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Outcome and prognostic indicators in 20 cats with surgically treated primary lung tumors

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Abstract

The purpose of this retrospective study of 20 client-owned cats was to describe the clinical signs, surgical interventions, histological features, stage and treatments of primary lung tumors removed by surgical excision, and to determine which factors significantly influence survival. Any cat that underwent surgical resection of a primary lung tumor between 2000 and 2007 was included in the study. Patient records were reviewed and signalment, clinical signs, preoperative diagnostics, surgical findings and histopathological results recorded. Histological reports were reviewed and scored using World Health Organization criteria. The Kaplan–Meier test was used to evaluate each potential prognostic factor with survival. Twenty cats met the inclusion criteria. The presence of clinical signs (such as dyspnea) at the time of diagnosis ($P = 0.032$), pleural effusion ($P = 0.046$), stage M1 ($P = 0.015$), and moderately and poorly differentiated tumors on histopathology ($P = 0.011$) were factors that were significantly correlated with reduced survival times. The median survival time of the 20 cats was 11 days. Cats presenting with no clinical signs had a median survival time of 578 days post-surgery vs 4 days post-surgery when presented with clinical signs. Cats staged T1N0M0 lived longer than cats at other stages ($P = 0.044$). Of the cats that survived to the time of suture removal, median survival time was 64 days. The results indicate that the presence of clinical signs, pleural effusion, moderately and poorly differentiated tumors on histopathology, evidence of metastasis and any stage beyond T1N0M0 are negative prognostic indicators for cats with primary lung tumors. The findings demonstrate that cats that presented with clinical signs, pleural effusion, any stage other than T1N0M0, or moderately and poorly differentiated tumors on histopathology had a poor prognosis. Therefore, extensive preoperative diagnostics, including computed tomography scans, should be performed before considering surgical intervention in these cats. These findings may be used to guide therapeutic decision-making in cats diagnosed with primary lung tumors.

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Introduction

In dogs with surgically removed primary lung tumors, the presence of clinical signs,[1] pleural effusion,[2] lymph node involvement,[1,3] World Health Organization (WHO) tumor-node-metastasis (TNM) stage[4] and histological grade[1,3,4] have all been found to influence survival. These factors are a critical guide to therapeutic decision-making, including the decision to operate for removal of the primary neoplasm. The literature on pulmonary neoplasms in cats is more limited. Previously, survival factors were reported for 21 cats after surgery was performed to remove a primary lung tumor.[5] These 21 cats were a subgroup of 86 cats examined in another study on primary lung tumors in cats.[6] In that report, histological grade was the only factor found to influence survival in cats operated on for primary lung tumors.[5] The remaining literature on primary lung tumors in cats focuses on individual case reports or small case series in which surgery may not have been perfor med.[7–24] Analysis of survival information would be a useful tool in recommending whether to operate on primary pulmonary neoplasms in cats.

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The purpose of this retrospective study was to evaluate a cohort of cats with primary lung tumors treated with surgical excision and to determine which factors significantly influenced survival. Factors evaluated included signalment, presence of clinical signs, preoperative diagnostic findings (eg, radiography and fine-needle aspiration [FNA]), surgical findings, histological findings and staging.

Materials and methods

Criteria for inclusion

The medical records of all cats that underwent surgery at MedVet Medical and Cancer Centers for Pets for a primary lung tumor from 1 January 2000 to 31 December 2007 were evaluated. Cats were included in the study if they had a complete medical record, had surgical resection of a histologically confirmed primary lung tumor, had recovered from surgery and had postoperative follow-up.

Data collection

Information collected from the medical records included weight, gender, breed and age at diagnosis, as well as clinical signs at presentation. Results of thoracic radiographs and fine-needle aspiration, and tumor location at surgery, as well as the WHO TNM stage and histological type and grade were also recorded.

Radiographs were interpreted by a single board-certified radiologist. Cytology and histopathology were performed through a veterinary diagnostic laboratory (IDEXX Laboratories, Worthington, OH, USA) by multiple pathologists. All 20 cats had thoracic radiographs. A solitary lung mass was noted in 13 cases. Four cases were described as having disease within one specified quadrant of the lung, but not specifically noted to have multiple masses. Three cases did not have a specific number of masses listed in their medical records. The left lung field was affected in eight (40%) of the 20 cats, and the right lung field was affected in 10 (50%). In two cats (10%), the tumor was described as being present in both lung fields. Eleven cats had single lung lobectomies performed through lateral thoracotomy (left cranial lobe, n = 2; left caudal lobe, n = 4; right middle lobe, n = 1; right caudal lobe, n = 3; right accessory lobe, n = 1) and nine cats had multiple lung lobectomies performed (five via median sternotomy, four via lateral thoracotomy). The caudal lung lobes were more commonly affected than the cranial lung lobes. Lymph node biopsy was performed on the basis of visualized enlargement. Three cats had lymph node biopsies performed. Ten cats (50%) had FNA performed on the lung mass. The results were suggestive of neoplasia in six (60%), and were inconclusive or consistent with inflammatory changes in four (40%). Histopathological diagnosis and tumor grade as used in a previous study were recorded.[5] Tumor location was recorded in the surgery report.

Clinical staging was based upon the WHO TNM system for primary lung tumors:[1,6] T1 = solitary lung tumor, T2 = multiple tumors in one lung lobe, T3 = tumor invading adjacent tissues; N0 = no nodal involvement, N1 = tracheobronchial lymph node positive, N2 = extra thoracic lymph node positive; M0 = no pleural or distant metastasis, M1 = pleural or distant metastasis evident.

Survival time was calculated based on the length of time from the date of surgery to the date of death or date of data acquisition at last known contact while alive. Follow-up information was obtained by telephone interviews with the owners of each cat.

Statistical analysis

Univariate Kaplan–Meier analysis was used to assess the association between survival time and the following categorical variables: gender, presence of any clinical signs, presence of dyspnea, coughing, lethargy, weight loss, anorexia and dysphagia, presence of pleural effusion, TNM stage, presence of lymph node metastasis (N score), presence of distant metastasis (M score), tumor location, tumor type and tumor grade. The Mantel–Cox test was used to establish significance of differences in survival curves. Cox proportional hazards regression was used to assess the presence of a univariate association between continuous clinical findings (age at diagnosis and weight) and length of survival. The significance level for all testing was set at $P = 0.05$.

Results

Signalment

Twenty cats fitted the case inclusion criteria. Seventeen (85%) were domestic shorthair cats, two were domestic longhair cats (10%) and one (5%) was a Persian. Thirteen (65%) were male castrated and seven (35%) were female spayed. Mean weight was 4.8 kg (range 3.0–7.9 kg). Mean age at diagnosis was 11.6 years (range 5.0–16.0 years). There was no significant association between any signalment variable and survival.

Outcome

No cat died intraoperatively, and the mean anesthesia and surgery times were 76.0 mins (SD 42.3 mins) and 48.5 mins (SD 26.0 mins), respectively.

The 20 cats in this study had a median survival time of 11 days (range <1–1855 days). If only the 10 cats (50%) that survived the 10-day postoperative period were included, the median survival time was 64 days (range 14–1855 days).

All cats except one were dead at the time of manuscript preparation. Four cats were euthanased and 15 cats died. Three of the four cats were euthanased because of continued clinical signs postoperatively, and one was

euthanased owing to perceived poor prognosis associated with surgical findings. The one cat still alive at manuscript preparation (>550 days) presented with no clinical signs, was stage T1N0M0, and the tumor type and grade was well-differentiated papillary carcinoma.

Fourteen of 19 (74%) cats died owing to, or with signs consistent with, progression of the lung tumor, four of which were euthanased in the period immediately postsurgery to 2 days after surgery. Five of the 19 cats (26%) died of causes unrelated to the primary tumor (two cats with congestive heart failure at 31 and 578 days, respectively; two cats of unknown etiologies at 8 and 68 days, respectively; one cat with synovial cell carcinoma died at 730 days); three of these five cats initially presented with no clinical signs. A post-mortem examination was either not performed or declined by the owner.

Clinical signs and survival

Sixteen of the 20 cats (80%) presented with clinical signs. These included anorexia (n = 10; 50%), coughing (n = 10; 50%), lethargy (n = 5; 25%), weight loss (n = 5; 25%), dyspnea (n = 4; 20%) and dysphagia (n = 1; 5%). Of the four cats (20%) that presented with no clinical signs, the lung tumor was an incidental finding noted on routine radiographs taken for unrelated procedures. The median survival time of cats with clinical signs at presentation was 4 days (range <1–1855 days). The median survival time of cats without clinical signs at presentation was 578 days (range 68–730 days). The presence of at least one of the above clinical signs was significantly associated with shorter survival ($P = 0.032$). When each clinical sign was individually examined, only dyspnea negatively affected prognosis ($P = 0.005$). Dyspneic cats had a median survival time of 2 days (range 1–3 days) vs 31 days (range <1–1855 days) for cats without dyspnea. Three out of four of the cats surviving to 1 year had no clinical signs at presentation.

Preoperative diagnostics and survival

Five cats (25%) had evidence of pleural effusion on radiographs. The median survival time of these five cats was 2 days (range <1–60 days). The median survival time of the 15 cats without pleural effusion (75%) was 31 days (range <1–1855 days). The presence of pleural effusion was significantly associated with shorter survival ($P = 0.046$).

Histopathology and survival

Eighteen (90%) of the tumors were classified as adenocarcinoma. Of these 18 adenocarcinomas, 12 were further classified as either papillary/acinar (n = 11, 92%) or bronchioaveolar (n = 1, 8%). Other tumor types described included squamous cell carcinoma (n = 1, 5%) and histiocytic sarcoma (n = 1, 5%). Margins were not defined in many of the histopathology reports. Histopathological type was not significantly associated with survival.

The degree of differentiation was reported in 18 cats. Well-differentiated tumors were present in nine cats (50%), with a median survival of 68 days (range 2–1855 days). Moderately differentiated tumors were present in five cats (28%), with a median survival of 3 days (range 1–60 days). Poorly differentiated tumors were present in four cats (22%), with a median survival of 6 days (range <1–60 days). Cats with well-differentiated tumors had significantly longer survival times than cats with either moderately or poorly differentiated tumors ($P = 0.011$).

Staging and survival

Cats staged as T1N0M0 lived significantly longer (n = 6; $P = 0.044$) than cats with other stages. The T1N0M0 cats had a median survival of 190 days (range 8–730 days) vs 3 days (range <1–1855) for cats of other stages.

Three cats had lymph node biopsies performed. Cats staged as N1 (n = 3), irrespective of T stage, had significantly shorter ($P = 0.001$) survival times than those staged as N0 (n = 17). The median survival time of cats staged as N1 was <1 day (range <1–3 days) compared with the median survival time of 31 days (range 1–1855 days) for cats staged as N0. All cats staged as N1 were also staged as M1.

Cats with clinical stage of M1 (n = 9), irrespective of T stage had a significantly shorter survival time ($P = 0.015$) than those staged as M0. The median survival time of cats staged as M1 was 3 days (range <1–60 days) compared with the median survival time of 60 days (range 2–1855 days) for cats staged as M0. All cats staged as M1 had pleural metastasis present. Based on the WHO description, none was described as having distant metastasis.

Discussion

The results of this study indicate that the presence of respiratory signs, pleural effusion, any stage beyond T1N0M0, evidence of metastasis, and moderately or poorly differentiated tumors were useful negative prognostic indicators for cats with primary lung tumors (see Table 1). The presence of any one of these prognostic features was associated with short survival times in cats, which will help guide therapeutic decision-making, including the decision to remove the primary neoplasm surgically. These results were generally similar to those reported in dogs with one important distinction: median survival time in cats appeared to be shorter than that of dogs (overall, 11 days in cats vs 120 days in dogs).[1–4] The underlying reason for this is unknown; however, it is possible that cats do not show clinical signs until the disease is more advanced than in dogs or that primary lung tumors in cats are more aggressive than in dogs, related to differences in the biological behavior of tumors between species, such as is seen with osteosarcoma in cats vs dogs.

Table 1 Review of variables found to be of significance for survival in cats with surgically operated primary lung tumors

Prognostic factor	Cats affected (n)	*P* value
Clinical signs present	16	0.032
Dyspnea present	4	0.005
Pleural effusion present	5	0.046
Tumor graded moderately or poorly differentiated	9	0.011
Clinical stage other than T1N0M0	6	0.044
Lymph node metastasis present	3	0.001
Pleural or distant metastasis present	9	0.015

The median survival time of the cats in this study was 11 days compared with a median survival time of 115 days in a previous study by Hahn and McEntee.[5] In their study, survival time was determined from cats that survived the immediate postoperative period (which was not defined). If the cats that did not survive to suture removal were removed from our study (n = 10, 50%), the remaining 50% had a median survival time of 64 days. In our study, all but one of the cats that died during the postoperative period (within the first 10 days) had high grade T and/or M stage, whereas only three (30%) of the cats that survived beyond the time of suture removal had high grade T or M stage, emphasizing the importance of the WHO TNM staging system on prognosis. In dogs, T1N0M0 stage resulted in the best survival times; in a recent study, the median survival of dogs staged T1N0M0 was 555 days vs 72 days for any other stage.[4] Similar to dogs, the cats in this study staged as T1N0M0 lived significantly longer (median survival time 190 days) than cats with any other staging (median survival time 3 days). This information is critical when considering surgery for these patients. The presence of clinical signs at the time of diagnosis of a feline primary lung tumor has not been previously reported to influence survival time. In dogs, the presence of clinical signs has been regarded as a poor prognostic indicator.[1] The cats in our study with no clinical signs at presentation were diagnosed with a primary lung tumor as an incidental finding. As such, these cats were not clinically affected by the tumor and appeared in relative good health. All of the cats without clinical signs were staged T1N0M0 and graded as well-differentiated, both of which have also been shown in this study to be associated with significantly longer survival times. Three out of four of the cats surviving for 1 year were patients that presented with no clinical signs. When each clinical sign was evaluated individually, dyspnea showed a significant relationship to survival. Fifty percent of the animals with dyspnea had pleural effusion, 75% were staged as M1 and 50% were staged as T3. Therefore, it is easy to deduce that animals with the clinical sign of dyspnea were likely to have advanced disease and a poorer prognosis. Based on these findings, surgical removal of primary lung tumors in cats with respiratory signs may not result in an improved outcome. Cats with pleural effusion secondary to primary lung tumors have been noted previously;[6,7] however, its influence on survival time has not been reported. Pleural effusion has been shown in dogs to be associated with shorter survival times.[2] Cats with pleural effusion in this study lived a significantly shorter time postoperatively than those without pleural effusion (median 2 days vs 31 days, respectively). Eighty percent (4/5) of the cats with pleural effusion were staged as M1.

Radiographs were the most common diagnostic test performed on these cats. In humans, computed tomography (CT) has been commonly used in cases of suspected lung cancer.[25] CT has been considered to be more sensitive in confirming lesions than plain radiography, as well as being able to diagnose smaller lesions not visible on radiographs.[25] CT was not available in our hospital during the study period, with the exception of 2007. Since acquiring the capacity for CT, we have used it in cases with primary lung tumors to better visualize the mass/masses seen on radiographs, as well as in search of metastatic disease and lymph node size. This modality has also been used to better visualize and define the local lymph nodes prior to surgery in humans and dogs.[25] In humans, standard guidelines have been developed to relate lymph node size with prognosis.[26] Direct evaluation of the effect of metastasis to regional lymph nodes could not be made in this study owing to low numbers and all cats staged as N1 also being staged as M1. Larger numbers of cats with known lymph node metastasis and no metastasis elsewhere would be needed in order to assess directly this relationship. Based on the results of this study, we will not operate on cats with primary lung tumors noted on radiographs without a preoperative CT scan.

FNA was found to be a preoperative test with low sensitivity in these cats as 40% of the results were not diagnostic. The specificity of FNA could not be assessed because cats without primary lung tumors were not studied. In one study in humans, ultrasound or CT-guided FNA was performed to further evaluate masses noted on radiographs and CT. False-negatives were present; therefore, aspirates were interpreted with caution and further diagnostic studies were indicated.[26] There is considerable debate amongst specialists in our practice as to the benefit of FNA in these cases. Given the low sensitivity and potential risk associated with the procedure, FNA may not be indicated as part of the preoperative work-up in cats with primary lung masses. The true specificity and sensitivity of FNA in cases of thoracic masses in cats should be investigated further.

As previously shown in a study of cats by Hahn and McEntee,[6] the caudal lung lobes were more commonly affected in the present study. However, the significance of this finding is unknown owing to the low numbers of individually affected lung lobes. Greater patient numbers would be needed to analyze accurately any relationship of lung tumor location and survival.

Currently, the WHO divides pulmonary adenocarcinoma into papillary, acinar, solid or mixed adenocarcinomas (previously bronchogenic adenocarcinoma) and bronchioalveolar carcinomas.[27] The histological division between the types is not well elucidated, and differentiation can be problematic.[27] The most common tumor encountered in the cats in this study was adenocarcinoma (90%), which is in agreement with previous studies.[5,6,7,27] Ninety-two percent of the adenocarcinomas were of papillary or acinar (previously bronchogenic) origin, which is also in agreement with previous studies.[5,6] Unfortunately, only one tumor was noted to be of bronchioalveolar origin; hence, any comparison to the tumors classified as papillary or acinar, and their effects on prognosis, could not be investigated.

Tumor differentiation was shown to be significantly associated with survival in these cats. In the study by Hahn and McEntee,[5] cats with tumors graded as moderately differentiated lived longer than those with poorly differentiated tumors (median survival times of 698 and 75 days, respectively). In this study, cats with moderately or poorly differentiated tumors had shorter survival times (median survival times of 3 and 6 days, respectively) compared with 68 days for cats with well-differentiated tumors. Differentiation has been one of many features evaluated in the grading scheme of tumors, and has been associated with biological behavior in many tumors in dogs and cats.[28] Increasing differentiation has generally been correlated with slower, less aggressive, biological behavior.

The retrospective nature of this study meant that we relied on medical records and owner recollection, which have inherent limitations. The perioperative and surgical treatments were performed by multiple veterinarians, which may have introduced inconsistencies in the data. Another limitation was the low numbers of lymph node results recorded. This could have been a result of poor record keeping, inadequate lymph node sampling or a combination of the two. Lymph node sampling has been reported to be an important step in the staging and treatment of lung cancer in humans.[26] Varying techniques in obtaining a diagnosis of lymph node involvement in humans have been developed, ranging from simple sampling techniques to full dissection and removal.[29] These techniques are associated with low morbidity and mortality when performed carefully and correctly.[26,29,30] Given that many similarities in prognostic factors were shown here between dogs and cats, one can only assume that the significance of lymph node involvement noted in humans and dogs could also be true in cats. Future studies will need to focus on this issue. Lastly, the histopathology data were obtained from pathology reports in the medical records. Over an 8-year study period, multiple pathologists from a single reference laboratory were used to assess the biopsies. Furthermore, the WHO classification of lung tumors changed during this time period.[27] Ideally, a single pathologist would have reviewed all of the samples using the current WHO definitions in order to increase the consistency of diagnosis for statistical purposes.

Conclusions

Our findings are in agreement with previous studies in that the survival time for cats with primary lung tumors is short. In addition, we have shown that the presence of respiratory signs (specifically dyspnea), pleural effusion, any stage beyond T1N0M0, evidence of metastasis, and moderately or poorly differentiated tumors are useful negative prognostic indicators for cats with primary lung tumors. The caudal lung lobes appeared to be more commonly involved; however, the clinical relevance of this remains unknown. The most common primary lung tumor in this study was adenocarcinoma. Cats in which a primary lung tumor was diagnosed prior to development of clinical signs were likely to have a low-grade tumor and longer survival times. This information is critical for decisions regarding surgery and treatment of primary lung neoplasms in cats. This study also brings into question whether surgery should be pursued in cats presenting with dyspnea and/or pleural effusion, as well as giving great support to preoperative CT scans in all cats with primary lung tumors prior to surgical consideration.

Conflict of interest The authors do not have any potential conflicts of interest to declare.

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