Description of the prevalence, histologic characteristics, concomitant abnormalities, and outcomes of mammary gland tumors in companion rats (*Rattus norvegicus*): 100 cases (1990–2015)

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OBJECTIVE
To describe the prevalence, histologic characteristics, concomitant abnormalities, and outcomes for various types of mammary gland tumors in companion rats (*Rattus norvegicus*).

DESIGN
Retrospective case series.

ANIMALS
100 client-owned rats.

PROCEDURES
Medical records of companion rats that had an SC mass and were examined at a veterinary teaching hospital between 1990 and 2015 were reviewed. Information regarding the signalment, age at mass detection, reproductive sterilization status, histologic diagnosis of the SC mass, location of the initial and all subsequent SC masses, treatments administered, and clinical outcomes was extracted from each record and summarized.

RESULTS
105 SC masses were initially detected in 100 rats. The most prevalent SC mass identified was mammary gland fibroadenoma (56/105 [53%]), followed by mammary gland carcinoma (13/105 [12%]). Overall, 26 of 105 (25%) masses were malignant. Sexually intact males were more likely to have nonmammary SC tumors than sexually intact females. In rats receiving no adjunctive treatment after excision of a mammary gland fibroadenoma (n = 16), a second fibroadenoma was detected 1 to 8 months after initial excision, at a median of 4.5 months after surgery. A concomitant pituitary gland tumor was identified in most rats with mammary gland fibroadenoma (21/28 [75%]) and other types of mammary gland tumors (10/17 [59%]). Fourteen of 35 (40%) rats with mammary gland fibroadenoma had concomitant reproductive tract abnormalities.

CONCLUSION AND CLINICAL RELEVANCE
Results suggested that, like other species, companion rats with SC masses should undergo a thorough diagnostic workup that includes histologic examination of the excised mass. (*J Am Vet Med Assoc* 2016;249:1170–1179)

According to a 2012 AVMA survey,[1] > 3 million rodents are kept as companions in the United States. Mammary gland fibroadenoma is the most common spontaneous SC tumor of rats.[2] Rats have 6 pairs (3 thoracic pairs, 1 abdominal pair, and 2 inguinal pairs) of mammary glands that extend from the neck to the inguinal region.[3–5] The incidence of spontaneous mammary gland tumors in rats is high, ranging from 30% to 67% in female Sprague-Dawley rats.[6] Adenocarcinomas represent < 10% of spontaneous mammary gland tumors in rats[7]; thus, not all veterinarians recommend histologic analysis of SC masses after removal. Moreover, the effect of surgical resection of spontaneous SC masses on survival time of affected rats is controversial owing to the fact that mammary gland fibroadenomas frequently recur.[7] Anecdotally, the time to recurrence for mammary gland fibroadenomas in rats has been reported to be as brief as a few months after surgical excision.[4] In 1 study,[7] survival rates did not differ significantly between laboratory rats that did and did not undergo surgical excision of mammary gland tumors, although the author noted that surgical excision of SC masses subjectively improved the welfare of affected rats. Overall, the consensus of the veterinary community appears to be that surgical excision of an SC mass in a rat is beneficial as long as the affected animal is deemed an acceptable anesthetic candidate. Historically, rats with mammary gland tumors have not undergone extensive diagnostic testing, and excised tumors are frequently not histologically analyzed on the basis of the assumption that the mass was most likely benign in nature.[4]

ABBREVIATIONS

FNA	Fine-needle aspirate
GnRH	Gonadotropin-releasing hormone

Concomitant abnormalities in companion rats (*Rattus norvegicus*) with spontaneous mammary gland fibroadenomas are poorly described. Mammary gland fibroadenomas are associated with prolactinemia in some strains of laboratory rats.[8–11] Prolactin secretion increases subsequent to a decrease in the secretion of dopamine from the pituitary gland in geriatric rats[12] and persistent low concentrations of progesterone, constant estrus, or cessation of ovulation in female rats.[7,13,14] In some laboratory rat strains, including the Sprague-Dawley,[12] Fisher,[15] and Wistar[16,17] strains, pituitary gland adenomas develop in > 80% of rats > 24 months old. Some geriatric rats with mammary gland fibroadenomas develop concurrent prolactin-secreting, lactotroph, pituitary gland tumors, but there is some debate whether those tumors are incidental findings given the high frequency of both tumor types in geriatric rats.[7,16] Prolactin-secreting adenomas are the most common type of pituitary gland tumor in laboratory rats.[12,16,17] Pituitary gland adenomas are classified as chromophobic, acidophilic, basophilic, or mixed on the basis of the staining affinities of the tumor cells.[12] Chromophobic adenoma is the most frequently classified type of pituitary gland tumor.[7,12] In laboratory rats, pituitary gland tumors usually arise from the pars distalis, although tumors arising from the pars intermedia have been described, and pituitary gland carcinomas are rare.[16] In companion rats, pituitary gland tumors have been reported in 3 females and 4 males[12,18]; the tumor in one of the male rats was confirmed to be a prolactin-secreting pituitary gland adenoma.[12] The pituitary gland tumors in companion rats were not associated with the development of mammary gland tumors, and those rats were examined primarily because of neurologic signs.[12,18]

In laboratory rats, prophylactic reproductive sterilization can prevent the development of spontaneous mammary gland tumors.[7] The incidence rate of mammary gland tumors in female rats that underwent ovariohysterectomy at 90 days old was significantly less than that for older sexually intact female rats, and reproductive sterilization of rats between 5 and 7 months of age reduced the incidence rate of spontaneous SC tumors from 73.8% to 5.3%.[19] The prevalence of pituitary gland tumors is also low in ovariectomized Sprague-Dawley rats.[7] The effect of reproductive sterilization at the time of mammary gland tumor resection in older rats has not been investigated in a controlled study; however, there is an anecdotal report[20] that the incidence rate of a second primary mammary gland tumor in such rats is lower than that in rats that did not undergo reproductive sterilization at the time of mammary gland tumor resection. It is generally accepted that most chemically induced mammary gland tumors regress following ovariectomy in laboratory rats. However, in a study[21] of 50 laboratory rats that underwent bilateral ovariectomy in conjunction with resection of a chemically induced mammary gland tumor, the mammary gland tumor recurred within 2 months after ovariectomy in 45 (90%), and the tumors in approximately half of those rats were aggressive and lacked estrogen receptors. Treatment options and outcomes need to be evaluated in companion rats with mammary gland tumors, especially those with SC masses.

The objectives of the study reported here were to describe the prevalence, histologic characteristics, concomitant abnormalities, and outcomes for various types of mammary gland tumors in companion rats. We hypothesized that mammary gland fibroadenomas would be the most prevalent type of SC mass diagnosed in companion rats, that companion rats with mammary gland fibroadenomas would have concomitant abnormalities in the reproductive tract and pituitary gland, and that most mammary gland fibroadenomas would recur or multiply within a few months after initial diagnosis regardless of surgical or medical treatment implemented.

Materials and Methods

Case selection

The electronic medical record database of the William R. Pritchard Veterinary Medical Teaching Hospital at the School of Veterinary Medicine, University of California-Davis was searched for records of companion rats that were necropsied or had a histologic evaluation of an SC mass performed between 1990 and 2015. Search terms included "rat," "subcutaneous," "skin," "mass," and "tumor." Rats were excluded from the study if the SC mass was located on the head rostral to the mandible, tail, or a limb.

Medical records review

For each rat eligible for study inclusion, data extracted from the medical record included the signalment, reason for examination during the visit at which an SC mass was initially detected, reproductive status and age at the time of reproductive sterilization (if applicable), diagnostic test (FNA, biopsy, or necropsy) results, histologic diagnosis of the initial SC mass identified, treatments administered, clinical outcome, and location of the initial and all subsequent SC masses. The location of each mass was recorded as cervical (caudal to the mandible and cranial to the shoulder region), axillary (caudal or medial to the elbow joint and cranial to the xiphoidal appendix), laterodorsal (dorsal to the elbow and stifle joints), ventral (ventral portion of the thorax or abdomen not included in the axillary and inguinal locations), or inguinal (caudal to the pelvis and cranial to the tail; **Figure 1**). For rats with > 3 SC masses, mass location was recorded as multifocal regardless of the locations of the individual masses. The location of the mass was determined on the basis of the clinician's description or photographs provided in the medical record of each rat. A sub-

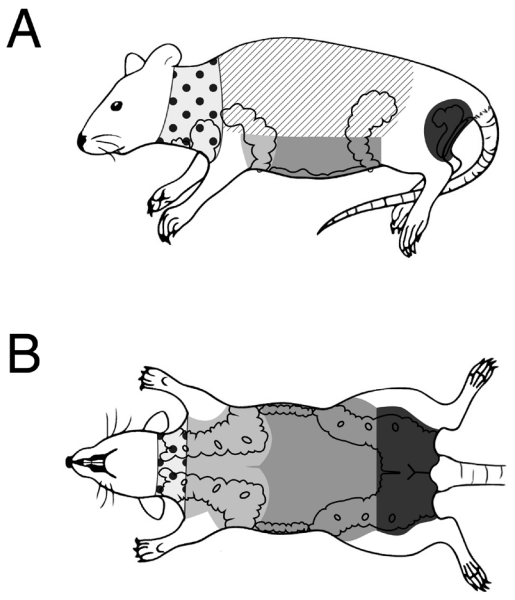

Figure 1—Schematic drawings of the lateral (A) and ventral (B) aspects of a rat that depict the regions (cervical [caudal to the mandible and cranial to the shoulder region; polka dots], axillary [caudal or medial to the elbow joint and cranial to the xiphoidal appendix; light gray], laterodorsal [dorsal to the elbow and stifle joints; stripes], ventral [ventral portions of the thorax and abdomen not included in the axillary and inguinal locations; medium gray], and inguinal [caudal to the pelvis and cranial to the tail; dark gray]) used to categorize the location of SC masses in 100 companion rats (*Rattus norvegicus*) that were examined at a veterinary teaching hospital between 1990 and 2015. (Copyright 2015 by Delphine Grosset. Reprinted with permission).

sequent SC mass was defined as any mass located in the previously defined locations after the initial SC mass was excised; thus, a subsequent mass was not required to be located in the same area or have the same histologic characteristics as the initial mass. A second primary tumor was defined as an SC tumor that developed at or near the site of a previously resected tumor or at a distant location. Outcome was defined in terms of survival time, time from initial diagnosis to development of another SC mass, or loss to follow-up.

For some rats, the reproductive tract underwent histologic examination following surgical sterilization, and those results were reviewed. Necropsy results included gross and histologic evaluation of a variable set of tissues including the brain, eyes, tongue, esophagus, stomach, intestines, trachea, lung, spleen, liver, gallbladder, urinary bladder, kidneys, reproductive tract, heart, skeletal muscle, lymph nodes, and SC masses, when applicable. A cosmetic necropsy was performed on 25 rats, which precluded evaluation of the brain, eyes, and joints of those study subjects. Fresh tissues were fixed in neutral-buffered 10% formalin, gradually dehydrated with alcohol and xylene, and embedded in paraffin. The paraffin-embedded tissues were cut into 4-µm-thick sections, stained with H&E stain, and evaluated by a board-certified veterinary pathologist and pathology resident. For the present study, a board-certified veterinary pathologist (MKK) reviewed all tissues for consistency. Prolactin immunohistochemical staining[a] was performed on 3 pituitary gland masses.

Statistical analysis

Descriptive statistics were generated by use of a commercially available software program.[b] Masses were categorized into 1 of 5 categories (fibroadenoma, other benign mammary gland tumor, malignant mammary gland tumor, malignant nonmammary gland tumor, or nonneoplastic mass) for analysis of risk factors associated with each type of mass. Fisher exact tests were used to evaluate the respective associations between histologic diagnosis of the SC mass and mass location, sex, and presence of a concurrent pituitary gland tumor. Values of $P \leq 0.05$ were considered significant. When a test had a $P \leq 0.05$, the contribution of each cell to the test result was calculated to identify which categories were primarily responsible for the significant difference. All tests were performed with statistical software.[c,d]

Results

Rats

The medical records for 280 rats were evaluated. Of those 280 rats, 100 had at least 1 SC mass identified during the initial physical examination (initial SC mass) and were eligible for study inclusion. The study included 17 sexually intact males, 1 neutered male, 77 sexually intact females, and 5 spayed females. For the 5 spayed females, the median age at ovariohysterectomy was 10 months (range, 3.5 to 19 months). The reason for the initial veterinary examination was the presence of an SC mass for 72 rats, whereas the remaining 28 rats were examined for various reasons including lameness, lethargy, dyspnea, neurologic abnormalities, corneal ulceration, ectoparasitism, vaginal bleeding, and vaginal prolapse.

Histologic diagnosis of SC masses

Collectively, 105 initial SC masses and 37 subsequent SC masses were identified in the study population **(Table 1)**. Of the 105 initial SC masses, 66 (63%) were benign, 26 (25%) were malignant, and 13 (12%) were nonneoplastic. The most common tumor identified was mammary gland fibroadenoma (n = 56 [53%]) followed by mammary gland carcinoma (13 [12%]). Of the 37 subsequent SC masses, 25 (68%) were benign and 12 (32%) were malignant; none of the subsequent SC masses were nonneoplastic. Similar to the initial SC masses, the most common tumor identified among the subsequent SC masses was mam-

Table 1—Frequency distribution of various histologic diagnoses for 105 initial SC masses and 37 subsequent SC masses identified in 100 companion rats (*Rattus norvegicus*) that were examined at a veterinary teaching hospital between 1990 and 2015.

Mass category	Histologic diagnosis	Initial SC masses	Subsequent SC masses
Benign mammary gland tumors	Fibroadenoma	56	24
	Adenoma	4	1
	Myoepithelioma	1	0
Malignant mammary gland tumors	Carcinoma	13	6
Benign nonmammary gland tumors	Sebaceous duct cystadenoma	2	0
	Lipoma	2	0
	Peripheral nerve sheath tumor	1	0
Malignant nonmammary gland tumors	Leiomyosarcoma	2	1
	Spindle-cell sarcoma	3	1
	Hemangiosarcoma	1	0
	Melanocytoma	1	0
	Malignant chordoma	1	0
	Mixed adnexal carcinoma	1	0
	Fibrosarcoma	4	4
Nonneoplastic lesions	Abscess	2	0
	Multifocal mastitis	1	0
	Cyst	3	0
	Mammary gland hyperplasia	5	0
	Mammary gland fibrosis	1	0
	Marked multifocal ductal ectasia	1	0

A subsequent SC mass was defined as any SC mass located at an area other than the head rostral to the mandible, tail, or a limb that was identified after the initial SC mass was excised. A subsequent mass was not required to be located in the same area or have the same histologic characteristics as the initial SC mass.

mary gland fibroadenoma (n = 24 [65%]), followed by mammary gland carcinoma (6 [16%]).

Age was not significantly associated with histologic diagnosis. The age at diagnosis ranged from 8 to 54 months for rats with mammary gland fibroadenomas and from 12 to 36 months for rats with mammary gland carcinomas; however, the median age at diagnosis was 24 months for both groups of rats.

The frequency distributions for mass location and sex by histologic diagnosis for the 105 initial SC masses were summarized **(Table 2)**. Histologic diagnosis was significantly ($P = 0.002$) associated with mass location. Mammary gland fibroadenoma was the most common neoplasm identified in the axillary region. The proportion of mammary gland fibroadenomas in the axillary and ventral regions was significantly greater than the proportion of mammary gland fibroadenomas at other locations.

Histologic diagnosis was also associated with sex. Mammary gland fibroadenoma, the most frequently identified type of initial SC mass, was significantly ($P = 0.003$) more likely to develop in sexually intact females and males than in neutered females and males (Table 2). Additionally, 11 of 13 malignant mammary gland tumors were identified in sexually intact females. Most initial SC masses in sexually intact males were nonmammary gland tumors, and that cell was the primary contributor (contribution, 15.5) to the result of the Fisher exact test. Of the 5 spayed female rats in the study, 1 had a hemangiosarcoma, 1 had a mammary gland carcinoma, and the remaining 3 had mammary gland fibroadenomas. The 3 spayed females that developed mammary gland fibroadenoma underwent ovariohysterectomy at 3.5, 5, and 12 months old, respectively.

Correlation between histologic diagnosis and cytologic evaluation of FNAs of SC masses

An FNA was obtained from 9 of the 105 initial SC masses and submitted for cytologic evaluation. The cytologic results were inconclusive for 5 of the 9 aspirates. The cytologic results for the aspirates of 2 masses were suggestive of malignancy, which was consistent with the histologic diagnoses for those masses. Cytologic results for an aspirate obtained from a mammary gland carcinoma were suggestive of septic inflammation, whereas those for a mammary gland fibroadenoma were suggestive of a hematoma, most likely because of contamination of the aspirate with blood. Overall, cytologic evaluation of an FNA obtained from an initial SC mass resulted in the correct conclusion for only 2 of the 9 masses aspirated.

Treatments and outcome

Treatments implemented included surgical excision of the SC mass, chemotherapy, surgical or chemical neutering with a GnRH agonist, and administration of an antiprolactinemic drug. Thirty-three of the 54 (61%) rats with mammary gland fibroadenoma were euthanized without treatment. Those rats were euthanized at a median of 2 months (range, 0.5 to 12 months) after the initial physical examination because of tumor progression. The remaining 21 rats with mammary gland fibroadenoma underwent surgical excision of the mass. One of those rats died while anesthetized. Of the remaining 20 rats, 13 underwent 1 excisional biopsy or mass excision procedure, whereas 6 underwent 2 excisional biopsy procedures and 1 underwent 3 excisional biopsy procedures be-

Table 2—Frequency distributions for mass location and sex by mass type for the 105 initial SC masses identified in the rats of Table 1.

Variable	Fibroadenoma	Other benign tumor	Malignant mammary gland tumor	Malignant nonmammary gland tumor	Nonneoplastic lesion
Mass location					
Cervical	1	0	0	2	2
Axillary	25	2	5	3	2
Ventral	9	2	1	0	1
Inguinal	14	1	6	4	7
Laterodorsal	4	4	1	4	1
Multifocal	3	1	0	0	0
Sex					
Sexually intact male	4	6	1	4	5
Neutered male	0	0	0	1	0
Sexually intact female	49	4	11	7	8
Spayed female	3	0	1	1	0

Cervical masses were located caudal to the mandible and cranial to the shoulder region. Axillary masses were located caudal or medial to the elbow joint and cranial to the xiphoidal appendix. Laterodorsal masses were located dorsal to the elbow and stifle joints. Inguinal masses were located caudal to the pelvis and cranial to the tail. Ventral masses were located on the ventral portion of the thorax or abdomen at areas not included in the axillary and inguinal locations. Multifocal masses were defined as > 3 masses within the same patient, regardless of the location of the individual masses.

See Table 1 for remainder of key.

cause of recurrent masses. Thus, those 20 rats collectively underwent 29 excisional biopsy procedures.

Of the 20 rats that underwent successful excision of an initial mammary gland fibroadenoma, 12 developed a second primary tumor, 6 were lost to follow-up, and 2 died or were euthanized for reasons unrelated to the mammary gland fibroadenoma. Fifteen of those 20 rats had no adjunctive treatment, and 8 of those rats developed a recurrent mammary gland fibroadenoma 1 to 8 months (median, 4.5 months) after excision of the initial tumor. The median survival time for the 15 rats that underwent surgical excision of the initial mammary gland fibroadenoma without adjunctive treatment was 7.4 months after excision of the initial mammary gland fibroadenoma.

Three of the 48 (6%) sexually intact females with mammary gland fibroadenoma underwent an ovariohysterectomy either in conjunction with (n = 2) or 7 months after (1) surgical excision of the initial tumor. All 3 of those rats developed a subsequent mammary gland fibroadenoma at 1, 2, and 13 months after excision of the initial tumor (1 to 6 months after ovariohysterectomy). The rat that developed a subsequent mammary gland fibroadenoma 13 months after the initial tumor was excised was the one that underwent an ovariohysterectomy 7 months after the initial tumor was excised. That rat underwent surgical excision of the subsequent tumor at the time it was diagnosed and was later euthanized. The median survival time for the 3 rats that underwent ovariohysterectomy was 6 months (range, 2 to 14 months) after diagnosis of the initial mammary gland fibroadenoma.

A 12-month-old sexually intact female rat with mammary gland fibroadenoma was administered 2 successive deslorelin acetate implants[e] (4.7 mg, SC, q 15 mo). Cabergoline[f] (0.6 mg/kg [0.27 mg/lb], PO, q 72 h for 2 weeks) was added to the treatment regimen after implantation of the second deslorelin implant. That rat was initially examined because of 2 large, multilobulated, nonulcerative, and noninfiltrative SC masses in the axillary region. At the time of surgical incision, those masses measured 3.6 and 4.7 cm in diameter. Twelve months after the first deslorelin implant was administered, the owner was informed that the duration of action for the deslorelin implant > 12 months after administration in rats was unknown. The owner declined administration of a new implant at that time. Three months later, 2 soft SC masses were detected in the right axillary and inguinal regions. The owner declined surgical excision of the masses in favor of medical management. A second deslorelin implant was administered and cabergoline was administered for 2 weeks, after which time the implant was expected to be efficacious.[22] The size of the masses remained fairly stable for 5 months after implantation of the second deslorelin implant and then began to increase. The owner elected to forego further anti-tumor treatment and instead chose to care for the rat palliatively at home until it died. The owner also declined a necropsy, so the histologic diagnosis of the subsequent SC masses was not determined.

Another 12-month-old sexually intact female rat with mammary gland fibroadenoma was administered a deslorelin implant[g] (4.7 mg, SC) once 5 weeks after surgical excision of the tumor. No subsequent SC mass was detected during the 12 months after administration of the implant, at which time the rat was euthanized because of lymphocytic leukemia.

Of the 13 rats with mammary gland carcinoma, 6 underwent surgical excision of the mass, 5 were euthanized without treatment, and 2 were lost to fol-

low-up after the initial examination. Of the 6 rats that underwent surgical excision of the tumor, 4 developed subsequent mammary gland carcinomas, 1 died while anesthetized, and 1 was lost to follow-up after the procedure. The tumor had metastasized to the regional lymph nodes at the time of mass excision or necropsy in 4 of those rats. One rat was administered intralesional cisplatin[f] (1.6 mg, q 1 wk). That rat underwent 2 excisional biopsies and had recurrence of the mammary gland carcinoma in the inguinal area twice. The last recurrence was only 4 days after the last intralesional cisplatin treatment, and that rat was subsequently euthanized. The median survival time for the rats with mammary gland carcinoma that underwent surgical excision of the tumor was 4 months after initial examination.

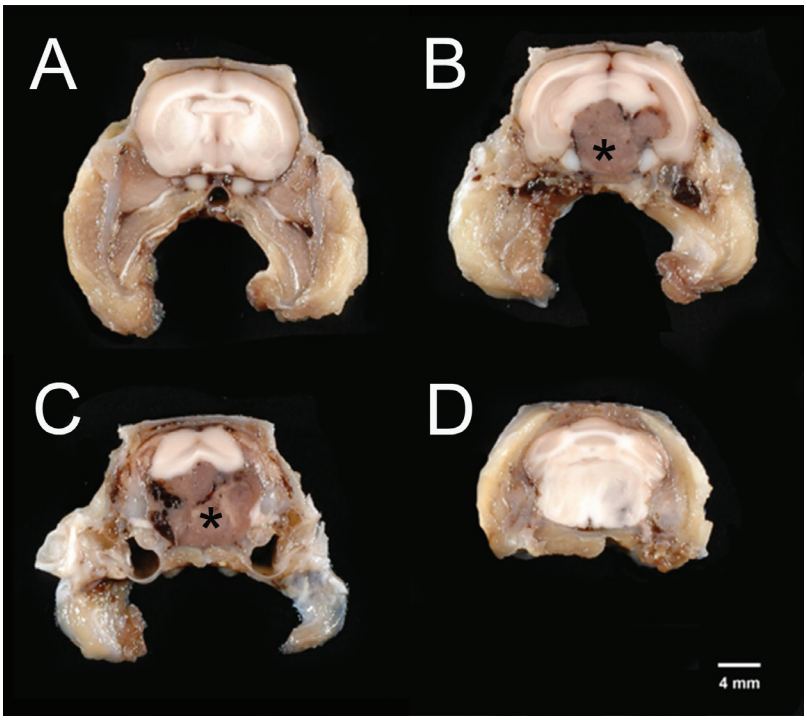

Figure 2—Photograph of serial transverse sections of the caudal portion of the skull and brain of a 24-month-old sexually intact female companion rat with a mammary gland fibroadenoma and a concomitant pituitary gland adenoma (asterisk). Section A was obtained through the cerebrum at the level of the optic nerves, section B was obtained through the cerebrum at the level of the hippocampus, section C was obtained at the level of the tympanic bullae, and section D was obtained at the level of the cerebellum and medulla oblongata. Notice that the tumor is causing substantial compression of the brain in sections B and C. Bar = 4 mm.

Concomitant abnormalities and necropsy findings

Of the 54 rats with mammary gland fibroadenoma, 29 had a complete necropsy performed, 6 had a cosmetic necropsy performed, and 11 were alive or lost to follow-up; a necropsy was declined by the owner for the remaining 8 rats. Of the 35 rats with mammary gland fibroadenoma that underwent a necropsy, 14 (40%) had concomitant reproductive tract abnormalities that included cystic endometrial hyperplasia (n = 4), endometrial polyps (3), adenomyosis (2), and paraovarian cysts and abscesses, chronic suppurative metritis, stromal uterine tumor, severe testicular atrophy, and myxoma (1 each).

A complete necropsy was performed on only 13 of the 26 rats with malignant neoplasms, and metastatic disease was detected in 5 of those rats. In 4 rats with mammary gland carcinoma, the tumor had metastasized to the regional lymph nodes, and 1 of those rats also had pulmonary metastasis. One rat with malignant chordoma had pulmonary metastases.

A pituitary gland tumor was identified in 31 of the 45 (69%) rats that underwent a complete necropsy. Of those 31 pituitary gland tumors, 15 (48%) were located in the pars distalis, 1 (3%) was located in the pars intermedia, and 1 (3%) was characterized as a macroadenoma that encompassed both the pars distalis and pars intermedia **(Figure 2)**. The location was not described in the necropsy report for the remaining 14 pituitary gland tumors. Five (16%) of the pituitary gland tumors were characterized as chromophobic pituitary gland adenomas; the staining properties were not characterized for the remaining tumors.

The pituitary gland was examined for 28 of the 29 rats with mammary gland fibroadenoma that underwent a complete necropsy. A pituitary gland tumor was identified in 21 of those 28 (75%) rats; no pituitary gland abnormalities were detected in the remaining 7 (25%) rats. Of those 21 tumors, 18 were pituitary gland adenomas and 3 were pituitary gland carcinomas. Three tumors underwent immunohistochemical staining for prolactin; 2 stained positive for prolactin and 1 stained negative for prolactin.

The pituitary gland was examined for 17 rats that had SC masses that were not identified as mammary gland fibroadenomas. A pituitary gland adenoma was identified in 10 of those 17 rats. The presence of a pituitary gland tumor was not significantly (P = 0.33) associated with the histologic diagnosis of the SC mass.

Discussion

Results of the present study indicated that the most prevalent SC mass identified in companion rats was mammary gland fibroadenoma (56/105 [53%]) followed by mammary gland carcinoma (13/105 [12%]). The number of rats with mammary gland fibroadenoma in the present study might have been artificially decreased relative to the number of rats with mammary gland fibroadenoma in the general companion population because rats examined at a refer-

ral hospital likely have masses that are more invasive or otherwise difficult to surgically excise, compared with rats examined at primary care hospitals. The prevalence of mammary gland carcinoma in the companion rats of the present study was 3 times greater than that (4%) reported for sexually intact and ovariectomized Sprague-Dawley rats.[7] Twenty-eight of the 100 (28%) rats evaluated in the present study were brought to the veterinary hospital for reasons other than an SC mass, which emphasizes the importance of a complete physical examination that includes careful palpation of SC tissues for all patients. Moreover, given that 25% (26/105) of the SC masses identified in the companion rats of this study were malignant, a thorough diagnostic workup that includes histologic examination of excised masses is recommended for all rats with SC masses just as it is for other species.

Mammary gland fibroadenoma frequently developed in the axillary and ventral regions of the rats of the present study, which was not surprising because mammary gland tissue is the most extensive in those areas.[5] However, a fairly small number of rats with mammary gland fibroadenoma were evaluated in this study, and the results may not accurately reflect the association between tumor type and mass location. Additional rats with mammary gland fibroadenoma need to be evaluated to better elucidate the correlation between mass location and tumor type.

In the companion rats of the present study, mammary gland fibroadenoma developed more frequently in sexually intact females and males than in the neutered females and males. A similar finding has been reported in laboratory rats.[7] In the present study, 3 spayed females developed mammary gland tumors including 3 fibroadenomas and 1 carcinoma. This was not unexpected because, although ovariectomy decreases the risk of mammary gland tumor development in laboratory rats, that risk is not completely eliminated.[7,19] Additionally, subclinical mammary gland neoplasia can be present at the time of ovariohysterectomy in some rats and continue to progress despite surgical sterilization.

It is unknown whether pituitary gland tumors have a causal role in the development of reproductive tract abnormalities and mammary gland fibroadenoma because the prevalence of pituitary gland tumors did not differ significantly between rats with and without mammary gland fibroadenoma in the companion rats of the present study as well as the laboratory rats of other studies.[7,16] In the present study, prolactin secretion was detected by immunohistochemical staining in only 2 of the 3 pituitary gland tumors evaluated for such. Of the 2 rats with a mammary gland fibroadenoma and concomitant uterine adenomyosis, 1 had a pituitary gland carcinoma and the other had a chromophobic pituitary gland adenoma. Uterine adenomyosis is defined as the presence of fully differentiated endometrial glands in the myometrium,[23] is associated with hormonal factors,[23,24] and has been described in females of numerous species.[23–25] In Wistar rats, adenomyosis can be experimentally induced by isografting the anterior pituitary gland, which suggests a link between pituitary gland hormones and the development of that lesion.[26] Thus, companion rats with uterine adenomyosis should be further evaluated for the presence of a pituitary gland mass. In human patients, treatment of uterine adenomyosis includes administration of GnRH agonists and hysterectomy.[23] The efficacy of administration of GnRH agonists for the treatment of uterine and mammary gland lesions in rats has yet to be determined.

The most frequently identified reproductive tract lesion in the companion rats of the present study was uterine cystic endometrial hyperplasia. Uterine cystic endometrial hyperplasia is defined as an increase in the size and number of endometrial glands in conjunction with cystic glandular dilation.[27] It is caused by chronic or repeated progesterone stimulation associated with estrogen priming after repeated estrous cycles without pregnancy.[27] In rats, endometrial hyperplasia can be induced by administration of estrogen,[28] and in rodents, it can also be induced by zearalenone secreted by fungi in contaminated food.[27] In human patients, endometrial hyperplasia is treated by the administration of GnRH agonists.[29] The 4 rats with endometrial hyperplasia in the present study also had mammary gland fibroadenoma, and 3 of the 4 had a pituitary gland tumor. It is unknown whether a common hormonal factor could have caused both the mammary gland fibroadenoma and uterine endometrial hyperplasia in those rats. Further studies are necessary to investigate the potential link between uterine lesions, mammary gland fibroadenomas, and pituitary gland tumors in rats. Ovariohysterectomy may be indicated for female rats with mammary gland tumors because they frequently have concomitant reproductive tract abnormalities. Some contraceptive techniques may also limit the progression of certain reproductive tract lesions in affected rats.

In the present study, an FNA was performed on only 9 SC masses, and the cytologic results were diagnostic for only 2 of those 9 aspirate samples. In older male rats with polyarteritis nodosa, FNA may be contraindicated because the procedure is associated with hemorrhage.[30] Therefore, the benefit of performing an FNA on an SC mass should be weighed against the risk to the patient and the expense for the owner. The use of FNA as a modality for diagnosis of mammary gland tumors in dogs is also controversial.[31] Cytologic evaluation of FNAs obtained from SC masses as an aid for the diagnosis of mammary gland tumors in rats needs to be assessed in a large population of rats.

Eight of the 15 companion rats of the present study with mammary gland fibroadenoma that underwent surgical excision of the tumor without any adjunctive treatment developed a subsequent tumor at a median of 4.5 months (range, 1 to 8 months) after surgical excision of the initial tumor. Furthermore, all 3 sexually intact female rats with mammary gland fi-

broadenomas that underwent an ovariohysterectomy in conjunction with or soon after surgical excision of the initial tumor developed subsequent tumors. These findings can be used by veterinarians as preliminary prognostic information when discussing realistic treatment options and outcomes with owners of companion rats with mammary gland fibroadenoma. However, additional studies that involve a larger number of rats than that evaluated in the present study are necessary to definitively determine the effect and timing of ovariohysterectomy on mammary gland tumor development and recurrence. Additionally, the proportion of second primary tumors reported for the companion rats of this study was likely biased because some rats that developed a subsequent SC mass were likely not brought back for reevaluation at the veterinary teaching hospital and older rats might have died from unrelated causes prior to development of a second primary tumor. Strictly speaking, in both veterinary and human medicine, the term recurrence is used to designate a histologically similar mass that develops at the same location as the initial mass.[32] A fibroadenoma detected in the same mammary gland from which an initial primary fibroadenoma was previously excised might have been present microscopically at the time the initial tumor was resected; therefore, we have called such tumors second primary tumors in this study.

In the present study, 2 companion rats with mammary gland fibroadenoma received adjunctive treatments that included cabergoline and deslorelin. Cabergoline is a dopaminergic receptor agonist and prolactin antagonist and is not approved for veterinary use in the United States.[12] Laboratory rats have been used extensively as models for the treatment and prevention of breast cancer in human patients.[19,21,23] The administration of prolactin antagonists prevents the development of spontaneous mammary gland fibroadenoma in some strains of laboratory rats[8] and decreases the size of some experimentally induced mammary gland tumors in laboratory rats.[33–35] However, in many rats, tumors recurred at the same location within 1 to 9 weeks after administration of the prolactin antagonist was discontinued.[34] The dose of cabergoline administered to the rat of the present study was the same as that used to treat companion rats with pituitary gland adenoma.[12,36] Cabergoline was selected rather than bromocriptine, another prolactin antagonist, because its duration of action is much longer than that of bromocriptine. Results of a study[36] indicate that administration of 0.6 mg of cabergoline/kg, PO, to laboratory rats suppressed serum prolactin concentration for up to 6 days, whereas administration of the same dose of bromocriptine suppressed serum prolactin concentration for only 6 hours. Dopaminergic receptor agonists have been anecdotally advocated as a prophylactic treatment for mammary gland tumors in rats,[37] despite the fact that the hormonal receptors present on mammary gland tumors of companion rats have not been elucidated.

Deslorelin is a GnRH agonist, which causes desensitization and downregulation of the anterior pituitary gland. In male laboratory rats, administration of deslorelin results in the downregulation and internalization of GnRH receptors and inhibition of follicle-stimulating hormone subunit β synthesis by pituitary gland gonadotrophs.[29] It is presumed there is a transient increase in the secretion of gonadotropin hormones that lasts for approximately 2 weeks following the administration of a deslorelin implant in rats.[22] That was the reason cabergoline was administered for the first 2 weeks after administration of the deslorelin implant to one of the rats of the present study. Other GnRH agonists also prevent the development of mammary gland carcinoma in laboratory rats used in an experimental tumor induction model.[38] Deslorelin has been used as a contraceptive in male and female rats since 2011, although its reversibility remains unknown[22,39–41]; however, to our knowledge, its use as an adjunctive treatment for mammary gland fibroadenoma in rats has not been described. The reason that deslorelin was administered to only 2 rats of the present study was likely because it did not become commercially available in the United States until 2012.[42] In rats, serum progesterone and estradiol 17β concentrations are suppressed for up to 12 months after implantation of a 4.7-mg deslorelin implant.[39] For some types of tumors in rats, estrogen and prolactin are important factors in the promotion stage of carcinogenesis, but a more aggressive phenotype may develop as the tumors progress such that tumor growth becomes independent from hormone influence.[21] The effects of the 4.7-mg deslorelin implant > 12 months after implantation in rats have not been evaluated.[39] In the present study, a second deslorelin implant was administered 15 months after the first to 1 rat because of the emergence of a new SC mass. Implantation of the second implant stabilized mass growth for only 5 months after which the mass began to increase in size. Unfortunately, the owner of that rat declined to have a necropsy performed, and it is unknown whether the increase in the size of the mass 5 months after implantation of the deslorelin implant was caused by premature loss of efficacy by the implant, a decrease in the responsiveness of the tumor following repeated implant placement, or evolution of the tumor receptors toward an aggressive phenotype that could not be regulated by reproductive hormones. Because only 2 of 54 rats with mammary gland fibroadenoma received deslorelin, we cannot make any definitive conclusions regarding the efficacy of that GnRH agonist for the treatment of that type of tumor, and additional research is necessary.

Cisplatin is a platinum-based chemotherapeutic agent that has been used to decrease experimentally induced tumor development in the mammary glands of rats in models of human breast cancer.[10,43] In the present study, only 1 rat received intralesional cisplatin, and we cannot draw any conclusions regarding its effectiveness.

Limitations of the present study include its retrospective nature and the evaluation of companion rats examined at only 1 veterinary hospital. The results may not be applicable to companion rats that originate from a different genetic pool elsewhere in the world.

In the present study, mammary gland fibroadenoma was the most frequent type of SC mass identified in companion rats examined at a veterinary teaching hospital between 1990 and 2015, with a prevalence of 53% (56/105). However, 26 of 105 (25%) initial SC masses evaluated in this study were malignant, which suggested that, like other species, the standard of care for rats with SC masses should include a thorough diagnostic workup with histologic examination of the excised mass. The histologic diagnosis of an SC mass is important for prognostic purposes and the development of a treatment protocol to prevent mass recurrence. Further studies are necessary to investigate adjunct treatment protocols, including the use of GnRH agonists and chemotherapeutics, for companion rats with mammary gland fibroadenoma or other benign or malignant SC masses.

Footnotes

a. Anti-prolactin antibodies CMA-140, Cell Marque Corp, Sigma-Aldrich Co, Rocklin, Calif.
b. Excel, Microsoft Office, version 14.4.3, Microsoft Corp, Redmond, Wash.
c. Stata/IC, version 13.1, StataCorp LP, College Station, Tex.
d. StatXact, version 10.0, Cytel Software Corp, Cambridge, Mass.
e. Suprelorin, Virbac, Carros, France.
f. Cabergoline compounded suspension, 2 mg/mL, Diamondback Pharmacy, Scottsdale, Ariz.
g. Cisplatin, 1 mg/mL, Cardinal Health, Dublin, Ohio.

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From this month's *AJVR*

Use of manual alveolar recruitment maneuvers to eliminate atelectasis artifacts identified during thoracic computed tomography of healthy neonatal foals

Kara M. Lascola et al

OBJECTIVE
To evaluate use of single manual alveolar recruitment maneuvers (ARMs) to eliminate atelectasis during CT of anesthetized foals.

ANIMALS
6 neonatal Standardbred foals.

PROCEDURES
Thoracic CT was performed on spontaneously breathing anesthetized foals positioned in sternal (n = 3) or dorsal (3) recumbency when foals were 24 to 36 hours old (time 1), 4 days old (time 2), 7 days old (time 3), and 10 days old (time 4). The CT images were collected without ARMs (all times) and during ARMs with an internal airway pressure of 10, 20, and 30 cm H_2O (times 2 and 3). Quantitative analysis of CT images measured whole lung and regional changes in attenuation or volume with ARMs.

RESULTS
Increased attenuation and an alveolar pattern were most prominent in the dependent portion of the lungs. Subjectively, ARMs did not eliminate atelectasis; however, they did incrementally reduce attenuation, particularly in the nondependent portion of the lungs. Quantitative differences in lung attenuation attributable to position of foal were not identified. Lung attenuation decreased significantly (times 2 and 3) and lung volume increased significantly (times 2 and 3) after ARMs. Changes in attenuation and volume were most pronounced in the nondependent portion of the lungs and at ARMs of 20 and 30 cm H_2O.

CONCLUSIONS AND CLINICAL RELEVANCE
Manual ARMs did not eliminate atelectasis but reduced attenuation in nondependent portions of the lungs. Positioning of foals in dorsal recumbency for CT may be appropriate when pathological changes in the ventral portion of the lungs are suspected. (*Am J Vet Res* 2016;77:1276–1287)

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