CHAPTER 9
Management of Multifocal Bronchioloalveolar Carcinoma (BAC)

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Introduction

The management of advanced bronchioloalveolar carcinoma (BAC) must begin with the caveat that this clinical entity has been the subject of changing definitions and is no longer recognized as a discrete subtype of lung cancer by the new classification system for adenocarcinomas developed by the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) [1]. While BAC had historically been defined histologically as an adenocarcinoma that does not invade the basement membrane or lung parenchyma, the new IASLC/ATS/ERS classification of adenocarcinomas classifies a noninvasive adenocarcinoma as *adenocarcinoma in situ* for a solitary lesion and *lepidic predominant adenocarcinoma* (LPA) for a multifocal process with the same histologic appearance if nonmucinous, or alternatively mucinous adenocarcinoma for what were previously termed nonmucinous and mucinous BAC, respectively.

Nevertheless, there has historically been a discordance between the recommendations of many leading pathologists and the use of terms like BAC in clinical practice [2], and it remains to be seen whether the new classification will be widely adopted by the clinical oncology community. As patients continue to be diagnosed by pathologists with BAC and clinicians routinely approach and publish about this group of patients as a distinct clinical entity, it remains relevant to discuss their clinical management within the functional definitions that persist in practice.

It is also necessary to offer several caveats in discussing management recommendations in this setting. The term BAC is applied to a broad range of patients who are heterogeneous in their histologic findings, natural history, molecular features, and responses to therapy [2], while trials dedicated to BAC are very infrequent, small in number, and may include such a variable population that definitive conclusions remain elusive. Moreover, even within the same individual patient, different lesions may demonstrate variable pace of progression, invasiveness, radiologic features, and molecular profiles, though these observations remain poorly characterized in publications. By necessity, therefore, as is true of the new proposed reclassification of lung adenocarcinomas, no recommendations made about multifocal BAC can be offered on the basis of level 1 evidence but rather can only be provided on the basis of significant clinical experience with this patient population, combined with extensive conversations with others who share a similarly extensive experience.

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Heterogeneity in the presentation with advanced BAC

Multifocal BAC, at least as it is recognized functionally in clinical practice, is an extremely heterogeneous disease setting. Radiographic findings may demonstrate a very indolent process that may include a few scattered subcentimeter ground glass opacities, a widespread miliary pattern, or diffuse parenchymal infiltrates that are extremely difficult to distinguish from bacterial pneumonia [3,4]. BAC may progress at a rate that can vary from barely perceptible growth over years to virulent progression over weeks. Pathologically, what is termed BAC often includes not only a strictly noninvasive component ("pure BAC"), but often also microscopic areas of invasive disease. It may be mucinous, nonmucinous, or a mix of both components. As with other lung adenocarcinomas, multifocal BAC may sometimes present with an *EGFR* mutation, *KRAS* mutation, *ALK* rearrangement, or sometimes other identifiable but rare molecular features that have significant implications for responsiveness to our available systemic therapies.

Even within the same patient, different areas of disease may demonstrate varying rates of progression, metabolic uptake on positron emission tomography (PET) scans, solid vs. nonsolid component on imaging, invasiveness vs. noninvasiveness on pathologic examination, and molecular marker profiles. In addition, areas of indolent disease may, over time, become invasive and more aggressive in rate of progression [5]. This wide array of clinicopathologic scenarios, despite all being loosely classified under the same category of multifocal BAC, is likely to be best managed through a corresponding diversity of management strategies. What is optimal management for a steadily progressing, widely multifocal miliary pattern of progression and an activating *EGFR* mutation is not likely to be the optimal treatment for a patient with 4–5 very small ground-glass opacities in different lung lobes that are growing imperceptibly over three years of follow-up scans.

Our staging system, published case series, and clinical trial eligibility do not make distinctions among the varied presentations and natural histories of what is defined as multifocal BAC (Figure 9.1). Nevertheless, proposed treatment considerations are discussed below based on a range of clinical presentations that merit individualized therapeutic strategies rather than a unified approach based on amalgamation of distinct patterns.

Because of the heterogeneity of the disease and its potential indolence, there is a significant potential for patients to be overtreated based on patient and/or physician anxiety and a compulsion to "treat the scan" or the stated diagnosis even when the objective findings indicate a natural history of the disease that on a trajectory of many years. In fact, this leads some patients with a more indolent process to experience significant limitations based on serial resections or prolonged systemic therapy for asymptomatic and even clinically irrelevant disease. Conversely, many clinicians remain nihilistic of the potential utility of chemotherapy for advanced BAC or reflexively dismiss the concept of local therapy for what may technically be multifocal but actually has only a single clinically significant focus that is growing at a far greater pace than any other background disease, and for which local therapy may be a very appropriate recommendation.

Evaluating Multifocal BAC

Though BAC is most commonly (50–85% of cases) diagnosed as a solitary nodule highly amenable to surgical resection, multifocal disease may present as satellites within a single lobe (60–65% of multifocal disease), multiple lobes of one lung (20–25%), or bilateral lung nodules (10–15%) [6–8].

In light of the variability of presentations, natural history, and heterogeneity of the disease process in an individual patient (potentially with one or a few areas of disease progressing at a fast rate against a relatively indolent disease process in the background), it becomes particularly helpful to characterize the features of multifocal BAC in an individual patient before developing and committing to therapeutic interventions. This initial characterization includes careful assessment of symptomatology, evaluation of the pace of the cancer and

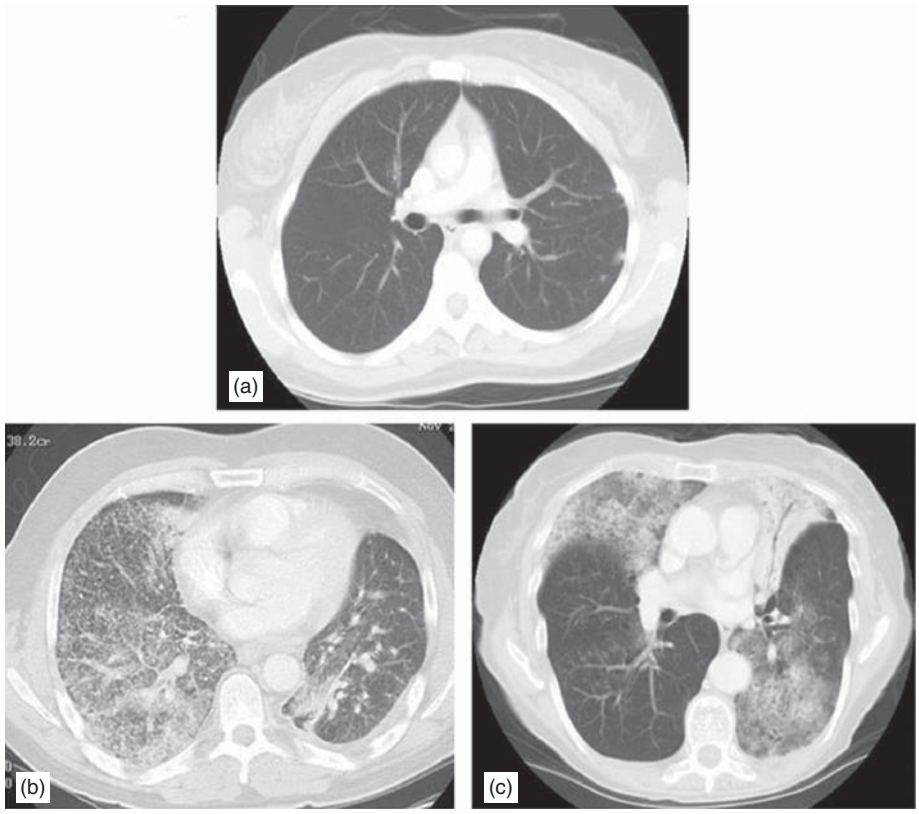


Figure 9.1 Range of case scenarios presenting with advanced BAC. a: Asymptomatic woman with minimal scattered ground-glass nodules (GGNs) (shown in left lower lobe). b: Miliary pattern of diffuse nonmucinous BAC in very symptomatic patient with dyspnea and nonproductive cough. c: Multilobal consolidation from mucinous BAC in patient with productive cough and dyspnea.

whether that is uniform or discordant across a patient's foci of disease, and, to the extent available, an assessment of the pathological findings that includes meticulous assessment of invasiveness and determination of a molecular profile that can shape recommendations for systemic therapy.

Symptomatology

BAC is commonly detected as an incidental finding in an asymptomatic patient who undergoes chest imaging for a routine pre-operative evaluation or nonspecific complaints. Up to two-thirds of patients with BAC (any stage) present with asymptomatic imaging findings, with symptomatic patients most commonly presenting with cough (30–50%), dyspnea (15%), weight loss (10–15%), hemoptysis (5–10%), or chest pain (5–10%) [9–11].

Bronchorrhea, a symptom of multifocal BAC characterized by copious production of thick, frothy sputum, is observed in approximately 5–10% of patients with BAC. In severe cases, patients may produce up to 1–2 liters of fluid per day, leading to significant electrolyte imbalances, as well as hypoxemia from intrapulmonary shunting [12–14]. Specific management considerations for bronchorrhea are discussed further below.

Natural history and imaging findings

Very commonly, the symptomatic and radiographic resemblance of advanced BAC to an infectious or inflammatory process leads to an initial trial of antibiotics and/or steroids, and sometimes multiple courses, for several weeks to months before it is concluded that the clinical and radiographic

findings are not readily reversible with these treatments and a period of follow-up. The severity of initial symptoms and trajectory of progression, or lack thereof, are very relevant factors to be considered prior to initiating interventions with anticipated morbidity.

PET scans have become integrated in the workup of lung nodules, infiltrates of unknown etiology, as well as the routine staging of established lung cancers. It is common for pulmonary lesions to be discounted and a PET scan interpreted as inconsistent with malignancy if they do not demonstrate significant uptake. BAC lesions, however, are often characterized by an indolent natural history, very often with a volume doubling time of one to several years [15–17], which is typically associated with a metabolic rate too low to register as abnormally elevated on a PET scan [18]. Moreover, subcentimeter, nonsolid lesions will often not be of sufficient size and cellular density to reach the threshold of detection of a PET scan. In contrast, more significant hypermetabolism of known or presumed BAC lesions on PET scan is highly associated with invasive disease, greater malignant behavior, and inferior survival [19–21].

In this setting, a PET scan without appreciable hypermetabolism of lesions noted on chest CT may be considered as a false negative [22, 23]. Nevertheless, the lower uptake often seen on PET scans is consistent with the slower natural history and overall significantly more favorable prognosis of many patients with BAC, potentially with a survival of many years, including with multifocal disease [9, 10, 24]. This prolonged natural history is indicated by the terminology of the new classification of solitary lesions that reclassifies smaller unifocal lesions of nonmucinous, noninvasive adenocarcinomas from BAC to *adenocarcinoma in situ*, underscoring the very significant potential for overtreatment if therapeutic strategies intended for an invasive cancer process are applied. Though the practical implications for managing multifocal BAC/LPA are not specifically addressed in the new classification proposal [1], this designation is associated with a very favorable survival when reviewed specifically for differences in clinical outcomes when divided among lung adenocarcinoma subtypes under the new schema [25].

Another implication of the term of *adenocarcinoma in situ* is the implication from this terminology that the noninvasive *in situ* form of this disease, often referred to as BAC or pure BAC, represents a pre-malignant condition that evolves into invasive, malignant lung adenocarcinoma. Though this is presumed to be the case [26], it remains unclear whether the noninvasive adenocarcinomas are particularly prone to evolve into invasive lung adenocarcinoma, as more than half of a series of cases of both noninvasive lesions and synchronous invasive adenocarcinoma did not share the same K-ras mutation [27].

Interventions to manage multifocal BAC

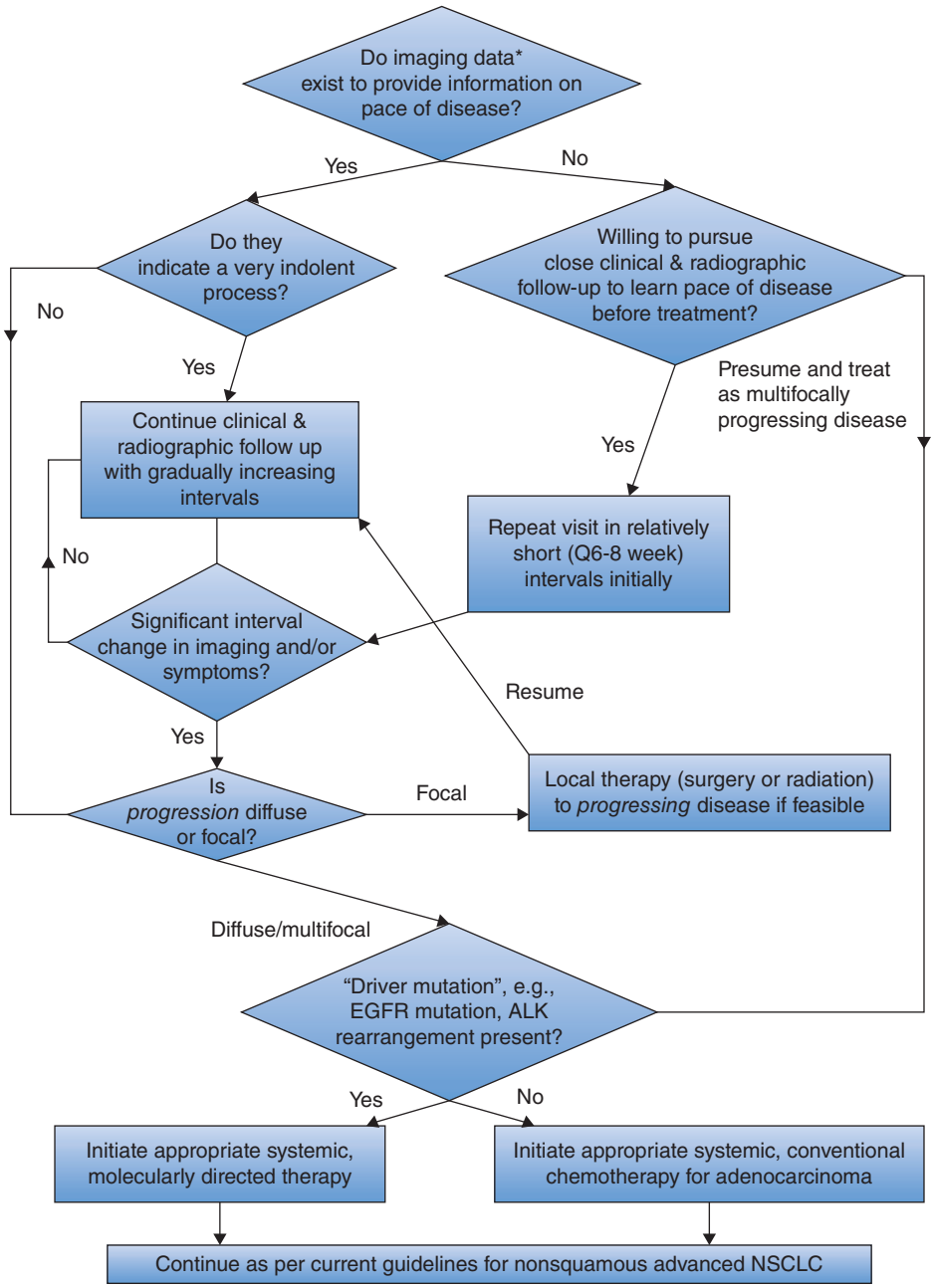
There are several critical questions that should emerge early in the process of determining an optimal approach for managing what is functionally termed multifocal BAC (see proposed algorithm in Figure 9.2).

Is the multifocal disease encompassed within a single lobe or lung?

The most current revision of the NSCLC staging system (7th edition) reflects the potential utility of surgery for multifocal disease in one lobe or pneumonectomy if several lobes of the same lung involved in absence of disease in other areas [28–35].

Changes made in the most recent revision of the AJCC staging system for non-small cell lung cancer (NSCLC) consider satellite nodules within the same lobe as the primary tumor as T3 disease, and in the absence of nodal or distant metastatic involvement, this is now considered stage IIB, compared with stage IIIB in the 6th edition of AJCC staging [36]. Similarly, nodules in a separate lobe of the same lung as the primary tumor are now defined as T4 rather than M1 disease, defined as stage IIIA disease in the absence of nodal or distant metastatic disease, compared with stage IV NSCLC in the prior version of the NSCLC staging system [37].

These revisions reflect the more favorable prognosis of patients, who most commonly have AIS/BAC histology in these additional nodules,



*Comparison films showing minimal interval change, and/or PET with very low maximal SUV

Figure 9.2 Proposed algorithm for management of asymptomatic multifocal BAC.

compared with patients who shared the same stage in the 6th edition of the AJCC staging system. However, it is important to note that the lower stage does not imply that the biology of the underlying disease clearly makes local therapy an optimal approach. Patients with AIS/BAC histology demonstrate a distinct natural history and pattern of progression compared with other NSCLC histologic subtypes that makes it appropriate to consider treatment strategies as distinct compared with the recommendations for other NSCLC subtypes, but the new staging system is not predicated on evidence that patients with satellite AIS/BAC nodules in the same lobe or other lobes of the same lung clearly benefit from surgery. The staging system is based on overall survival alone, whether this is improved by surgery or not.

Several studies have demonstrated that patients with satellite nodules in the same lobe can feasibly undergo resection and demonstrate no evidence of recurrence for many years [28, 38–42]. In the face of an indolent multifocal disease process, however, patients may potentially live as well and as long with no surgery. In the absence of comparative data to direct recommendations for or away from resection, it is certainly reasonable to defer to judgment of the treating physicians, along with patient preference and consideration of performance status, patient comorbidities, and the pattern of disease, to pursue primary surgery, favor systemic therapy, or pursue a strategy of initial attentive clinical and radiographic follow-up with consideration of treatment based on the pattern of change over time.

Is the patient symptomatic, or is there any progression at a clinically significant rate?

Because the natural history of *adenocarcinoma in situ*/multifocal BAC is often extremely indolent, it is important to first clarify whether treatment with a potentially morbid therapy is indicated. While advanced BAC may present as a symptomatic and sometimes even fulminant disease, patients may also be classified as having multifocal BAC on the basis of asymptomatic, scattered subcentimeter GGNs that demonstrate a doubling time of several years and may not change perceptibly over the course of one or more years. Even in patients with larger and/or more widespread lung nodules, these radiologic findings may remain asymptomatic and minimally changing on follow-up imaging for many years.

In patients with minimally progressing multifocal BAC, it is challenging to justify therapeutic interventions accompanied by treatment-related toxicities that can only worsen patient quality of life in the setting of an asymptomatic process that poses an exceptionally minimal threat to survival over a trajectory of many years. While it is always appropriate to review a range of treatment options with an individual patient, it is critical to recognize that this situation represents a fundamentally different situation than a highly PET-avid, metastatic invasive lung adenocarcinoma that clearly demonstrates progression between scans obtained over an interval of one or a few months during the initial workup.

In many cases, patients have had a PET scan that documents a very low SUV consistent with an indolent natural history, or serial imaging that has documented extremely indolent progression over many years prior to the pursuit of a tissue diagnosis. With the benefit of hindsight to illustrate the course over many years, the primary motivation for intervention is often based on patient and/or physician anxiety or is reflexive, based on a tissue diagnosis that mentions carcinoma, despite all signals suggesting that this may not be a clinically relevant threat in terms of either cancer-related symptoms or survival.

If there is evidence of progression at a clinically significant pace, is this a unifocal (or arguably "oligo-focal") or multifocal process?

In light of the heterogeneity of the disease, it is appropriate to ask whether, even in the setting of multifocal disease, the clinically relevant progression is unifocal or multifocal. Here again, as the revised lung adenocarcinoma classification attempts to highlight, it is valuable to distinguish between an indolent process (implied by the *in situ* moniker) that may progress in the background over many years to decades and a faster-progressing process

that poses a more immediate threat in terms of cancer-related symptoms and survival.

The critical distinction between progression as a more focal versus diffuse process emerges because it may be very appropriate to favor a local therapy, most commonly surgery or radiation, in the setting of *unifocal* progression, even if this is against a background of multifocal disease (Figure 9.3). While a discordantly faster growth rate than other lesions may potentially be interpreted as sufficient evidence of unique biology in the progressing lesion, additional evidence may be available in terms of a transition from nonsolid to solid, greater metabolic uptake on PET, and/or evidence of invasive carcinoma based on a biopsy of the progressing lesion.

Functionally, unifocal progression may be interpreted as analogous to a solitary lesion. While the oncology community has historically defined multifocal BAC as clearly stage IV and therefore appropriately limited to systemic therapies, it is helpful to consider the implications of the revised classification. In the setting of a diffuse premalignant *in situ* process, the presence of a solitary focus of clinically significant progression against a background of minimal change should not preclude local treatment of the focus of progression. The central issue is whether a solitary area of progression is estimated to be the likely driver of a patient's prognosis, or alternatively, whether it is more likely that diffuse progression aside from the leading area of progression is likely to limit a patient's quality of life and/or survival. This is essentially a question of the differential growth rate between the leading area of progression and additional areas of disease: if the difference is very significant, it is quite appropriate to consider local therapy, even if there are additional lung lesions detectable.

Approach to unifocal progression in the setting of multifocal disease

The question of whether to pursue surgery, radiation, or an alternative local therapy such as radiofrequency ablation, cryotherapy, or another less established intervention may be approached in essentially the same way as someone who does not have background lesions consistent with multifocal disease, as long as the background lesions demonstrate a very indolent growth pattern. A recently published single center series [43] demonstrated that among 39 patients with suspected multifocal BAC but a single "dominant nodule", only 9 patients (23%) demonstrated radiographic progression of an unresected nodule over a mean duration of followup of over 30 months.

Given the significant risk of multifocal progression in the future f compared with patients who have no visible lesions, the potential to treat definitively with stereotactic body radiation therapy (SBRT) has emerged as an appealing option with minimal morbidity and a realistic potential for definitive treatment here. In a setting in which the value of local therapy remains poorly established, there may be a particular value to interventions that are associated with minimal risk. Analogous to the well described clinical setting of "precocious metastasis" that is sometimes associated with very prolonged survival following local therapy of the solitary metastatic focus [44, 45], this situation may be considered as "precocious progression" and approached similarly.

In an era of minimally invasive video-assisted thoracoscopic (VATS) surgery and greater availability of stereotactic radiosurgery (SRS), it is increasingly feasible and even tempting to pursue serial local therapies for multifocal disease that demonstrate metachronous multifocal progression over time. While this may be a very reasonable and even optimal approach if the interval between treatments is measured in years and treatments are limited to areas of demonstrated progression and not just identifiable, stable GGNs, there is a danger that may appear in clinical practice of multiple resections and/or radiation-directed treatments for what is, in essence, truly diffuse and multifocal progression if these lesions demonstrate changes over an interval of only several months.

It is necessary to acknowledge that there are no evidence-based guidelines to dictate a doubling time or interval for which it is appropriate to recommend serial local therapies. However, the value of serial local interventions is dubious if progression in multiple lesions is demonstrated over a course of less than a year. Moreover, there is a very real

risk that the functional loss of significant amounts of functional lung parenchyma from serial surgeries or radiation treatments may lead to an overall harm of the patient if further progression within the lungs is very likely to lead to more loss of functional lung tissue. It is regrettable to have patients undergo resections of two lobes or a pneumonectomy for a process that should, on careful reflection, be recognized as highly likely to demonstrate multifocal progression.

Similarly, isolated small series have described the potential to pursue lung transplantation surgery for patients with pneumonic BAC or multifocal BAC [46–51]. Though they note encouraging short-term results, recurrence has been a very common outcome with prolonged follow up [47, 52]. Nevertheless, data from the United Network for Organ Sharing Registry notes a 5–7 year posttransplant survival of 57% among a total of 29 patients who underwent lung transplantation for multifocal BAC, compared with 50% for the entire population of lung transplant recipients. Overall, while the role for lung transplantation for patients with advanced BAC remains undefined, this is not a strategy amenable to widespread application.

As noted above, several groups have also reported on the feasibility of multiple resections, either synchronously or sequentially, for multifocal lung nodules [28, 38–42]. These series have not distinguished between lesions that are growing at a clinically significant rate and those that are visible but demonstrate little or no progression over prolonged follow-up. Notably, the surgical literature largely refers to such cases as separate primary tumors, often citing the circular argument that those patients who demonstrate favorable prognosis must by definition have had separate primary cancers, rather than considering that this is actually an indolent clonal but multifocal process. Unfortunately, recurrence of lung nodules is a common occurrence after surgery for multifocal disease [34, 53].

It is critical to recognize that BAC may often follow an indolent pattern of progression that would be associated with a favorable outcome in the short term whether *any* intervention is pursued or not. In addition, the patients offered such interventions may well be subject to selection bias and be uncharacteristically young and fit or have a disease indolent enough to be amenable to traveling for opinions at multiple centers. It therefore remains unknown whether more heroic interventions in the setting of multifocal BAC translate to clinical benefit or whether such patients are likely to do unusually well regardless of treatment, perhaps specifically enriched by selection bias for these more aggressive interventions.

In this setting, it is important to highlight the distinction between what *can be done* and what *should be done*. Though many patients and physicians may feel a bias toward pursuing the most aggressive strategy possible, overtreatment has a very real potential to cause harm if local therapies are truly futile because they are applied in a setting of multifocally progressing disease. Nevertheless, if we consider specifically the pattern of progression in an individual case, multifocal BAC arguably represents a setting in which a local therapy may be quite defensible and even optimal if considered judiciously for selected patients.

Palliative surgery

In rare cases, surgery may be a consideration as a palliative intervention even if more diffuse progression is seen. Particularly in the unique setting of "pneumonic BAC", a clinical picture in which a patient demonstrates an extensive infiltration that looks extremely consistent with pneumonia involving one or more lobes (Figure 9.1c), surgery may be considered as a palliative intervention to alleviate severe cough, bronchorrhea, or dyspnea caused by "shunting", where blood perfusing these extensively infiltrated areas of lung is not aerated. Though progression shortly after surgery is the pattern most typically seen in such cases [54], isolated reports have supported the concept of palliative surgery as a means of controlling severe symptoms in patients without other appealing treatment options [55, 56].

Systemic therapy for multifocal BAC

Because of the potential for AIS/BAC to demonstrate a very indolent natural history, an initial

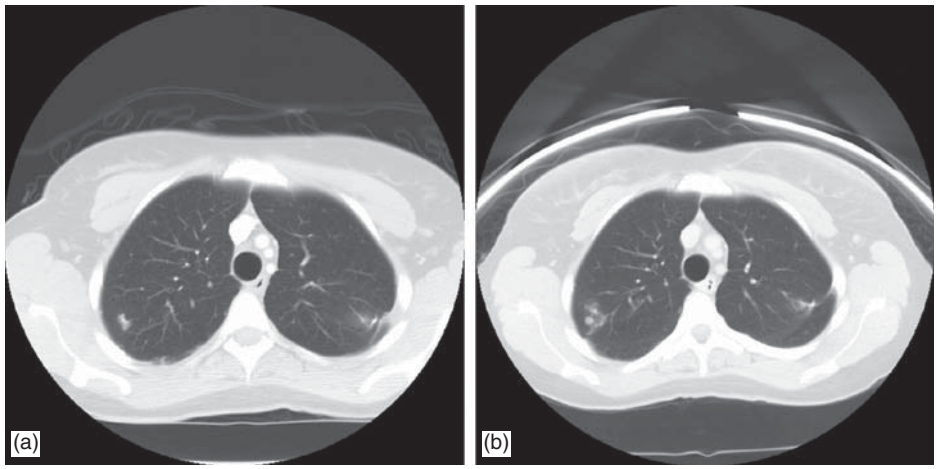


Figure 9.3 Progression over 17 months (from A to B) of a single focus of disease in the right upper lobe of a in a woman with multifocal BAC. All other lesions remained stable over this interval. She was treated with stereotactic body radiation therapy (SBRT) to the only lesion demonstrating appreciable interval progression.

question is whether immediate treatment with systemic therapy is clearly indicated, even with multifocal disease and a more diffuse pattern of progression. Whether imaging demonstrates a few limited foci of asymptomatic subcentimeter GGNs or a more extensive pattern of disease visible on CT imaging, it is appropriate to consider an interval of clinical and radiologic follow-up without immediate treatment in asymptomatic or minimally symptomatic patients. If a slow pace of interval change on scans obtained prior to diagnosis is available, this can often provide confidence that rapid radiologic change and clinical decline during initial observation with a repeat CT scan in 6–8 weeks is very unlikely. Though resistance from anxious patients (and physicians) may limit the application of this strategy, many patients can avoid treatment-related side effects for months or years, while the additional observation can provide valuable insight into the natural history for an individual patient's case. Particularly if patients are instructed to convey any significant change in symptoms, an initial period of attentive follow up is extremely unlikely to obviate the opportunity for the treatment options available.

Similarly, it is helpful to avoid discarding a generally effective therapy prematurely, based on the appearance of an equivocal small nodule or subtle progression of existing GGNs. If the natural history of multifocal BAC is likely to follow a trajectory of several years, whether due to effective therapy, the biology of the underlying disease, or both, it is easy to exhaust multiple appealing treatment options long before a patient has a decline in performance status or diminished motivation to receive further therapy. While it is appropriate to recognize clinically significant progression and not continue to administer clearly futile therapy, it is also optimal to be resistant to discontinuing a well-tolerated treatment that is associated with very modest, equivocal progression in an era in which the high resolution of our scans may document clinically irrelevant progression based on subtle appearance of new tiny lesions or minimal interval growth or PET-identified increased hypermetabolism in existing lung lesions.

Historically, multifocal BAC has not been consistently distinguished from other subtypes of NSCLC in trials of systemic therapy for advanced NSCLC. In most cases, patients with multifocal BAC have been eligible for trials for a broad range of NSCLC subtypes, despite demonstrating a more favorable prognosis for this stage compared with patients with metastatic invasive adenocarcinoma [57].

The more favorable prognosis of patients with multifocal BAC is also now reflected in the most recent revision of the AJCC staging system for NSCLC, which designates disease outside of a single lung but within the chest as M1a disease, which is associated with a more favorable prognosis than is seen in stage M1b, defined by metastatic spread outside of the chest. While this change reflecting superior survival in patients with cancer limited to the chest includes patients with pleural effusions and/or pleural implants, many of the patients with stage M1a NSCLC in the database that led to the staging revision [37] had what was considered to be multifocal BAC, associated with a relatively indolent pattern of disease and a comparably favorable survival compared with other NSCLC subtypes presenting with stage IV disease [57–59].

Importantly, the definition of BAC in both retrospective and prospective clinical trials of systemic therapy has generally not been subject to central histologic review, instead relying on the terminology used in pathology reports or physician assignment of histology. Studies that have subjected tumor tissue to central histologic review have clearly demonstrated that there is considerable variability in what is called BAC in practice, with a more loose use of this pathologic descriptor in broad clinical settings than is felt to be warranted by expert reviewers of lung pathology [2,60]. Studies directed at multifocal BAC have continued to generally pursue a practice of more lenient, local definition of BAC, but the work on central review of BAC pathology has underscored the heterogeneity of what is called BAC in trials of advanced NSCLC. Moreover, within the realm of advanced BAC, patients may have extremely variable natural histories and disease burdens yet still remain eligible for the same trials.

There has been a prevalent view of BAC as being unresponsive to conventional chemotherapy, or at least less responsive to chemotherapy than other NSCLC histologies. In part, this may be related to the association of greater chemo-responsiveness with fast cell turnover and disease natural history [61], but it is likely to be in part related to the difficulty in assessing response to therapy in patients whose cancer is less likely to appear as solid, discrete and measurable lesions than invasive NSCLC.

Despite the prevalent view in the oncology community that BAC is poorly responsive to chemotherapy, the limited data on the subject indicate that the response rate (RR) to conventional chemotherapy is actually comparable to that seen in other NSCLC histologic types. A retrospective review of patients treated at Mayo Clinic revealed a response rate of 32% for patients with BAC, versus 33% for patients with other NSCLC subtypes [62].

Limited prospective trial data on patients with advanced BAC also supports the view that conventional chemotherapy may have activity in BAC that is in the same range as what is expected in broader NSCLC populations. A study of single agent paclitaxel in 58 patients with advanced BAC who received by continuous infusion over 96 hours revealed a RR of 14% and stable disease (SD) in another 40%, and a median overall survival (OS) of 12 months [63]. A smaller trial of paclitaxel administered over 3 hours demonstrated a RR of 11%, with SD in another 50%, and a median OS of 8.6 months [64]. Finally, a report describes the results with a range of chemotherapy approaches given as second line therapy in 43 of 47 patients who had progressed on first line gefitinib in the French IFCT-0401 trial [65] described further below. The specific chemotherapy administered included platinum-based doublet chemotherapy in 38 (with a taxane in 29, gemcitabine in 9), five receiving single agent chemotherapy (gemcitabine in 3, pemetrexed in 2). The RR was 21% for the broad range of regimens administered, with a median PFS of 3 months. Although the small numbers preclude any conclusive thoughts on the comparison of different chemotherapeutic options, it is interesting that the RR with a platinum/taxane regimen was 28%, vs. 0% with the platinum/gemcitabine combination, and prolonged responses were seen in both patients receiving pemetrexed (PFS 10 and 32 months). Though limited to anecdotal reports, others have also noted particularly gratifying responses to pemetrexed in some patients with advanced BAC, including

mucinous BAC with a pneumonic clinical picture [66, 67].

Early work with oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib identified that BAC histology was among the clinico-pathologic features associated with a high probability of response to EGFR TKIs [68, 69]. Combined with frequent anecdotal reports of dramatic and prolonged responses to EGFR TKIs in patients with BAC, this work led to the development of multiple trials of EGFR TKIs in advanced BAC, which all confirmed encouraging efficacy. A four-center phase II trial of erlotinib 150 orally per day in 101 patients with advanced BAC, most of whom previously untreated (N = 74), demonstrated a RR of 22% and median OS of 17 months [60]. A multicenter SWOG phase II trial of 136 patients with advanced BAC, 101 of whom were chemotherapy-naïve, administered gefitinib at 500 mg/day, yielding a RR of 17% in chemonaïve patients and 9% among patients who had received prior chemotherapy [70]. Finally, a multicenter French study of 99 previously untreated patients with advanced BAC who received gefitinib 250 mg/day demonstrated a RR of 13%, with another 16% experiencing SD [71].

Over the last several years, however, clinical variables such as histology have largely been superseded by molecular marker results with regard to association of substantial clinical benefit from targeted therapies like EGFR TKIs. For instance, in the IPASS trial of Asian never-smokers or remote prior smokers with a lung adenocarcinoma, a very significant difference in outcome with gefitinib vs. standard chemotherapy was seen in patients with an activating mutation in the *EGFR* gene compared with those with *EGFR* wild type [72], a finding that definitively illustrated that the presence or absence of this molecular marker trumps clinical and pathologic variables in predicting clinical benefit with EGFR TKI therapy.

In terms of the potential utility of the anti-angiogenic agent bevacizumab, a SWOG follow-up phase II study to the S0126 trial of single agent gefitinib tested the combination of erlotinib and the anti-angiogenic agent bevacizumab in 78 patients with advanced BAC [73]. The results revealed a RR of 18%, with a median PFS of 5 months, and median OS of 17 months. Though not remarkably superior to the prior SWOG experience with gefitinib alone, the more recent trial included relatively few never-smokers, who were preferentially enrolled on a competing trial of the same regimen, so these results may be considered as encouraging. Nevertheless, in the absence of a prospective randomized trial, the incremental value of bevacizumab, whether added to chemotherapy or EGFR TKI-based therapy, in patients with advanced BAC otherwise remains undefined. Because such patients were eligible for the ECOG 4599 trial of carboplatin/paclitaxel with or without bevacizumab that demonstrated a survival benefit with the active drug it is certainly reasonable to include this agent in otherwise appropriate patients.

Though limited, data from studies of BAC have supported the concept that the association of BAC histology with benefit from EGFR TKIs is likely primarily due to the enrichment for patients with *EGFR* mutations among those with advanced BAC [74, 75], and specifically the nonmucinous subtype of BAC [60, 75–78]. *EGFR* mutations were detected in 26% of a series of 86 patients with BAC, all of whom had nonmucinous BAC (22/69 vs. 0/17) (71). Similar results were seen in smaller Italian series, in which *EGFR* mutations were seen in 30% of patients with nonmucinous and 0% of patients with mucinous BAC [54]. Finally, results from tissue from 44 of 59 Japanese patients with BAC or adenocarcinoma with BAC features revealed that *EGFR* mutations were present in 15% of patients with mucinous BAC vs. 58% with nonmucinous BAC, while *KRAS* mutations were present in 70% vs. 29%, respectively [79]. Nevertheless, recent reports have also documented the variability of molecular profiles of different lung nodules within the same patient [80–82].

These differences in molecular profiles have been associated with differences in responsiveness to EGFR TKI therapy in the trials that have evaluated this question. In the four-center study of single agent erlotinib described above [60], the RR among patients with an *EGFR* mutation was 87%, compared with 7% among those with *EGFR* wild type; the difference in median PFS was 13 vs. 2 months,

respectively. Conversely, the presence of a *KRAS* mutation in this study was associated with a RR of 0%, compared with 32% in patients with *KRAS* wild type, consistent with the widely observed very low probability of objective response or significant clinical benefit from EGFR TKIs in advanced NSCLC [83–85].

A more recent French phase II trial, IFCT-0504, randomized patients with previously untreated advanced BAC to either erlotinib or standard chemotherapy carboplatin/paclitaxel, with all patients crossing over to the other therapy at progression and then receiving pemetrexed as third line therapy [86]. Among 130 eligible patients, 46% had nonmucinous BAC and 41% had mucinous BAC, with 13% undetermined subtype. This trial demonstrated a RR of 39% vs. 53%, median PFS of 3.2 vs. 6.1 months, and median OS of 20.2 vs. 16.4 months for erlotinib vs. chemotherapy, respectively. Subset analysis revealed that a significant interaction with nonmucinous vs. mucinous subtype: specifically, patients with nonmucinous BAC demonstrated a comparable PFS from the two approaches, while patients with mucinous BAC demonstrated a superior PFS with chemotherapy (HR 2.86). However, molecular marker studies were not reported, so it is very possible, if not probable, that differences in efficacy were fundamentally correlated with differences in the relative incidence of activating *EGFR* mutations in patients with nonmucinous vs. mucinous BAC.

Another recently identified driver mutation of lung cancer is a rearrangement of the *anaplastic lymphoma kinase* (*ALK*) gene. The oral ALK inhibitor crizotinib has recently been identified as an optimal systemic therapy approach for patients with an *ALK* rearrangement [87], for which this agent is now FDA approved [88]. Though only recently identified and still not well studied for individual and relatively uncommon lung cancer subtypes, several reports have highlighted that an *ALK* rearrangement is disproportionately seen in patients with adenocarcinoma with bronchiololalveolar features [89, 90].

In summary, though data of any systemic therapies specifically for patients with multifocal BAC remains limited, the association in advanced BAC of dramatic and prolonged responses to EGFR TKIs with the presence of an activating mutation in the *EGFR* gene and the absence of a *KRAS* mutation strongly suggests that such patients be approached in the same way as other patients with advanced NSCLC. Specifically, if it is determined that a patient with multifocal BAC has symptoms and/or progression that warrants initiation of systemic therapy, the optimal treatment is likely to be guided by the presence or absence of a "driver mutation," just as is the current standard of care for a stage IV invasive lung adenocarcinoma. Patients with an *EGFR* mutation or *ALK* rearrangement are most likely to demonstrate significant an objective response and significant clinical benefit from an oral EGFR or ALK inhibitor, respectively; while patients whose cancer demonstrates wild type with regard to *EGFR* or *ALK* are most appropriately directed to conventional chemotherapy as initial treatment. Importantly, clinical data available at this time do not support the view that either chemotherapy or EGFR TKI therapy is futile in patients with advanced BAC.

Bronchorrhea

As noted previously, bronchorrhea can be a severe symptom most commonly associated with the BAC subtype of lung cancer. Though consistently effective therapy has remained elusive, some of the treatment approaches that have demonstrated limited success, essentially in the form of case studies, have included corticosteroids [91, 92] and nonsteroidal anti-inflammatory drugs [93, 94]. Otherwise, the most effective intervention for managing bronchorrhea has been successful treatment of the underlying disease, primarily with systemic therapy such as an EGFR TKI [95–97]. Successful treatment of bronchorrhea with crizotinib in *ALK*-positive patients with mucinous BAC have also been seen in anecdotal cases from clinical practice.

In some cases, surgery has been pursued as a palliative intervention, with mixed success [13, 98].

Overall, bronchorrhea remains a difficult symptom to manage and one for which there is no

recognized beneficial intervention aside from effective treatment of the underlying BAC process, when possible.

Conclusions

Though the latest reclassification of lung adenocarcinoma [1] favors no longer using the term bronchioloalveolar carcinoma, it almost exclusively discusses small and solitary lesions and provides very little discussion or insight about the multifocal disease process recognized clinically as advanced BAC. Though recognized in part for its significant variability in natural history and response to therapy, it is characterized as a distinct clinical entity by its significant potential to follow an indolent course, even when multifocal, and for its association with a relatively high incidence of *EGFR* mutations that are associated with often dramatic and prolonged responses to EGFR TKIs.

In light of the potentially indolent progression of multifocal disease, it is often extremely valuable to determine the pace of progression for the disease in an individual patient before initiating therapy, at least in someone what does not have a significant disease burden or symptoms clearly related to their cancer. If patient and physician anxiety can be allayed by the absence of clinically significant progression on interval scans leading up to or following diagnosis, many patients will demonstrate no clinically significant progression over a prolonged period of many months or even years, with some patients never demonstrating disease progression that causes symptoms or limits survival relative to other comordities or a normal lifespan.

Once the admittedly subjective threshold clinically significant and threatening progression is demonstrated, it can be useful to distinguish advanced BAC from most other NSCLC settings by questioning whether the progression is unifocal/limited or a more diffuse process. Many patients with multifocal BAC can have a single nodule progress at a pace that is uniquely faster than a background of nodules that continue to demonstrate relatively indolent or imperceptible change. Because very indolent nodules may well prove to be clinically insignificant, they can be discounted and a patient considered for local therapy if surgery or radiation would otherwise be appropriate for this treatment approach based on the location of the progressing disease, patient performance status, and competing comorbidities.

For patients who demonstrate diffuse, multifocal progression of disease that would be broadly defined as the clinical entity of advanced BAC, treatment recommendations are the same as those that would be recommended for patients with another form of advanced lung adenocarcinoma. The best evidence currently available suggests that the widely cited high probability of response of advanced BAC, and specifically nonmucinous BAC, to EGFR TKI therapy, is predicated upon the high incidence of activating mutations in the *EGFR* gene in such patients. Therefore, whether the diagnosis is clinically or pathologically defined as nonmucinous or mucinous BAC, decisions on systemic therapy are best directed by the presence or absence of molecular driver mutations such as an *EGFR* mutation or *ALK* rearrangement that should lead to a recommendation for an EGFR TKI or ALK inhibitor, respectively, if present, or conventional chemotherapy-based treatment with or without bevacizumab if a clinically relevant driver mutation is not identified.

Because the prevailing evidence suggests that patients with advanced BAC may respond to standard chemotherapy-based treatment comparably to other patients with advanced NSCLC, it is not recommended that patients be denied the opportunity to benefit from chemotherapy based on the widely held but not evidence-based perception that such patients do not respond to standard chemotherapy. This view may well be a product, in large part, of the difficulty in assessing response radiographically in many patients with multifocal BAC.

Overall, multifocal BAC represents a clinical setting in which there is a significant risk of overtreatment that may be detrimental to the patient if it is directed by anxiety or reflexive initiation of aggressive therapy, whether local or systemic. With an extremely variable clinical course that may potentially pose no threat to quality of life or survival over an extended period, pulmonary lesions that

are asymptomatic and demonstrate little or no progression may be discounted, meaning that particular focus should be paid only to clearly progressing disease, which should otherwise be approached like other forms of NSCLC. The treatment strategy should include consideration of local therapy if the disease progression is very limited, while the optimal systemic therapy should be directed by the presence or absence of clinically relevant molecular markers if progression is diffuse.

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