

ANSWERS ABOUT CANCERS (Part 1 – On the Nature of Neoplasms)

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Tumors are space filling lesions
For the cell growth we don't know the reasons
They expand and can spread
From the toe to the head
They're the host's own parts guilty of treason.
(Leslie Sobin, 1978)

Following routine vaccinations, neoplasia is the most common reason for ferrets to visit their veterinarians, a far higher frequency than in any other type of pet. The possibility that their pet may have a tumor will strike terror into the heart of any dog or cat owner, but from the typical ferret owner is more likely to elicit a deep sigh and a resigned "Here we go again...". This is certainly not to imply that ferret owners love their pets any less, but when you share your life with ferrets, dealing with neoplasia is an all-too-familiar scenario.

For such a common occurrence, owners (and veterinarians) often contact me with questions about "ferret cancer" that belie a deep-seated lack of understanding on neoplasia in general. A basic understanding of neoplasia is paramount for the diagnosis, treatment, and provision of long-term care for what is likely the majority of our pets. This article will deal with neoplasia ("tumors" to many ferret owners) on a general basis, and subsequent articles in this series will focus in more depth on those most commonly seen in domestic ferrets, (i.e., insulinoma, adrenal disease, and lymphoma).

Let's start at the beginning – what is a neoplasm? In its most simple terms, a neoplasm is a proliferation of cells that is of no use to the body. The body possesses efficient mechanisms that keep the various populations of cells in each organ in the proper proportion for optimal performance. In the adult animal, this system is overridden only when injured tissue requires repair. Additionally, the immune system of the body is constantly on the prowl for any cell that shows a different appearance that it should have

- in short, treating cancer cells like a foreign invader, and destroying them before they have a chance to proliferate in large numbers. Neoplasms are simply aggregates of cells that have escaped these mechanisms and begin to divide and grow on their own.



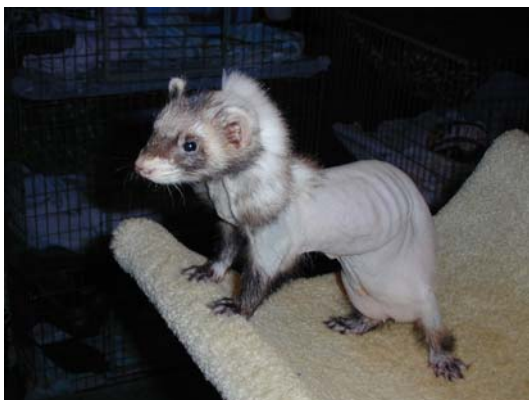
Can you pick out the adrenal ferret?

As you would expect, tumors often result in overall growth of the affected organ - most tumors, regardless of site, appear as a lump or swelling. Neoplastic growth is very costly to the body. In many organs, the growth of a neoplasm replaces viable, working tissue, resulting in progressive organ dysfunction, and in some cases, failure. In some organs, such as the brain, even tiny neoplasms can result in catastrophic clinical signs such as seizures, blindness, or paralysis. On the other hand, larger and less complex organs, such as the liver, may continue to function normally until almost completely replaced by a neoplasm. When neoplasms are extensive or involve multiple organs, the nutrients required for continued growth are extracted at the expense of the rest of the body, resulting in marked weight loss (known as "cancer cachexia") – a sure sign of problems ahead.

In many cases, tumor growth may not be the biggest problem facing the ferret patient. Neoplastic cells generally retain all of the properties of the cell from which they were derived, including the ability to secrete hormones. For example, insulinomas (neoplasms of the insulin-producing islet cells of the pancreas) not only grow independently, but worse for the ferret, secrete insulin without regard to the feedback mechanisms that normally regulate blood glucose levels.

A very important concept in understanding neoplasia in ferrets (or any other species) is that of **benign** versus **malignant**. These two terms provide a good assessment of the long-term outcome (or **prognosis**) associated with a neoplasm. The determination as to whether a neoplasm is benign or malignant is based largely on the pattern of the neoplasm's growth (as seen at surgery or autopsy) and maturity of the neoplastic cells (as seen under the microscope).

Benign neoplasms are generally composed of mature cells, a feature which not only limits their growth rate and potential, but also their ability to **metastasize**, or break off and grow additional tumors in other tissues. Not only do benign neoplasms grow slowly, but also they may stop growing altogether, and even regress. The majority of benign tumors are easily treated by surgical excision – if you remove them completely, you have little to worry about. However, as discussed above, growth is not everything to these tumors. The mature cells that compose them will continue to do what they do best – liberate hormones (as in the case of insulinomas or adrenal adenomas) or make other products such as bone (osteomas), fibrous connective tissue (fibromas), or simply large masses of dividing cells which eventually interfere with the function of host tissue.



Hair loss along the thorax, flanks, and abdomen is characteristic of a ferret with an adrenal neoplasm. (Photo courtesy of Lisa Shortley)

Malignant neoplasms are quite a bit more problematic, from their excessive growth potential to the wider range of substances which they may produce. Simply, malignant neoplasms do whatever they want to do. Malignant cells often lack much of the cellular machinery of their normal counterparts, allowing them to

forget about production or other normal cellular function and focus on uncontrolled growth. Some malignancies release wildly excessive levels of normal hormones, or substances that are totally foreign to their normal function in the body.



A large squamous cell carcinoma expands and deforms the mandible of this ferret.

The most dangerous feature of malignancies is their ability to **metastasize**. The ability to break off and to survive in the hostile environment of a foreign tissue is no mean feat – and large malignancies literally bombard the body with small clusters of cells to every conceivable tissue of the body. Not all malignancies possess this ability, and luckily the two most common, insulinoma and adrenal carcinomas only rarely do this, but lymphoma, the third most common ferret neoplasm, is very adept at it. In fact, the vast majority of lymphomas are present in many tissues at autopsy. The term **metastatic potential** refers to the possibility of a particular tumor giving rise to other neoplasms at distant sites. For example, many malignancies of the skin and connective tissues have **low metastatic potential** (but may aggressively infiltrate local tissue), while lymphomas have **high metastatic potential**.

One of the most common questions that I am asked is “Why do ferrets develop so many tumors?” The truth is that we don't know... yet. Many theories abound, with little concrete evidence to back them up. The tremendous genetic investigation that is currently revolutionizing the way we look at human neoplasia is only beginning in veterinary medicine, and is probably several years away in the ferret. Environmental factors, largely centered on the trappings of domestic life – early neutering, formulated diets and altered photoperiods - have been incriminated in the

higher incidence of neoplasia in North American ferrets versus their European counterparts, but these theories have yet to be proven in any controlled study. Chemical carcinogens, while able to cause neoplasia in ferrets in experimental settings, have not yet been identified as common causes largely because pet ferrets closely share their human owners' carcinogen-free environments. We are not totally clueless about factors that result in the development of neoplasia in the ferret, however. A viral cause for some forms of lymphoma has been strongly implicated in recent years, although the virus itself has yet to be identified. Lymphoma has also been causally linked to inflammatory bowel disease in ferrets, although the triggers for the development of a malignancy out of a pre-existent inflammatory lesion (which actually happens in only a handful of cases) remain unclear.

The diagnosis of most ferret neoplasms is often based solely on clinical signs and the results of a good physical examination, and in such cases, extensive diagnostic testing is unnecessary. The two most common neoplasms in ferrets, insulinoma and adrenal tumors both have characteristic and easily recognizable symptoms. Many other tumors, such as those of the skin, muscle, and bone generally result in obvious deformity, and the majority of abdominal tumors can be identified via palpation by alert clinicians. Truly, few silent tumors exist in this species, so the chances are excellent that your ferret's neoplasm will be identified early in its progression. (The one exception to this rule, is lymphoma, which may be well advanced before the animal exhibits any clinical signs, especially in young ferrets.)



Chordomas are common low-grade malignant tumors that often present at the tip of the tail. Removing the tip of the tail results in a surgical cure.

Additional testing is most often used to confirm a diagnosis, precisely locate a neoplasm, or denote the extent of damage to host organ. Bloodwork may help to ascertain the extent of damage to affected organs, such as the liver, kidneys, or bone marrow, but only rarely will disclose the actual presence or nature of a neoplasm. (A notable exception is leukemia, a lymphoma in which the malignant cells circulate in the peripheral blood. About 10% of all lymphomas in ferrets are leukemic.) Other diagnostic tests such radiographs and sonograms may help in pinpointing the location of a neoplasm, such as the right or left adrenal gland, but are actually required in a low number of cases.

In general, the appropriate treatment for most ferret neoplasms is surgical excision. The complete surgical excision of benign neoplasms will be curative – these tumors are generally well delineated, and are often easily removed. Surgical excision is also the first line of defense with malignant tumors. Due to their predisposition to rapidly invade adjacent tissue and metastasize to other organs, early surgical intervention when dealing with malignancies may mean the difference between a very good prognosis and a very poor one.

I get a lot of questions about the use of chemotherapy and radiation in ferrets for the treatment of non-resectable malignancies. These are often difficult questions to answer = every malignancy differs in its susceptibility to chemotherapy and radiation, and many practices are not equipped to administer either of these types of therapy.

Of the two, chemotherapy is by far the most widely used, and finds its most appropriate employment in the treatment of lymphoma. Successful chemotherapy protocols often require a complex interplay of drugs administered intravenously at specific times, and estimates of success rates (a success is considered when the disease-free interval significantly exceeds that seen with palliative therapy alone) average about 10% in lymphoma cases. Chemotherapeutic drugs are administered intravenously and travel throughout the body seeking susceptible cancer cells (or unfortunate normal cells with similar affinities for chemotherapy drugs), and are best utilized in animals where metastasis is widespread.

Radiation therapy is generally administered only at large referral centers or veterinary colleges, as the machine used to generate, project, and focus the radiation beam is very expensive. As the beam of radiation is tightly focus on a single spot, radiation is best used on single, solitary tumors that cannot be surgically removed. Currently, radiation therapy is rarely used in ferrets, and its application in many neoplasm types has yet to be investigated.

As stated at the outset, the incidence of neoplasia is far higher in the ferret than any other domestic species. Over half of American ferrets will develop either an insulinoma or adrenal gland neoplasm (or perhaps both.) Skin tumors and lymphomas are also very commonly seen. The incidence of neoplasia in the ferret increases with age – likely as a result of a progressive weakening of the body’s immune surveillance mechanism and its ability to identify neoplastic cells and destroy them at an early point in their development. The so-called “golden age” of tumors in ferrets is between five and seven years and it is during this time when we should be especially vigilant with our pets.

Early identification and treatment is key to minimizing the impact of neoplasia in your pet. A watchful eye will often spot trouble signs well in advance, when treatment options are at their most effective. For the ferret, neoplasia may be a fact of life, but for the owner, it’s a fact that’s always worth a challenge.

“Tumor”-nology

When ferret health is discussed, neoplasms are often the central topic of interest. It helps to know the correct lingo in order to keep up. Here’s a quick primer on basic terms and concept that you should be familiar with.

Neoplasm – from the Greek (literally, a “new growth”). The most appropriate term for a spontaneous proliferation of cells which has escaped the body’s ability to control cellular growth. Neoplasms serve no useful purpose, and grow at the animal’s expense. All neoplasms arise from a pre-existing cell type in the body, and most perform the functions of that cell type, such as making and releasing hormones (such as with insulinomas), or producing structural materials, such as with osteomas (bone tumors).

Tumor – a word with a long and storied heritage, but little specificity. Cornelius Celsus, a Roman physician, utilized the word “tumor” (literally, a swelling) as one of the four cardinal signs of inflammation – along with rubor (redness), calor (heat) and dolor (pain). Hence, tumor may be applied to any type of swelling, to include an abscess, or even a traumatic injury, although it is most commonly used today to refer to a neoplasm.

Cancer – from the Latin (literally, “crab”). A synonym for a malignancy (see below), this term is often misused when used to describe a benign neoplasm. Use of this term generally reflects high emotions (“My ferret has cancer”), but truly, most ferret neoplasms are not cancerous. The derivation of this word comes from a malignant neoplasms propensity to finger into a tissue, reminiscent of the many legs and tenacious grip of a crab.

Benign – A neoplasm that closely resembles the tissue of origin and generally show high cellular maturity. This maturity limits the overall rate of growth, ability to invade other tissues, and the ability to metastasize (see below).

Malignant – The “mafia bosses” of the neoplasm world. Malignant neoplasms do what they want, when they want. They grow quickly, and quickly grow through adjacent tissue (a process known as **infiltration**). Malignant tumors may produce a wide range of substances, often unrelated to the tissue from which they arise. They commonly recur following excision, and may migrate to other tissues (see **metastasis**) below. Malignant tumors, if untreated, may be lethal to the host.

Metastasis – The process in which a **malignant neoplasm migrates to a distant site**, perhaps a different organ entirely, and grows at that site. This is a major cause of mortality in animals (and humans) with malignant neoplasms, as these tumors may cause dysfunction in one or more organs systems of the body.

