Neoplastic considerations for spaying and neutering dogs

Evan Sones
Animal Cancer Care Clinic, Ft. Lauderdale, FL

Abstract

Neutering of companion animals is common practice in the United States and many other parts of the world. There is growing concern that the uniform recommendation of neutering is detrimental to the pet population by affecting normal functions of other body systems. This may predispose these animals to disease, including, but not limited to, neoplastic conditions. Although the mechanisms of these changes are largely unknown, there is a growing number of studies showing a correlation between cancer and neuter status. A review of these articles, as provided here, can be beneficial to inform practitioners, enabling a more thorough discussion of spay and neuter with their clients.

Keywords: Spay, neuter, neoplasia, cancer

Introduction

Spay and neuter have long been the standard of care recommendations for pet dogs and cats in the US. Two common reasons given for this instruction are behavioral modification and population control. However, gonadectomy and the subsequent lack of sex hormones can impact many other processes in the body and may influence development of other diseases, including cancer.

The mechanism by which sex hormones, or lack thereof, influence development or progression of cancer is not always clear. Hormone receptors are present in a number of canine tumors, including mammary tumors,[1-6] perianal gland tumors[7]and meningiomas.[8] The level of hormone receptors may also influence outcome in treatment of meningiomas.[9] Removing the sex hormone influence can help to improve outcome in perianal gland tumors[10] and tumors of the reproductive tract.[11,12] The opposite effect can be seen when administering exogenous hormones, that can lead to development of tumors in dogs and cats.[13,14]

The influence of sex hormone exposure and development of mammary tumors is well known. If a dog is spayed prior to the first estrous cycle, the risk of mammary cancer is only 0.5%. This risk increases to 8% if spayed after the first estrus, then increasing to 26% after the second.[15] There was not a significant decrease in risk of developing mammary cancer if spayed after the second estrus in this original study, although there was some benefit found in later studies.[15-18] Spay after development of mammary carcinoma does not seem to influence the outcome for dogs, except in certain subsets.[19]

Other cancers of the reproductive tract can be reduced significantly by spay and neuter. Removing the gonad eliminates the risk of cancer development for uterine, ovarian, and testicular tumors. Vaginal leiomyomas are an uncommon, benign tumor of intact female dogs, and rarely occurs in spayed dogs. Spay at the time of leiomyoma removal decreases the risk of recurrence after even incomplete removal.[11,12]

Prostatic carcinoma is an uncommon cancer in male dogs.[20-23] There has been an increase in the risk of developing prostatic cancer in neutered dogs. This increase in risk ranges from 2 to 8 times that of intact stud dogs.[24,25]

Lymphoma is a very common cancer in dogs.[26,27] A large, multi-institutional retrospective study using the Veterinary Medical Database compared ~ 15,000 canine lymphoma patients with 1.2 million dogs from the general population. This study identified a decreased risk of developing lymphoma in intact female dogs, about half the likelihood of spayed females, intact males, or neutered males.[28]

Transitional cell carcinoma of the urinary bladder has a higher incidence in female dogs, with a risk ratio ranging from 1.71 to 1.91:1 of females to males.[29-31] The underlying cause of this

increased risk in females is not known to be hormonally influenced. However, 1 study reported increased risk in both sexes with gonadectomy.[26] Also, the risk of transitional cell carcinoma of the prostate is higher in neutered dogs.[25]

Early, smaller studies on canine osteosarcoma showed some variation in sex predilection, with some indicating males have an increased risk and some indicating females.[31-36] However, a much larger review of 1,775 patients did not show any sex predilection.[37] Neutering does carry some increased risk of developing osteosarcoma in 2 studies.[8] The first found a 1.9 times increased risk in spayed females and 1.4 times in neutered males.[38] The second found an increased risk of 1.3 fold in neutered compared to intact male dogs.[39]

Hemangiosarcoma was more likely in spayed females, which were about 2 times more likely to develop hemangiosarcoma compared to intact females.[40] This association was also present for cardiac tumors, with spayed females having a 4 times higher relative risk compared to intact females.[41] This study also found diagnosis of cardiac hemangiosarcoma was 5 times greater in spayed females.[41] Although not as robust, there was also an increased risk of 1.6 for heart tumors in neutered males when compared to their intact counterparts.[41]

There have been a number of studies attempting to determine any relationship between gonadectomy and the development of cancer in specific breeds. One study reviewed 683 Rottweilers and found an increased risk of osteosarcoma if the dog was neutered prior to 12 months of age. This held true for both male and female Rottweilers.[41]

Golden Retrievers have been evaluated due to the high incidence of cancer in this breed. In a group of 759 Golden Retrievers, females spayed after 12 months of age had an increased risk of hemangiosarcoma, 4 times greater than females spayed before 12 months or intact females.[42] This was not the case for males in the same study.[42] Lymphoma is also more common in spayed and neutered Golden Retrievers, with an increased risk of 3 - 4 times.[42] In male Golden Retrievers castrated before 1 year of age, the risk for developing lymphoma was increased by 3 times.[42] Lastly, Golden Retrievers were evaluated for the risk of developing mast cell tumor in relation to reproductive status. There was an increased incidence of mast cell tumor in female Golden Retrievers that were spayed prior to first year at 2.3% and after first year at 5.7%, when compared to intact females at 0%.[42] There was no difference in the incidence between castrated and intact males in this same study.[42]

A final breed specific study evaluated risk and age of onset of cancer in Vizslas. This study found a similar increased risk to Golden Retrievers of developing lymphoma, with an increase of 3 - 4 times in castrated or spayed Vizslas.[42,43] The risk of developing a mast cell tumor was also higher, increased by ~ 2 - 4 times than that of intact Vizslas.[43] These mast cell tumors also developed at an earlier age.[43]

Gonadectomy potentially has some influence on lifespan in dogs. In reviewing > 40,000 dogs in the US, there was an increase in average lifespan from 7.9 to 9.4 years with gonadectomy. The benefit was higher in females with an increase in life expectancy of 26%, and only 14% in males.[44] In sterilized dogs, in this study, transitional cell carcinoma, osteosarcoma, mast cell tumors, and lymphoma were all more common; mammary tumors were less common; and there was no difference in the incidence of melanoma, squamous cell carcinoma, and prostate cancer.[44]

Discussion

Information presented here must be taken with the proverbial “grain of salt”. These studies show an association between gonadectomy and a change in the risk for certain cancers. However, the cause is generally not known, although certainly theories exist. Development of cancer is generally multifactorial and involves many environmental and exogenous factors, as well as endogenous factors, such as genetics and exposure to sex hormones.

There are also considerations when interpreting the studies presented here. These studies are often breed specific and we must be careful in extrapolating this to the general population of dogs. There is also likely a case selection bias in that many of these studies are performed in

referral institutions. Client factors may influence which dogs are presented to a referral institution and this patient group may not represent a true general population of pets. Retrospective studies also have inherent bias, which is the nature of most of these studies.

Conclusion

The idea of individualized medicine is becoming more prevalent in human and veterinary medicine. This is the approach that should be utilized when determining the need for spay and neuter in companion dogs. There are many factors to consider when making this decision, which may not be readily apparent to the average pet owner. The American College of Theriogenologists and The Society For Theriogenology hold the position that "the decision to spay or neuter…should be made solely by the pet's owner with the direct input of their veterinarian and will be dependent on each particular animal's situation."[45] This statement should be upheld as often as possible to continue to practice the highest quality of medicine that is expected by current-day clients.

Conflict of interest

The author has no conflict of interest to report.

References

1. MacEwen EG, Patnaik AK, Harvey HJ, et al: Estrogen receptors in canine mammary tumors. Cancer Res 1982;42:2255-2259.
2. Rutteman GR, Misdorp W, Blankenstein MA, et al: Oestrogen (ER) and progestin receptors (PR) in mammary tissue of the female dog: different receptor profile in non-malignant and malignant states. Br J Cancer 1988;58:594-599.
3. Illera JC, Perez-Alenza MD, Nieto A, et al: Steroids and receptors in canine mammary cancer. Steroids 2006;71:541-548.
4. Millanta F, Calandrella M, Bari G, et al: Comparison of steroid receptor expression in normal, dysplastic, and neoplastic canine and feline mammary tissues. Res Vet Sci 2005;79:225-232.
5. Donnay I, Rauis J, Devleeschouwer N, et al: Comparison of estrogen and progesterone receptor expression in normal and tumor mammary tissues from dogs. Am J Vet Res 1995;56:1188-1194.
6. Geraldes M, Gartner F, Scmitt F: Immunohistochemical study of hormonal receptors and cell proliferation in normal canine mammary glands and spontaneous mammary tumours. Vet Rec 2000;146:403-406.
7. Pisani G, Millanta F, Lorenzi D, et al: Androgen receptor expression in normal, hyperplastic, and neoplastic hepatoid glands in the dog. Res Vet Sci 2006;81:231-236.
8. Adamo PF, Cantile C, Steinberg H: Evaluation of progesterone and estrogen receptor expression in 15 meningiomas of dogs and cats. Am J Vet Res 2003;64,1310-1318.
9. Theon AP, Lecouteur RA, Carr EA, et al: Influence of tumor cell proliferation and sex-hormone receptors on effectiveness of radiation therapy for dogs with incompletely resected meningiomas. J Am Vet Med Assoc 2000;216:701-707.
10. Wilson GP, Hayes HM: Castration for treatment of perianal gland neoplasms in the dog. J Am Vet Med Assoc 1979;174:1301-1303.
11. Thacher C, Bradley RL: Vulvar and vaginal tumors in the dog: a retrospective study. J Am Vet Med Assoc 1983;183:690-692.
12. Herron MA: Tumors of the canine genital system. J Am Anim Hosp Assoc 1983;19:981-994.
13. Stovring M, Moe L, Glattre E: A population-based case-control study of canine mammary tumours and clinical use of medroxyprogesterone acetate. APMIS 1997;105:590-596.
14. Misdorp W, Romijn A, Hart AA: Feline mammary tumors: a case-control study of hormonal factors. Anticancer Res 1991;11:1793-1797.
15. Schneider R, Dorn CR, Taylor DO: Factors influencing canine mammary cancer development and postsurgical survival. J Natl Cancer Inst 1969;43:1249-1261.
16. Taylor GN, Shabestari L, Williams J, et al: Mammary neoplasia in a closed beagle colony. Cancer Res 1976;36:2740-2743.
17. Sonnenschein EG, Glickman LT, Goldschmidt MH, et al: Body conformation, diet, and risk of breast cancer in pet dogs: a case-control study. Am J Epidemiol 1991;133:694-703.
18. Misdorp W: Canine mammary tumors: protective effect of late ovariectomy and stimulating effects of progestins. Vet Q 1988;10:26-33.

19. Kristiansen VM, Pena L, Diez Cordova L, et al: Effect of Ovariohysterectomy at the Time of Tumor Removal in Dogs with Mammary Carcinomas: A Randomized Controlled Trial. J Vet Intern Med 2016;30:230-241.
20. Navarro D, Luzardo OP, Fernandez L, et al: Transition to androgen-independence in prostate cancer. J Steroid Biochem Mol Biol 2002;81:191-201.
21. Cornell KK, Bostwick DG, Cooley DM, et al: Clinical and pathologic aspects of spontaneous canine prostate carcinoma: a retrospective analysis of 76 cases. The Prostate 2000;45:173-183.
22. Weaver AD: Fifteen cases of prostatic carcinoma in the dog. Vet Rec 1981;109:71-75.
23. Obradovich J, Walshaw R, Goullaud E: The influence of castration on the development of prostatic carcinoma in the dog: 43 cases (1978-1985). J Vet Intern Med 1987;1:183-187
24. Teske E, Naan EC, van Dijk EM, et al: Canine prostate carcinoma: epidemiological evidence of an increased risk in castrated dogs. Mol Cell Endocrinol 2002;197:251-255.
25. Bryan JN, Keeler MR, Henry CJ, et al: A population study of neutering status as a risk factor for canine prostate cancer. The Prostate 2007;67:1174-1181.
26. Kaiser HE: Animal neoplasia: a systemic review. In: Kaiser HE, editor, Neoplasms-comparative pathology in animals, plants and man, Baltimore: Williams & Williams. 1981.
27. Moulton JE, Harvey JW: Tumors of lymphoid and hematopoietic tissue. In: Moulton JE, editor: Tumors of domestic animals, 3rd edition, University of California Press; 1990.
28. Villamil JA, Henry CJ, Hahn AW, et al: Hormonal and sex impact on the epidemiology of canine lymphoma. J Cancer Epidemiol 2009:591753, 10.1155/2009/591753
29. Glickman LT, Raghavan M, Knapp DW, et al. Herbicide exposure and the risk of transitional cell carcinoma of the urinary bladder in Scottish terriers. J Am Vet Med Assoc 2004;224:1290-1297.
30. Norris AM, Laing EJ, Valli, VE et al: Canine bladder and urethral tumors: a retrospective study of 115 cases (1980-1985). J Vet Intern Med 1992;6:145-153.
31. Mutsauers AJ, Widmer WR, Knapp DW: Canine transitional cell carcinoma. J Vet Intern Med 2003; 17;136-144.
32. Brodey RS, Riser WH: Canine osteosarcoma: a clinicopathologic study of 194 cases. Clin Orthop Relat Res 1969;62:54-64.
33. Brodey RS, Sauer RM, Medway W: Canine bone neoplasms. J Am Vet Med Assoc 1963;143:471-495.
34. Brodey RS, Abt DA: Results of surgical treatment in 65 dogs with osteosarcoma. J Am Vet Med Assoc 1976;168:1032-1035.
35. Misdorp W, Hart AA: Some prognostic and epidemiologic factors in canine osteosarcoma. J Natl Cancer Inst 1979;62:537-545.
36. Spodnick GJ, Berg J, Rand WM, et al: Prognosis for dogs with appendicular osteosarcoma treated by amputation alone: 162 cases (1978-1988). J Am Vet Med Assoc 1992;200:995-999.
37. Ehrhart NP, Ryan SD, Fan TM: Tumors of the skeletal system. Withrow SJ, Vail DM, Page RL, editors, Withrow & MacEwen's small animal clinical oncology 5th edition, St. Louis (M0): Elsevier; p. 463.
38. Ru G, Terracini B, Glickman LT: Host related risk factors for canine osteosarcoma. Vet J 1998;156:31-39.
39. Priester WA, McKay FW: The occurrence of tumors in domestic animals. Natl Canc Inst Monogr 1980; 54:1-210.
40. Prymak C, McKee LJ, Goldschmidt MH, et al: Epidemiologic, clinical, pathologic, and prognostic characteristics of splenic hemangiosarcoma and splenic hematoma in dogs: 217 cases (1985). J Am Vet Med Assoc 1988;193:706-712.
41. Ware WA, Hopper DL: Cardiac tumors in dogs: 1982-1995. J Vet Intern Med 1999;13:95-103.
41. Cooley DM, Beranek BC, Schittler DL: Endogenous gonadal hormone exposure and bone sarcoma risk. Cancer Epidemiol Biomarkers Prev 2002;11:1434-1440.
42. de la Riva GT, Hart BL, Rarver TB, et al: Neutering dogs: effects on joint disorders and cancers in golden retrievers. PLos One 2013;8:e55937, 10.1371/journal.pone.0055937.
43. Zink MC, Farhoody P, Elser SE, et al: Evaluation of the risk and age of onset of cancer and behavioral disorders in gonadectomized Vizslas. J Am Vet Med Assoc 2014;244:309-319.
44. Hoffman JM, Creevy KE, Promislow DE: Reproductive capability is associated with lifespan and cause of death in companion dogs. PLos One 2013;8:e61082.
https://www.theriogenology.org/page/PositionStatements