

## **What is ACC? (Adenoid Cystic Carcinoma)**

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### **Where ACC Occurs**

ACC (Adenoid Cystic Carcinoma) is a rare and unique form of cancer that is known to be unpredictable in nature, with a typical growth pattern of being slow and gradual, but over time can be progressive, insidious and relentless. There are some general tendencies, such as the propensity for it to spread into surrounding nerve tissue or metastasize to other areas of the body, yet each patient can experience their own diverse patterns and issues. ACC occurs most commonly in the oral cavity with 58% of the primary tumors beginning in that area, but it can actually occur in as many as 38 different organs in the body. It is commonly considered to be a salivary gland tumor and grouped with other oral cancers in statistical studies since it occurs predominantly in that area. The oral area includes the major and minor salivary glands, roof of mouth (palate), floor of mouth, gums, tongue, pharynx and lips. Though it is often considered to be a salivary gland tumor, ACC actually occurs in the broader grouping of all types of secretory glands (glands that secrete fluids) including tear glands, sweat glands, mucus and excretory glands. Besides the oral cavity, ACC also occurs in the nose, nasal cavity, sinus, larynx, trachea, esophagus, ears, lungs, bronchus, brain, skin, lacrimal gland, breast, Bartholin's gland, vulva, cervix, and others. Upon initial diagnosis it is most often a single tumor that is located within a primary organ and in about 5% to 10% of the cases can include spread into lymph nodes. In a limited number of cases it may have already spread into adjoining areas through nerve invasion or metastasized to the lungs, liver or bone as well. This takes place most often when it has been misdiagnosed for years.

### **How Rare is ACC?**

Of the approximate 566,000 new cases of cancer diagnosed each year in the US, only about 1228 of them are ACC. Long term statistical information from the National Cancer Institute estimates that there are approximately 14,000 Americans alive today who are living with ACC or have dealt with it in the past. This is why it is classified as a rare or "orphan" disease. Many physicians see very few, if any, ACC patients in their practice since ACC occurs in only about one out of every 500 cases of cancer. This is the primary reason many patients have reported their difficulty in locating a physician with knowledge and experience with ACC. This is also why historically there has been very little funding provided for ACC research by the government, drug companies and large nonprofit cancer organizations. That is beginning to change.

### **Unpredictable and Relentless**

In addition to having such a small number of patients to study, a further complication in defining research and effective treatments for ACC is that it has some unique characteristics, with one those being that even though it tends to be slow growing, it is generally unpredictable. Some sources say that though it appears as a low-grade, slower growing malignancy, it is best approached as a high-grade cancer. The National Cancer Institute in its published PDQ (Physician Data Query) classifies ACC as a high-grade malignancy regardless of initial tumor staging or grading. ACC can have long

periods of indolence (no growth), followed by growth spurts regardless of initial prognosis or treatments. It can spread insidiously to other areas in the body, and be very difficult to locate when it spreads since there can be little or no symptoms until it has grown to a significant size. Tumor growth for ACC is often slow, and people may live a relatively long time with metastatic disease; however, recurrence of ACC (cancer that comes back after treatment) is quite common and can occur many years after initial treatment. This overall high variability of its natural course makes it difficult to accurately predict expectations and outcomes when considering a case-by-case comparison with a variety of patients in study groups and their diagnosis. Cancer survival statistics and expectations for ACC should be interpreted with a more broad perspective and some caution so that patients maintain some sort of long term vigilance and awareness. Statistical studies and reports are based on data from hundreds or even thousands of cases of this type of cancer in the United States, but the actual risk for any particular individual may differ. It is not possible to accurately tell a person how long he or she will live with ACC. As with many other issues with this disease, some people have lived as many as 30 or 40 years following initial diagnosis, while others with a more aggressive type may only live a few years. Because survival statistics are often measured in long term, multi-year intervals, the conclusions may not represent recent advances made in the treatment or diagnosis of this disease.

### **Hidden Growth and Misdiagnosis**

Because ACC generally begins to grow very slow, in many cases it can grow within an organ for several years and spread into surrounding tissue before it begins to exhibit any side effects such as pain, pressure or a lump. Also, upon reporting their initial symptoms to a physician, many patients have had their symptoms misdiagnosed as being a minor, more typical body issue, and this has continued over several years until such time that an MRI, CAT scan or biopsy is performed. This misdiagnosis has been reported by some ACC patients to have taken place over 5 to 10 years from their first reported symptom. Another possible initial misdiagnosis for ACC is that even when a needle biopsy is done on a suspect growth, a common misdiagnosis is that it is a benign, non-cancerous growth such as pleomorphic adenoma.

### **Treatments**

The most common treatment protocol and “gold standard” for treating initial ACC tumors is surgical resection with follow up radiation. In a fairly large number of cases these two standard treatments do stop the cancer and the patient has no recurrence in their life time. After the surgical removal of a tumor, the tumor sample is reviewed in a lab by a pathologist, and they report back that “negative” or clean margins were achieved; meaning all of the observable cancer was removed. If residual cancer is still in the surgical area, the pathologist will report “positive” margins. In learning to understand medical terms, this is one case when “positive” is bad and “negative” is good. Follow-up radiation treatment for any residual tumor left in the surgical area is the most common recommendation for treatment, with some oncologists recommending follow up radiation even with clean margins due to the tendency of ACC for invisible, microscopic spread. Because of the of high number of initial cases in the head and neck region, some patients have tumors that are not able to be surgically removed without causing major

damage to critical areas, and radiation treatment is the only alternative and recommended choice for treating these unresectable tumors. Post surgery radiation is always a very important treatment to consider and it is recommended to research the options and gather input from physicians who are familiar with ACC. In the last 10 years a variety of new, more precise, targeted, computer driven radiation systems have become available and are relatively widely available. Treatment choices and decisions for both primary and metastatic tumors can be varied and complex when taking into account the tumor size, location, number of tumors, adjoining critical organs, infiltration, recommendations from physicians, available treatment centers, financial and insurance resources, and the knowledge and comfort level for the patient. For years some patients have tried a large variety of chemo or targeted drug treatments by themselves or as part of clinical trials, but no single chemo or drug combination has shown itself to be effective for more than a few patients. Like most cancer patients many ACC patients also pursue a variety of Complementary and Alternative Medicine (CAM) protocols as part of their treatment plan and have reported various positive benefits.

### **Side Effects from Treatments**

ACC patients generally share a long list of a variety of common side effects that they have experienced both short term and long term. Surgery and radiation to the head and neck area can have a wide variety of issues caused by the removal and treatment of tissue in the oral cavity and surrounding areas, which can include chronic pain, dental issues and damage within the mouth and changes in facial appearance. Radiation side effects can affect many normal body functions causing issues such as dry mouth, nausea, hearing loss, tight jaw opening, speech impediment, and reduced eye sight. Besides the side effects from the initial surgery and radiation, the palliative treatments for managing those side effects can produce a second level of side effects as well. One example is brain swelling from radiation treatment in the head and neck area can cause nausea, which is normally treated with high dose steroids. But the long term side effects from the steroids can lead to connective tissue damage and premature cataracts.

### **Recurrence and Metastasis (“Mets”)**

Recurrence is defined as a return of cancer after treatment, and after a period of time during which the cancer cannot be detected. Even after achieving clean margins with no recurrence at the primary site of tumor, ACC has a high likelihood of metastasizing to other areas of the body over a period of years. This long term recurrence and spread of the disease to other areas of the body is the major cause of death from ACC rather than initial tumor treatment failure, though recurrence in original tumor area does happen. Metastasis occurs when cancer cells have broken loose at the primary site and moved to other regions of the body through the blood stream. These new tumors that show up elsewhere in the body are commonly called “mets.” The most common site of metastatic spread of ACC is to lungs, then liver, then bone. It is predicted by some medical papers that anywhere from 30% to 60% of all ACC patients will have recurrence somewhere in their body at some point, and some researchers have stated that this figure could be much higher if it were possible to track a larger number of patients over a longer period of time. This common characteristic of ACC is the reason that it is highly recommended

by knowledgeable physicians for ACC patients to have regular, annual X-ray or CT scans done on the lungs, and in some cases CT and MRI scans for other areas as well.

### **Ongoing Diligent Vigilance**

After initial diagnosis and treatment of the primary tumor, it is recommended by most knowledgeable ACC physicians that patients continue to have some sort of regular checkups, scans and tests done for the rest of their lives. This typically involves some combination of tests such as blood work, MRI, CAT scan, X-Ray or PET scans that are done at least annually depending upon the individual diagnosis and current condition with ACC. If recurrence takes place with some observed mets, the frequency and type of scans could change depending upon the prognosis.

### **Perineural Invasion and Perineural Spread in Nerve Tissue**

ACC has a tendency to invade the surrounding nerve sheathing near the primary tumor, which is known as perineural invasion. This microscopic invasion of the cancer cells into the linings of connected nerve tissue follows the “path of least resistance” and can be difficult for a surgeon to detect during surgery. Due to its microscopic size it may not even show up on MRI, CAT or PET scans. Even when achieving clean margins, it has been reported that this cancer has sometimes seemed to “skip” over areas and appear to have spread into a region close to the original tumor but not necessarily connected to it. This perineural spread into other regions require close monitoring especially for those nerves that lead back to the brain through the trigeminal nerve or into base of skull.

### **Age, Gender and Growth Patterns**

The median age for diagnosis is approximately 58 years, which is about 10 years younger than that for all cancers. There is a wide scope in ages, from teenagers to those in their 70's or 80's, with the largest number of patients in their 40's, 50's and 60's with almost the same percentage in the 40-50, 50-60 and 60-70 year ranges. There also appears to be a slightly higher occurrence in females (62%) than males (38%). This gender specific trend could be due to female organ incidence. Due to its tendency for slow growth in a majority of patients, ACC has a relatively indolent but relentless course. Unlike most carcinomas, most patients with ACC survive for 5 years, only to have tumors recur and progress in a substantial number of cases. In a recent long term study conducted at MD Anderson Cancer Center with a study of 160 ACC patients, 89% of the patients survived for 5 years, but that was reduced to 40% at 15 years. These statistical expectations were confirmed in the review of other ACC medical reports as well. This disease specific reduction was due to recurrence rather than failure to achieve local regional control at the primary site. Also, the clinical experience at that institution suggests that two populations of patients with ACC may exist with some surviving just years while others survive decades, with the solid cell histology type possibly being a contributing factor to the more aggressive type. More aggressive growth patterns can occur in some patients for their whole clinical course, while some patients can have a varied experience with both some faster and some slower growing tumors over a more long-term protracted course.

### **Three Major Structural Patterns (Histology and Pathology)**

Histology is the study of how cells appear in shape, color, size, structure and edge patterns as viewed under a microscope by a pathologist. For ACC there are three major histological growth patterns that each appears slightly different: cribriform, tubular and solid. It is possible to have a tumor consist of just one of the three patterns, but a mixed grouping is very common with a tumor having two or all three of the types. The solid pattern is associated with a more aggressive disease course, and is generally considered to be faster growing if the tumor consists of 30% or more of this type. ACC tumors are characterized by a distinctive pattern in which abnormal "nests" or cords of certain cells (epithelial cells) surround and/or infiltrate ducts or glandular structures within the affected organ. These structures are typically filled with a mucous-like material or contain abnormal fibrous membranes (hyaline membranes). Such characteristics are apparent during microscopic evaluation of the tumor cells.

### **Tumor Staging System**

Staging is a means to identify how serious a particular cancer tumor is by giving it a numerical classification as compared to other similar types of tumors. In the AJCC (American Joint Committee on Cancer) staging system for Salivary Gland Cancer there are three elements taken into consideration:

- Size of tumor with or without extension into surrounding tissue
- Lymph node involvement
- Distant metastasis at time of presentation of the original tumor

Size is graded on a beginning scale of T1 for a tumor 2cm or less in greatest dimension, up to a T4 which is a tumor more than 6cm in greatest dimension. Based upon the combinations of these three elements, a tumor is then classified as being Stage 1, 2, 3 or 4, with stage 4 being the most serious. ACC diagnosis is more unpredictable and patients can have different outcomes regardless of stage, but generally the larger the size of tumor and the presence of metastatic spread means the diagnosis should be treated more aggressively.

An additional staging system that is utilized in some medical papers for ACC is based upon tumor histology alone as seen from the standpoint of the pathologist.

Grade 1: cribriform and tubular histomorphology only

Grade 2: mixture of cribriform, tubular and solid growth pattern with less than 30% being of the solid histological type

Grade 3: greater than 30% and predominantly solid tumor histological type.

### **Tumor Grading and Differentiation**

Tumor Grade is a system used to classify cancer cells in terms of how abnormal they look under a microscope and how quickly the tumor is likely to grow and spread. Many factors are considered when determining tumor grade, including the structure and growth pattern of the cells. The standard AJCC grading system grades these from 1 through 4, with 1 and 2 being a less aggressive type of cancer, and 3 and 4 being more aggressive. One of the key elements used in determining tumor grade is Cell Differentiation. Differentiation refers to how mature (developed) the cancer cells are in a tumor. Differentiated tumor cells resemble normal cells and tend to grow and spread at

a slower rate than undifferentiated or poorly differentiated tumor cells, which lack the structure and function of normal cells and grow uncontrollably. Some oncologists will also simplify grading and simply use the terms high grade and low grade.

### **Causes of ACC**

The underlying cause of ACC is not known. The disease does not run in families and therefore is not presumed to be inherited as is the case with a small portion of cancers. In addition, ACC is not associated with smoking or alcohol consumption as are some cancers of the lung and the oral cavity. The reasonable working hypothesis is that ACC, like most cancers, is the result of environmental factors that cause normal cells to acquire genetic changes, leading to uncontrolled growth. Recent research has identified a common genetic alteration in many ACC tumors: a new fused gene (MYB-NFIB) created by the fusion of two broken chromosomes (numbers 6 and 9). It is likely that this "translocation" drives the development of many cases of ACC.

### **Research for Developing Effective Treatments and a Cure**

Prior to 2005, there was very limited research on ACC. The field suffered from a lack of funding, tumor specimens and animal models. The few researchers who spent a small portion of their time on ACC were unable to coordinate their efforts, share their findings easily or compete for large funding grants. Five years ago, the formation of the Adenoid Cystic Carcinoma Research Foundation (ACCRF) began to remedy the situation. Gradually, ACCRF's Scientific Advisory Board framed a Research Agenda, biobanking projects made tumor specimens available for studies, genomic studies began to narrow down the vulnerabilities of the disease, and new mouse models of ACC permitted drug screens. These advances attracted the attention of the National Institutes of Health, resulting in large government grants that built momentum for more ACC research.

There are two key steps in developing better treatments and a cure for ACC: (1) finding the molecular targets in tumor cells that are necessary for ACC to thrive, and (2) finding drugs that hit those molecular targets. The discovery of the MYB-NFIB fused gene and other various genomic studies have led to dramatic advances in the first step, throwing up new molecular targets that may be the Achilles' heel of ACC. And ACCRF has developed relationships with pharmaceutical companies to address the second step, knocking out those targets with new drugs that are more effective and have fewer side effects. Historically, clinical trials for ACC patients have involved random testing of drugs approved for other cancers. For the first time ever, forthcoming trials for ACC patients will have clear scientific rationales, supported by preclinical screening in mouse models, that provide the reasoning why a selected group of targeted drugs should work in their particular disease. These are monumental changes and ACC patients are fortunate to be at the leading edge of cancer research.