Most Common Types of Tumors
Blood/Lymph Tissue 22.6%
Urinary 17.7%
Skin 14.5%

- Malignant tumors are more difficult to treat and control, are more likely to have poor outcomes, and can be costly to manage if chemotherapy and/or radiation therapy is used.

Tumors in Westies by site of occurrence (62 animals total; number in parentheses is the number of neoplasms)

- Digestive System (7)
- Endocrine System (1)
- Epithelial and Melanocytic Tumors of the Skin (9)
- Hematopoietic/lymphoreticular System, including Malignant Lymphoma (14)
- Mesenchymal Tumors of Skin & Connective Tissue (3)
- Mammary Glands (5)
- Male Genital System (2)
- Nervous System or Eyes (4)
- Respiratory System (6)
- Urinary System (11)

The most common types of neoplasms, based on percentages were: hematopoietic/lymphoreticular system neoplasms including malignant lymphoma (14/62 = 22.6%) and urinary system neoplasms (11/62 = 17.7%).

While the information in this Veterinary Cancer Registry database search is very useful for identifying overall trends in the incidence of neoplasms in dogs, it has limitations. First, only a small number of total cases are submitted for entry into the database, and it is very likely that there are many more dogs with tumors whose records are not submitted for inclusion. Second, only cases in which there has been a biopsy confirmation of the tumor type are included. Many dogs with masses may not be biopsied and their information may not end up in the database. Third, it is very hard to tell if the numbers presented in the Veterinary Cancer Registry database represent all of the dogs at risk. There is no way to know how many Westies (or Scotties, or Cairns, or dogs of mixed heritage) are in the United States. As a result, we can only make rough estimates of 'dogs at risk' for developing neoplasms.

The work of breed clubs like the WFA in conducting surveys of health problems in specific breeds is one of the best ways to know how many Westies (or Scotties, or Cairns, or dogs of mixed heritage) live in the United States. Data from these organizations can help provide rough estimates of 'dogs at risk' for developing neoplasms and is a great help in making more accurate data available.

Bladder Cancer in Westies and Scotties

One type of cancer that is of very serious concern to owners of Westies and Scotties is bladder cancer. The medical designation of this type of malignant neoplasm is "transitional cell carcinoma" of the urinary bladder. Bladder cancer can occur in any dog breed, but is more common in Shetland Sheepdogs, Scottish Terriers and Westies. The median age of occurrence for dogs is around 8 years old.

There are several excellent websites which discuss bladder cancer in dogs, how this tumor is diagnosed and how it is treated. While owners may wish to "Google" this subject, a more comprehensive, scientific literature review and list of references are found at the end of this section.

A brief summary of important aspects of this disease will help to alert Westie owners that their dog may have a problem.

Bladder cancer develops from cells that line the urinary bladder and the kidney. There appear to be several factors that influence whether or not this neoplasm will develop. In dogs, the genome appears to play a major role, as some breeds (the short legged Scots breeds like Westies and Scotties) appear to have a higher incidence per capita than other breeds of dogs (see below). This increased breed incidence suggests that during the development of the breed, certain mutations in the genome were acquired and linked to desirable breed characteristics. It is very likely that several mutations may be present and research scientists are actively looking for them, in order to see what is causing cancer to develop. Remember, not every dog will inherit mutations that can lead to the development of cancer, and it

may take the complex interactions of several mutations to lead to the initiation and development of neoplasms.

One other important factor in the development of bladder neoplasms in Scotties, though not proven to be a factor in Westies, is exposure to certain environmental chemicals. Glickman and his colleagues at the Purdue University School of Veterinary Medicine have shown that repeated exposure to one type of common lawn chemical – phenoxy herbicides – may lead to an increased risk for developing bladder cancer. There are several other important factors (see below).

Diagnosing Urinary Bladder Cancer in Dogs

The first clinical signs that there may a problem with the health and function of the urinary bladder may be one or more of the following:

- Difficulty urinating
- Frequent attempts to urinate (a change in the pattern of urination)
- Dribbling urine
- Loss of housebreaking in adult dogs
- Blood in the urine ("hematuria), evidenced by pink or red spots on floors and carpets
- Abdominal tenderness

These signs only indicate a potential problem with the health and function of the bladder and are not specific for any disease. For example, these signs might indicate bladder infection, the presence of bladder stones, a neurologic problem leading to altered bladder function, or the presence of a neoplasm, among other diseases. However, if Westie owners detect any of these signs, it is important for them to take their dog to their veterinarian for further evaluation.

The veterinarian will perform a physical examination and suggest some additional tests to narrow down what is causing the dog to have signs of bladder disease. During the physical examination, it is very likely the veterinarian will gently palpate the dog's abdomen, paying attention for signs of tenderness, especially around the area of the urinary bladder.

The veterinarian may suggest collecting a urine sample, either by catching urine in a pan or a cup during spontaneous urination (a "freecatch' specimen), by passing a catheter into the bladder, or by taking a small sample with a syringe and needle, through the abdominal wall ("cystocentesis'). Urine samples collected with a catheter or by cystocentesis can be used for bacterial culture – to see if there is an infection present. Urine samples can also be analyzed for the presence of blood and to see what types of cells and other suspended materials are present. In some cases, veterinarians and clinical pathologists will identify clumps of cells that may indicate the presence of tumors.

It is very likely that your veterinarian will also suggest additional tests (see below). Recently, a test called the bladder tumor antigen test ("VBTA') was developed to help detect the presence of some unique proteins associated with transitional cell carcinoma in dogs. Other "tumor marker" tests that detect proteins in urine associated with the development of bladder cancer are also being developed. Eventually, these tests may be especially helpful in screening for the presence of a neoplasm.

It is quite common now for veterinarians to use radiography (the old term was "xrays"), ultrasonograpy, or computed tomography (CT) to look for masses in the bladder. Shown on the following page is a CT image of the urinary bladder of a Sheltie dog which was seen by a veterinarian for blood in the urine (See ***Figure 4,*** below). In this image, the arrow points to a dark mass (a "filling defect") which is a transitional cell carcinoma projecting into the center of the bladder. These imaging techniques are very helpful in differentiating between bladder stones and tumors.

Definitive Diagnosis and Options for Therapy

If there is a high likelihood that a tumor is present, your veterinarian may want to perform a surgical biopsy. This will involve general anesthesia, an exploratory surgical procedure of the abdomen, and opening of the urinary bladder. Some veterinarians will remove as much tumor as possible during this procedure. Others may choose to take a small biopsy to be sent to a pathologist (see above), and then to treat the bladder with one or more chemotherapeutic agents.

Chemotherapeutic drugs used to treat cancer of the urinary bladder in dogs are identical to those used to treat this neoplasm in people. All cancer chemotherapy drugs are given to kill tumor cells. They do this in a variety of ways, including interrupting tumor cell division, blocking tumor cell metabolism, breaking down tumor cell DNA and genes, or poisoning other tumor cell activities.

Cancer chemotherapy drugs are usually given by mouth or injection, or a combination of these methods. Treatment may continue for months, depending on the extent of the tumor, response of the tumor to therapy, and tolerance for the side effects of the drugs. Typical unpleasant side effects seen in some dogs may include vomiting and diarrhea, loss of energy, changes in patterns of urination, and potentially increased susceptibility to infections.

It is very important to know that veterinarians are experienced in treating cancer, that they understand the effects and side effects of drug therapy, and that they are trying to help you and your pet overcome a serious disease problem. Most side effects of drug therapy are transient and temporary, and can be managed with supportive care.

You need to discuss this with your veterinarian when deciding how and if to treat your dog. Most veterinarians will also discuss the use of medications to control any discomfort and will be candid about the probability of the treatments being effective.

The outlook ("prognosis") for dogs with bladder cancer is guarded and depends a great deal on:

- Initial size and location of the tumor
- Amount of invasion of the bladder wall and surrounding tissues in the abdomen
- Metastasis of tumor cells to lymph nodes and other locations
- Age and overall health of the dog

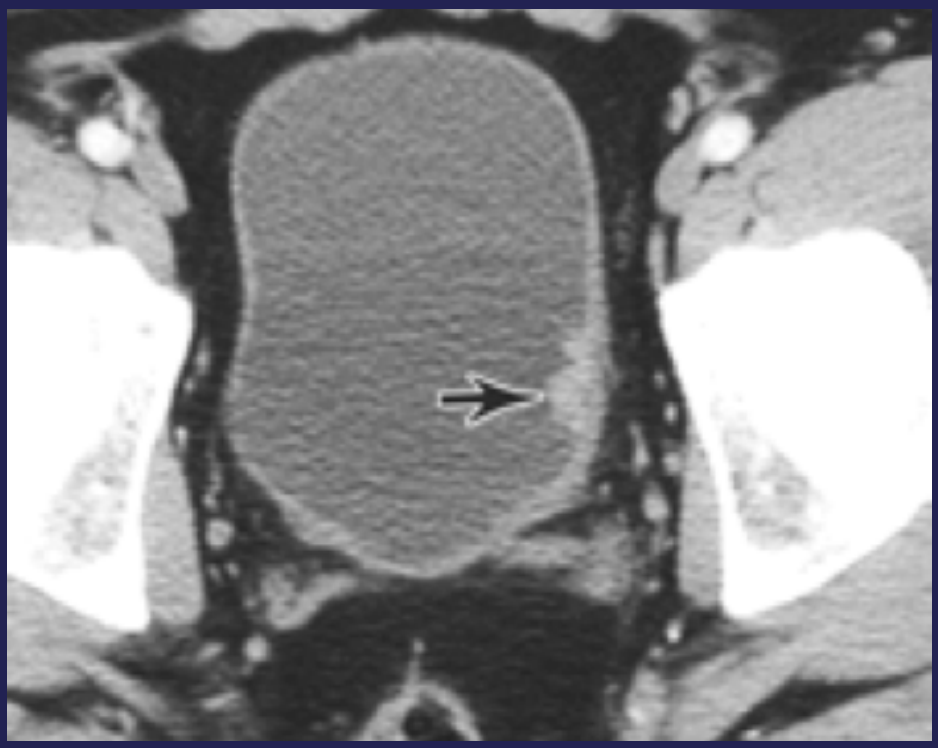

Figure 3 - A CT image of the urinary bladder of a Sheltie dog which was seen by a veterinarian for blood in the urine. The arrow points to a dark mass (a "filling defect") is a transitional cell carcinoma projecting into the center of the bladder.

- Type of tumor, including degree of differentiation and cellular patterning
- Response of tumor cells to chemotherapy
- Toxic side effects of chemotherapy

According to Dr. Deborah Knapp, et al, the median survival of all breeds of dogs with the early stages of transitional cell carcinoma is 218 days. For dogs with more advanced disease, the survival is about half of that interval. Of course, the outcome for any individual dog is hard to predict, but transitional cell carcinoma of the urinary bladder is one of the most serious health problems affecting Westies and other short legged Scots breed terriers (see below).

The early detection of bladder cancer in "high risk" dogs (including Scottish and West Highland White Terriers, Shetland Sheepdogs, among others) would allow more timely intervention (chemotherapy, surgery) and is likely to be associated with better prognosis. Development of simple, economical tests using urine specimens will allow life-long sampling of high-risk dog breeds and may decrease the devastating effects of bladder cancer in these breeds.

Transitional Cell Carcinoma

According to several excellent, comprehensive papers and review articles (Norris et al, 1992; Knapp et al, 2014), bladder cancer is common in all dogs; about 2% of all dogs in a post-mortem research study had bladder cancer. It is estimated, based on the size of the dog population, that there may be at least 15,000-20,000 new cases each year. Bladder cancer is especially common in several breeds of dogs. In one recent study, the odds that a particular breed would develop bladder cancer was compared against the odds that the disease would occur in mixed breed dogs. These comparisons involved calculating 'odds ratios' [OR], with an OR value of 1.0 meaning that a specific breed and mixed breed dogs were equally likely to develop bladder cancer. Furthermore, if the OR was greater than 1, then the breed was more likely to develop the disease. In that study, Scottish Terriers (OR=21.12), Eskimo Dogs (OR = 6.58), Shetland Sheepdogs (OR=6.05), West Highland White Terriers (OR=5.84), and Beagles (OR=3.09) were found more likely to develop bladder cancer (Knapp et al, 2014). In addition to breed-associated (genomic) predispositions, risk factors for the development of bladder cancer in dogs include advancing age (more common in middle-aged and older dogs), sex and neutering status (more common in female dogs than male dogs, and more common in neutered dogs), obesity (Glickman et al, 1989) and exposure to some chemicals, including commonly-used herbicide lawn treatments (Glickman et al, 1989, 2004; Knapp et al, 2013), water disinfection products (Backer et al, 2008) and older generation flea control products (Glickman et al, 1989).

As indicated above, bladder cancer is suspected in dogs with clinical signs of difficulty urinating, hematuria, changes in patterns of housebreaking, frequent attempts at urination, and evidence of pain when urinating. Many of these clinical signs resemble those seen dogs with bladder infection ("cystitis"). As a result, it is important for dogs with these clinical signs to be examined thoroughly by a veterinarian. In many of those cases, diagnostic testing will include urinalysis with cytology evaluation, hematology and chemistry profile (to include or exclude systemic and/or urinary tract disease), urine culture (to include or exclude inflammatory/infectious cystitis), and diagnostic imaging, such as ultrasonography (Hanazono et al, 2014), standard radiography with and without contrast agents, and computed tomography. While a definitive diagnosis may be made based on abnormal urine cytology findings, the gold-standard is by evaluating a biopsy specimen procured with cystoscopy under sedation/anesthesia. The cost of such a comprehensive work-up often will exceed several hundreds of dollars.

When the diagnosis of bladder cancer is made, most dogs have relatively advanced disease –tumor cell growth has penetrated the musculature of the bladder wall, or spread to tissues adjacent to the bladder in the abdomen (Higuchi et al, 2013), or elsewhere in the body (e.g., lung, lymph node, bone, and other sites) (Knapp et al, 2000). Dogs with bladder cancer are most commonly treated with single- or multi-agent chemotherapy, with remissions up to 50% being reported and median survival times ranging from 130-250 days (Robat et al, 2010; McMillan et al, 2011; Knapp et al, 2013, Fulkerson et al, 2015). Bladder resection, radiotherapy, or combinations of therapies are not commonly used in dogs. Dogs rarely are cured or live more than one year, even with therapy.

Routine screening for hematuria, which may be associated with bladder cancer in asymptomatic dogs, is not practical. This would require regular collection of urine samples, probably at least on a yearly basis. Likewise, routine screening of all dogs is not economically viable. Many owners would be reluctant to pay $25 -$75 for a yearly urinalysis, which might not be either sensitive enough or specific enough to detect a disease affecting less than 5% of 'normal risk' dogs.

For decades, veterinary clinicians have relied on examination of urine cytology as a reliable first diagnostic test when bladder cancer is suspected (primarily due to detection of hematuria and/or pain), followed by cystoscopic bladder inspection and biopsy of suspect lesions. Such methods are valuable in detection of high-grade bladder cancer, but lack sensitivity for detecting low-grade tumors (Lokeshwar et al, 2001).

Over this same period, veterinary clinicians and researchers have searched intensively for biological markers of tumor

growth that may be present in urine specimens (including cytologic markers) and biopsy specimens. The obvious value of these biomarkers would be rapid, sensitive/specific identification of bladder cancer, the ability to differentiate bladder cancer from inflammatory or degenerative diseases affecting the kidneys, bladder or urethra, and the ability to screen "high-risk" individuals for early bladder cancer. Biomarkers that might be present in urine would facilitate non-invasive, repetitive analysis without the need for sedation or anesthesia. A number of non-invasive biomarker probes have been developed. These include NMP-22 (a protein associated with apoptosis) (Grossman et al, 2005), BTA (bladder tumor basement membrane protein) (Irani et al, 1999), FISH (fluorescent, in-situ hybridization) probes for cell chromosomal abnormalities (UroVysion) (Hajdinjak et al, 2008), tumor sensitive monoclonal antibodies (ImmunoCyt) (Vriesema et al, 2001), and gene product-based assays (Allen et al, 1996; Borjesson et al, 1999; Mochizuki et al, 2015a,b; Decker et al, 2015).

None of these markers have gained wide acceptance, become a standard-of-care for patient screening, or are used for routine screening of either "normal-risk" or "high-risk" individuals – be they canine or human patients. They are somewhat costly, require some degree of expertise to achieve valid results, and are highly dependent on sample quality and stage of tumor growth. The fact these biomarker assays have not seen wide use in human medicine in nearly two decades makes it seem unlikely they will see wide use in veterinary practice, although multiplex marker approaches may have limited use (Bracha et al, 2014).

Most recently, a single mutation in the canine BRAF gene was identified in tissue samples obtained from some dogs with transitional cell carcinoma and urothelial/bladder cancer. This discovery was made by comparing the DNA and RNA sequences of genes from dogs with bladder cancer against those from dogs lacking cancer. This mutation changed a single amino acid in the BRAF protein, which was associated with development of cell proliferation and the development of cancer. (Mochizuki H et al, 2015). In subsequent work, a laboratory assay was developed to see if the mutation could be detected in cells shed in urine samples collected from dogs at high risk of developing either of these diseases (Decker et al, 2015). This assay has now been used suc cessfully to identify small masses in the bladder of dogs 3 to 4 months before they developed any clinical signs associated with the disease condition. This is an exciting step forward in helping detect these problems in dogs at the earliest possible time point, thereby improving their likelihood for a positive response to treatment. Additional information about this assay is available at www.SentinelBiomedical.com

In summary.

We collectively (owners, breeders, veterinarians, and research scientists) need to put forth our best efforts to identify the causes and to find effective treatments for tumors in our dogs.

We owe them that.

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