This may be because the diffuse, poorly defined lung lesions that typify BAC aren’t conducive to measuring tumor shrinkage in the same way as a more solid, circumscribed lung cancer.
But after years of being considered an unusual curiosity in the field of lung cancer, BAC became a source of much greater research focus when it was observed by lung cancer experts at Memorial Sloan Kettering and some other cancer centers that a minority of patients with advanced BAC can have a dramatic and rapid response to the emerging oral agents targeting the epidermal growth factor receptor (EGFR), such as gefitinib (also known as Iressa) and erlotinib (also known as Tarceva). Here you can see patient’s chest x-rays taken just 5 days apart and demonstrating the remarkable response obtained with Iressa over that short time.

In addition, these responses could also be very long-lasting, as shown in this pair of CT scans taken two years apart in a patient with widespread BAC.

In fact, this particular patient had a mixture of adenocarcinoma and non-invasive BAC, so the impressive responses are not just limited just to patients with the pure form of BAC.
This work led to trials of the EGFR inhibitors in advanced BAC. I led one study through the Southwest Oncology Group (SWOG) that administered Iressa at 500 mg per day to patients with advanced BAC or a mixture of adenocarcinoma and BAC. A total of 135 patients with either chemo-naïve or previously treated disease were enrolled, and we saw a response rate of 16% and a median overall survival of 13 months. However, these rather unimpressive results don’t really tell the whole story. Up to 30% of patients had prolonged stable disease even if they didn’t show a response and significantly better overall survival results were seen in certain groups. Women, never-smokers, patients who developed a rash, and those with a better performance status did particularly well. But some patients did remarkably well, including six patients who continued on Iressa without progression for four years or longer. A look at the clinical and molecular characteristics of these patients showed that not all of these patients were women or never-smokers, nor did they necessarily carry an EGFR mutation or show EGFR gene amplification.

In fact, none of these six patients met the criteria for a formal response, but rather they all showed very prolonged non-progression for years, some still ongoing.

A study conducted through Memorial Sloan Kettering looked at a similar population of 101 patients with advanced BAC or adenocarcinoma with BAC features and gave the oral EGFR inhibitor erlotinib, also known as Tarceva, at the standard dose of 150 mg daily. The response rate and survival were a little better than SWOG saw with Iressa, but what the investigators focused on was the particularly favorable results among patients with an EGFR mutation, who showed a response rate of 83% and a median survival of approximately two years. As shown in the so-called “waterfall plot” that shows tumor shrinkage by a bar going downward from the higher horizontal line, most of the best responses, at the far right, are gray bars that note patients with an EGFR mutation.
However, many patients with no mutation, who are shown as orange bars, and even some with K-Ras mutations and shown with blue bars, had good tumor shrinkage or at least stable disease.

This study with Tarceva also showed that responses were more common in never-smokers than in former or current smokers, and in women more than men. In addition, responses were only seen in the patients who developed a rash. There was no evidence that the best results were only in treatment-naïve patients, nor was there any suggestion that results were better for patients with pure form of BAC. If anything, the response rate was better in patients with a mixture of BAC and invasive adenocarcinoma, as shown at the bottom of the table below.

In the last few years, those of us with a major focus on BAC have come to recognize that the two main subtypes of BAC, known as mucinous and non-mucinous, may well have many important and clinically relevant differences, as briefly noted above. Specifically, survival with EGFR inhibitors appears to be best for patients with the non-mucinous BAC or a mixture of adenocarcinoma and BAC, and it’s rather poor with patients who have the mucinous subtype of BAC. This is illustrated in a set of survival curves from the SWOG 0126 trial of Iressa in BAC that I led, broken down by specific histology as interpreted by a central pathology lab.
As shown by the light blue bar, a few patients who were felt to have invasive adenocarcinoma and no BAC were actually enrolled by some institutions, highlighting the variability in interpretation of the BAC diagnosis from one center to another.

This same observation of far better results with Iressa with the non-mucinous subtype of BAC was also seen in a French study:

So while the work assessing differences between BAC subtypes is still preliminary, it appears that the favorable results with EGFR inhibitors are confined to patients with the non-mucinous subtype, and these are more likely to be never-smokers and carry an EGFR mutation. Greater responsiveness to standard chemotherapy agents may be seen in patients with the mucinous BAC subtype, although we have very little evidence to go by here.

Finally, as noted above, there is a plan to have the World Health Organization change the classification of the previously noted spectrum of adenocarcinoma to non-invasive BAC. This is described in detail in a post dedicated to this subject. It remains to be seen whether this will be
widely adopted and whether it will have an impact on clinical management.

To summarize, BAC is a unique subtype of lung cancer that accounts for about 2-4% of non-small cell lung cancer cases, but it's a component in about 15-20% of patients, in combination with invasive adenocarcinoma. Under the microscope, the pure form is noninvasive and spreads thinly over the walls of air sacs, interrupting gas exchange. On x-rays and CT scans, it typically appears as hazy infiltrates, often described as ground-glass opacities, or else as widespread small nodules within the lung only. The patient population typically includes a higher proportion of never-smokers and women than other lung cancer subtypes.

Among the most intriguing aspects in the study of BAC has been its response to treatment, which can include some of the most dramatic and long-lasting responses we ever see in lung cancer and it occurs consistently in a minority of patients who receive an oral EGFR inhibitor like Tarceva or Iressa. Responses may be more likely in certain patient subgroups and may be especially pronounced in patients with an EGFR mutation (this may be the main or only reason we have identified EGFR inhibitors as a preferred treatment for BAC). We are also gaining a new understanding that there may be clinically distinct subgroups even within the rather small population of patients with BAC. The non-mucinous subtype may be especially likely to respond to EGFR inhibitors, while pneumonic BAC, which is typically an aggressive mucinous BAC, has been especially difficult to treat effectively.

For additional information, including details on many aspects of what we've touched on here, please check the BAC folder within the subject archives.