THESIS

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The incidence of pulmonary neoplasms in dogs

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1. Introduction

The incidence of neoplastic transformation in the lung tissues of the animals is low. This is the opposite of what is seen in the human medicine, where lung tumor incidence are quite high. Actually the estimated death rates for both females and males are higher for lung cancers than compared to breast and prostatic cancers respectively. The lung neoplasms can be grouped into being primary or secondary in origin. Among the dog population, the primary lung tumors, as compared to the secondary lung tumors, are considered to be presented in lower proportion in prevalence (Withrow, 1996). Instead, the metastasis of cancerous cells from the mammary gland, bone, liver and spleen has been the major cause of neoplastic transformation of the lung tissues.

The purpose of this paper is to compare the prevalence of primary and secondary lung neoplasms in the dogs with a detailed description of the histopathological, pathological, clinical and diagnostic findings. Prevalence here refers to the total number of cases observed over a period of time. Both the old and new cases were taken into consideration. The aim is to demonstrate the higher occurrence of metastatic lesions as compared to the primary lesions in the lungs along with showing possible breed, age and sex predispositions.

2. Literature review

The first descriptions of pulmonary neoplasms came from human medicine. Its importance was considered to be higher than that in animals because of the malignant character and frequent diagnosis among the human population. A major cause behind these neoplasms revealed that cigarette smoke was a main contributor affect in the pathophysiology. Further studies revealed that these neoplasms in the lungs were mainly of primary origin (Bertazzolo et al., 2002). This is a big difference from dogs where the opposite is true. Instead of primary neoplasms, metastatic neoplastic involvement of the lungs are more common (Bertazzolo et al., 2002). Over the course of the year, the improvement in diagnostic studies have led to increased diagnosis of lung neoplasms in the dogs. These diagnostic studies included the availability of the full anamnesis of the patients

, giving extensive information about the clinical and radiological observations followed by detailed histological descriptions of the affected lung tissues. The earliest papers describing the diagnosis of pulmonary tumors out of canine necropsies were in the period between 1928 to 1959 (Brodey et al., 1965). During this time period, 10,000 canine necropsies were performed in Ohio. Out of these necropsies, 16 primary lung neoplasms have been detected: 12 being bronchiolar carcinomas, 3 bronchial carcinomas and 1 bronchial adenoma. Out of the bronchiolar carcinomas, 2 and all the bronchial carcinomas have metastasized.

Another study during this time period has been conducted parallel in 1949 (Mulligan). In this study they have performed 1,000 necropsies on dogs and made histological examination on each. It was found that out of the histologically confirmed cases, 2 were diagnosed as being adenocarcinomas. Both of the adenocarcinomas were characterized as being highly invasive and malignant. A few years later, in Germany, 16 more dogs with adenocarcinoma have been found out of 10,000 canine necropsies.

In the other part of the world at the Pathology Department of Bombay Veterinary College, 4 case histories have been outlined (Purohit and Sardeshpande, 1967). All of these involved the metastasis of cancerous cells to the lungs. In the first case, a female bull terrier presented with swelling in the head. Suspicion of osteosarcoma of the frontal bones was made and due to the poor prognosis, the dog was euthanized. On necropsy, nodular growths of different sizes were noted in the right diaphragmatic lobes. This growth was identified to be columnar cell carcinoma. In the other patient, a skin melanoma of a male boxer attributed to the metastatic spread to the lungs. The gross appearance of the lesion showed whitish nodules. In the clinical examination, labored breathing was presented. The third case involved a mixed breed dog with swelling in the limbs. On necropsy a large mass was on the right lung lobe. Histological examination revealed the mass to be an osteofibrosarcoma. In the last case of a male mix dog, columnar cell carcinoma in the lung was diagnosed showing necrotic areas.

At the University of Pennsylvania School of Veterinary Medicine, 29 primary lung tumor cases were identified among 72,000 hospitalized patients during the time period from 1952 to 1965 (Brodey et al., 1965). Going a little bit further, in 1979 not just the presence of primary lung neoplasms was demonstrated among a closed Beagle colony but also the typical age that these tumors would develop (Taylor et al., 1979). By 1985, the scientific paper written by Mehlhaff and Mooney showed that primary lung tumors, as rare as they

are, are increasingly diagnosed and therefore treated allowing for a better prognosis. This could be attributed to further advancements in diagnostic imaging techniques. An example for such would be the usage of CT that enables the visualization of even a small mass that would not be detected by an X-ray.

Parallel to the study of the primary lung neoplasms, secondary lung neoplasms were also described. A review of canine renal carcinomas for example between the time period of 1907 to 1972 revealed that the most common area that metastasis was seen were the lymph nodes and the lungs (Lucke and Kelly, 1976). Jumping a few years ahead, in 1997, a rare tumor of the kidneys originating from the transitional cells of the pelvis was noted to be squamous cell carcinoma (Dagli et al., 1997). This tumor was seen to metastasize to the lungs as well.

The cause of lung neoplasms in dogs is not well understood as unlike in the human medicine where the major contributor behind these neoplasms is cigarette smoking. In contrast, animals under experimental conditions may develop neoplastic malformations in the lungs when exposed to smoke, dyes, insecticides or other different doses of radiation. Another experiment showed that lung carcinomas can develop from inhaling tobacco smoke, dimethylbenzanthrocane and methyl-cholanthrene. However, it has been highlighted that the true incidence of the formation of "spontaneous canine lung tumors" is not known so far (Hahn et al, 1996).

3. Materials and Methods

The lung neoplasm cases in dogs were collected and are summarized in Table 1. It is important to mention that those cases were included in this paper that had definite histopathological diagnosis. Once the histopathological diagnosis was found, than individually the cases were further researched to obtain more information regarding the complete anamnesis of the patient, pathological, clinical, and further diagnostic imaging findings of the tumor itself. Unfortunately not all of the cases had these additional information available, but the ones who did, their findings are summarized in Table 2 seen in Appendix. The pathological and histopathological records at the Szent István Unversity's Pathology Institute were the primary source of collecting these lung neoplasm cases in the

dogs along with private cases. The time period at which these were looked at was from 2002 to the present year, 2017.

3.1 Histopathology slide preparation

In all cases, slides for histological examination were prepared and analyzed by Dr. Csaba Jakab. The initial step in preparing the slides for examinations is to collect lung tissue samples post mortem which is placed into a formalin solution of 10%. It is made sure that the sample is left in the formalin for at least 24 hours allowing the fluid to penetrate even the deeper tissues. This procedure is called fixation and the purpose of it is to prevent further autolysis of the tissue and to preserve the sample. Once fixation is complete, the tissue is cut into small, thin slices and placed into tissue cassettes. These cassettes are than placed into serial alcohol solutions from low concentration to high in order to dehydrate the tissues. After dehydration, the cassettes are immersed into a solution containing xylene to remove the water, and wax is placed on the surface to make cutting easier. The next step is to embed the tissue with paraffin. This block is made by melting paraffin onto the tissue cassette and then freezing it within 2 minutes. Than with a microtome, the very thin (approximately 5 micrometer) sections are cut from the paraffin block and these slides are than placed onto water bath to remove the wax layer. Once it is complete, the slices are fished out using a glass slide. The final step is to rehydrate the slides in order for them to be stained with hematoxyline and eosin. After the staining, a cover slip is placed onto the sample in order to adhere it to the slide so it doesn't move around when it is being examined under the microscope.

3.2 Autopsy

The proper dissections of the cases were performed according to the following written instructions. In the first step, the animals were examined externally for presence of any identification marks and any significant lesions. After skinning, a visual inspection of the intact thoracic area took place, followed by cutting through the muscles of the upper third of the thorax. Than with a bone shear, the ribs were cut through. In order to separate the sternum, the attachments with the diaphragm and the pericardium were cut off. Before the

removal of the lungs together with the cervical organs (tongue, esophagus, larynx) , the opened thorax was examined for the presence of exudates. If so present, care was taken to remove it and measure the amount. Than continuing with the removal of the lung, the deep skin muscles, lifting muscles of the tongue, and the inside muscles of the neck were cut by pushing the knife close to the mandible up to the symphysis. Thus, the tongue could be grasped and with a strong movement the cervical organs could be pulled backwards. The hyoid bones were severed with a knife in order to continue the intact removal. Holding the trachea and the esophagus on one hand, the stripping backwards of the organs was continued. Finally, the lung and the heart could be taken out along with them. Any connection to the wall of the thorax was cut. The gross pathological findings could be interpreted by knowing the normal appearance of the lungs and pleura. A healthy lung can be described as having a smooth surface, color being pale brick red, and the texture soft/spongy.

The lung lesions were described by examining the following:

- Shape
- Size
- Surface
- Color
- Texture

The pleura was also examined including both the parietal and visceral sheets. The findings were compared to the normal appearance of the pleura which is:

- Smooth
- Shiny
- Transparent

4. Discussion

Usually primary lung tumors are malignant, though they could be benign as well which is not very usual. The malignant tumors are highly invasive and appear as soliter masses. Later on with the progression, the cancerous cells migrate and thus creating small masses in other lobes. Both the right and the left side of the lung became affected but more specifically the cranial, caudal, middle and diaphragmatic lobes. This metastasis to distant

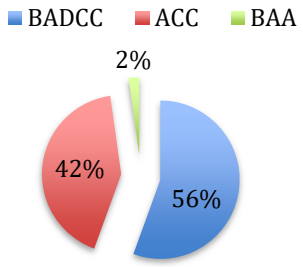
lobes can happen via hematogenous spread. As this occurs, it is hard to differentiate microscopically whether the metastasis occurred from pulmonary origin or whether it was the result of metastasis from other neoplasms located elsewhere in the body. The places that primary lung neoplasms can arise are from the conducting system (bronchogenic carcinoma), the transitional system (bronchiolar carcinoma), exchange system (alveolar carcinoma) and from the glands (bronchial gland carcinomas). In a simplified version, they can be of epithelial or of mesenchymal origin.

Secondary lung tumors are all malignant in character and arise from other malignant neoplasms located within other organs. As it will be seen in this case study, they can arise from epithelial cells as well as from mammary or thyroid carcinomas. In the other group, they can arise from mesenchymal origin as osteosarcoma, lymphoma, hemangiosarcoma or melanoma.

4.1 Primary lung neoplasm

The finding includes that out of the 200 cases, 45 were primary and 155 secondary in origin. As regarding to the definite diagnosis , out of the primary cases the following from the most prevalent to the least are listed: bronchioloalveolaris adenocarcinomas (BADCC: 25/45 =55.5%), anaplastic cell carcinomas (ACC: 19/45= 42.2%), and bronchiolo-alveolar adenoma (BAA: 1/45 = 2.2%) (Figure 1). Out of the BADCC, 17 were diagnosed as non-small cell carcinomas, and 2 as small cell carcinomas.

Figure 1. Incidence of Primary Pulmonary Neoplasms

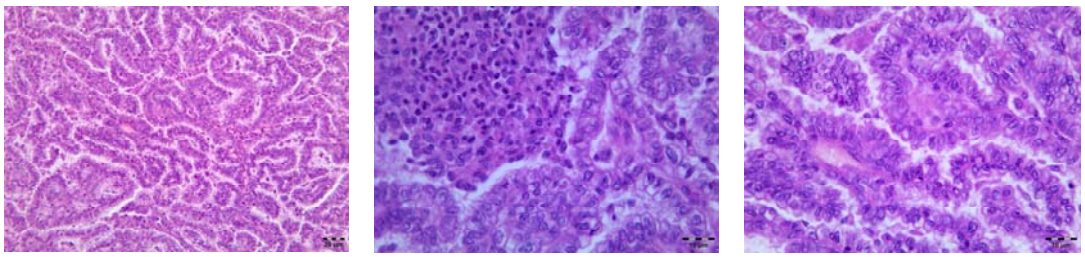


Among the primary lung neoplasms, bronchioloalveolars adenocarcinoma and anaplastic carcinomas have been found to be the most frequent type. Therefore, it will be discussed in more detail along with histiocytic sarcomas and the description of metastatic spread of primary pulmonary neoplasms.

4.1.1 Bronchiolar-alveolar carcinoma

Based on the classification as mentioned already, BADCC is classified as primary malignant pulmonary neoplasm. The cells of origin are epithelial but more precisely the distal bronchiole or alveolar regions are involved. The cancerous cells grow along the alveoli septae thus destroying it. They do not however invade the alveoli. Usually this spread is localized to one area of the lung and BADCC is termed to be soliter. However, rarely, but it can spread via the airways to other parts of the lung thus affecting a larger portion of the lung parenchyma. In this case, the BADCC is termed to be diffuse. BADCC can also be grouped into two histopathological variants: mucinous BADCC and non-mucinous BADCC. On the histopathological slides, they can exhibit a papillary, acinar or solid pattern. The tumor cells have a basophilic stain along with the cytoplasm. These tumor cells are composed of cuboidal to columnar cells forming a line (Figure 2).

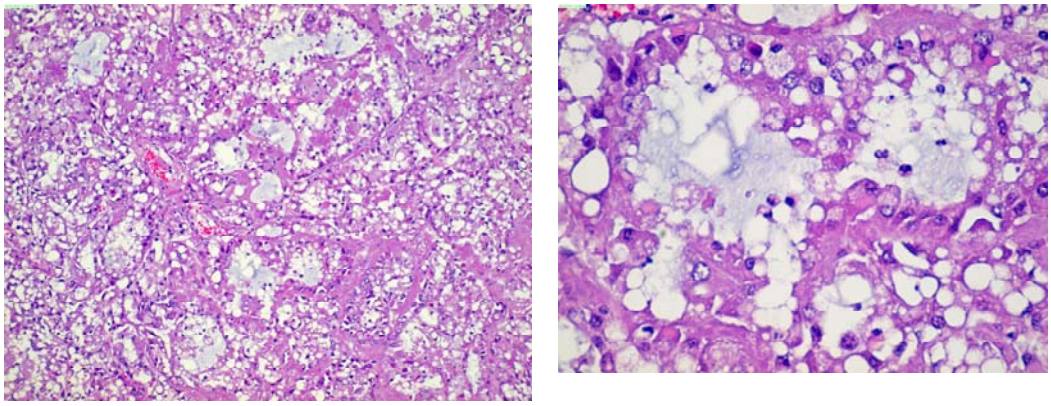
Figure 2. Hematoxylin and eosin stain of non-mucinous bronchiolar-alveolar carcinoma.



Left: 20x Middle: 10x Right: 10x

In the case of mucinous BADCC, the tumor cells consist of the same morphological appearance, but like the name contains, the cytoplasm is filled with mucinous deposition (Figure 3).

Figure 3. Microscopic image of mucinosus bronchiolar-alveolar carcinoma.



larger magnification (left image) smaller magnification (right image)

Other possible depositions which could be seen microscopically as well was described by Bertalazzo. It consist of necrotic cells, cholesterin and calcium. These calcium deposits are referred to as Psammoma bodies. It can form due to the calcification of either the tumor thrombi or the papillae tips.

On macroscopic examination of lung tissue invaded by BADCC, the metastatic spread within the lung lobes is well visible. The full cut service of a formalin prepared lung tissue revealed multifocal, white granules of variable sizes ranging from 1 mm to 1.6 cm in diameter. In the center, necrotic areas were noted (Figure 4).

Figure 4. Formalin prepared lung with bronchiolar alveolar carcinoma.

4.1.2 Anaplastic carcinoma

Anaplastic carcinomas are undifferentiated tumors that show a high proliferation of transformed cells of epithelial origin. They can be grouped into being small or large cell in origin. In the case of anaplastic small cell carcinomas, many round, small, hyperchromatic cells could be seen within the alveoli. Some neoplastic cells were found in the alveolar walls, but the overall framework of the alveoli was not destroyed. The cells stain basophilic and the round nuclei within the cells are visible (Figure 5). However, the cytoplasm is poorly seen. The cells shape range from being round, ovoid or spherical. In contrast to the variability in the shape, the size remain uniform throughout the slide.

On necropsy, superficial vessel formation can be seen along the surface of the lung (Figure 6/Left image). The lung texture on palpation felt to be firm and smooth. The lung showed mottled appearance with white to dark red in color. There is a multifocal distribution of the tumor throughout the lung lobes and on the cut surface it is visible that the whole parenchyma of the lung has been replaced by white, nodular masses and hemorrhagic areas could be noted in the deeper layers (Figure 6/Right image).

Figure 5. Anaplastic small carcinoma showing basophilic and round nuclei within the alveoli (H&E stain).

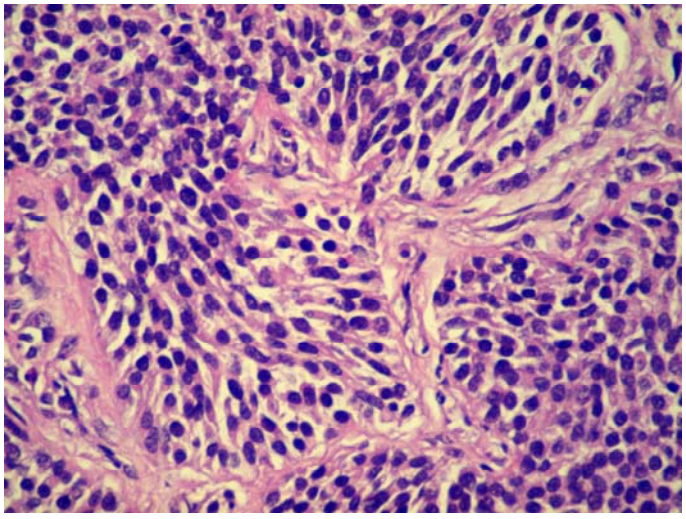
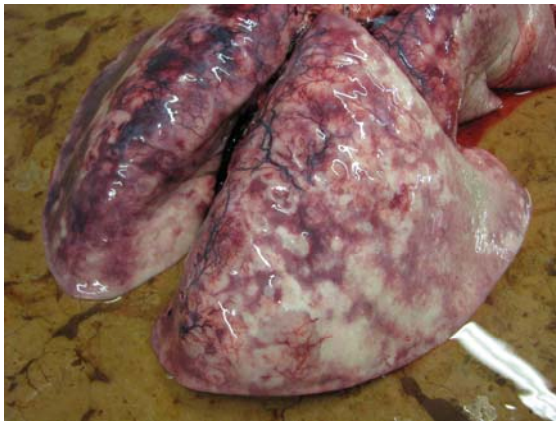
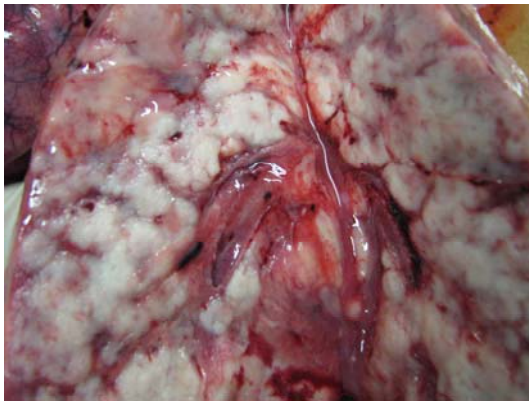


Figure 6. Gross appearance of anaplastic small cell carcinoma.



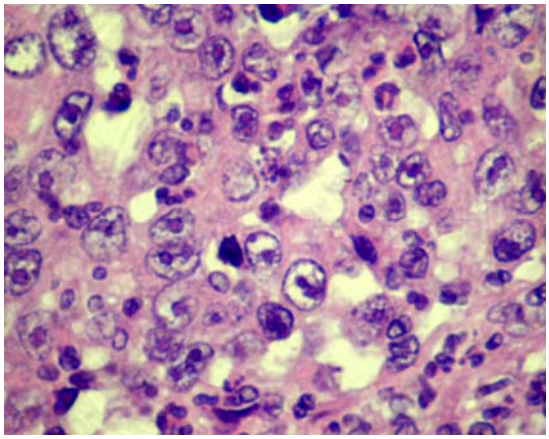
Left: Superficial vessel formation along the surface of the lungs can be noted.



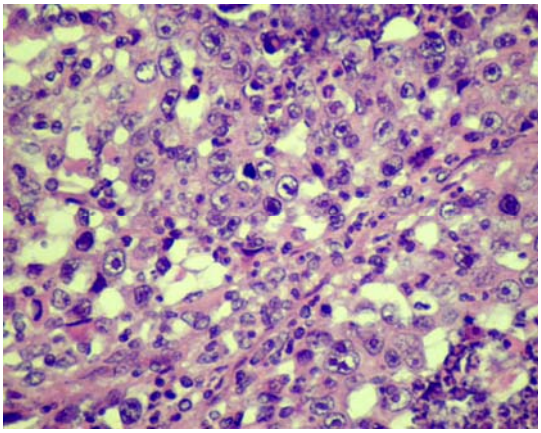
Right: On cute surface, hemorrhagic and necrotic center can be noted.

The pathological appearance of a non-small cell carcinoma is the formation of localized mass in the caudal lobes (Figure 8). The color of the mass is pale yellow. This solitary tumor is measured to be 6.5cm in diameter. On the cut surface of the tumor, the lesion appear to have whitish, nodular appearance (Figure 9). As seen in the case of small cell carcinoma, superficial vessel formation could also be noted (Figure 10). In a formalin prepared solution, the mass is well visible and can be measured to be 2.5 cm in diameter (Figure 11).

Figure 7. Magnification of large cell anaplastic carcinoma.



Large magnification



Small magnification

The large cell anaplastic carcinomas are defined as non-small cell carcinoma that lack the cytological characteristics of small cell carcinomas and squamous differentiation. As the name implies, they form larger neoplastic cells as the small carcinomas and can appear as differentiated, rosette cell type or as undifferentiated. In the differentiated form the cells are grouped forming rosettes. Whereas, in the undifferentiated form, the neoplastic cells appear in solid sheets. Other appearance that were noted in previous studies as well as in this one include the presence of numerous giant cells with both nuclear and cytoplasmic pleomorphism (Figure 7). Presence of tumor emboli in the bronchial and mediastinal lymph nodes were also seen in the same study (Bastianello et al., 1985).

Figure 8. Gross appearance large cell carcinoma forming localized lass in the lung lobe.

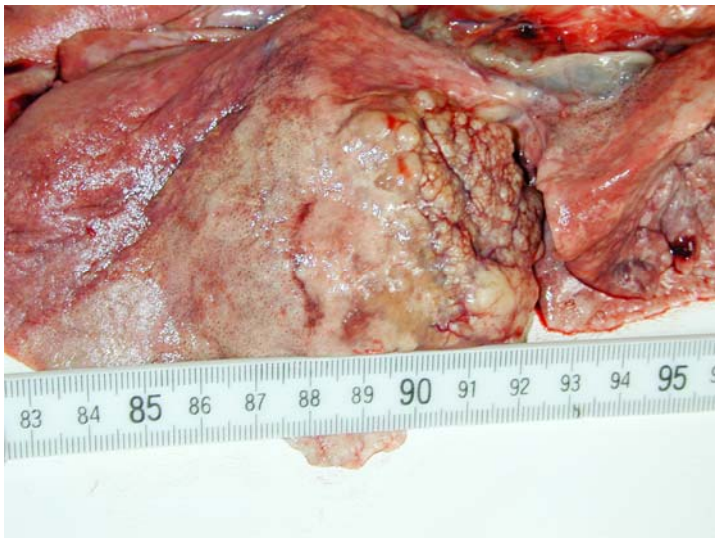


Figure 9. Cut surface of large cell anaplastic carcinoma.

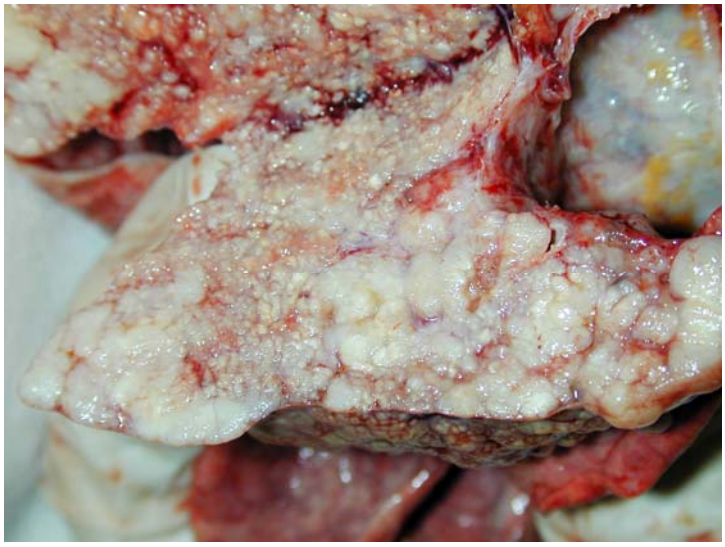


Figure 10. Superficial vessel formation with large cell anaplastic carcinoma.

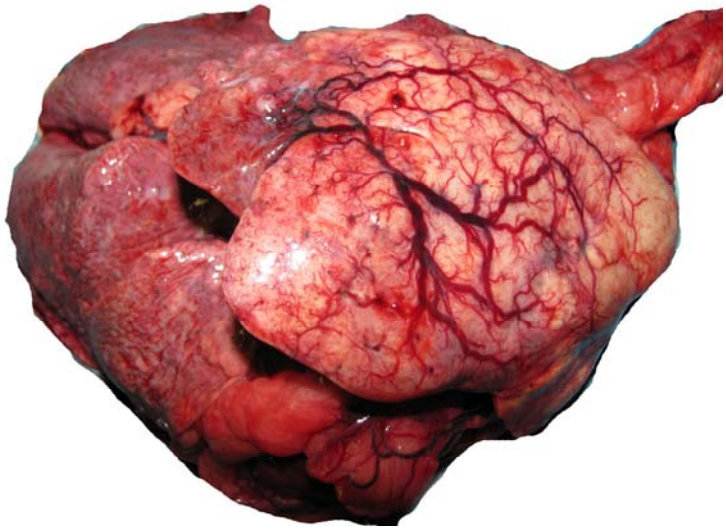
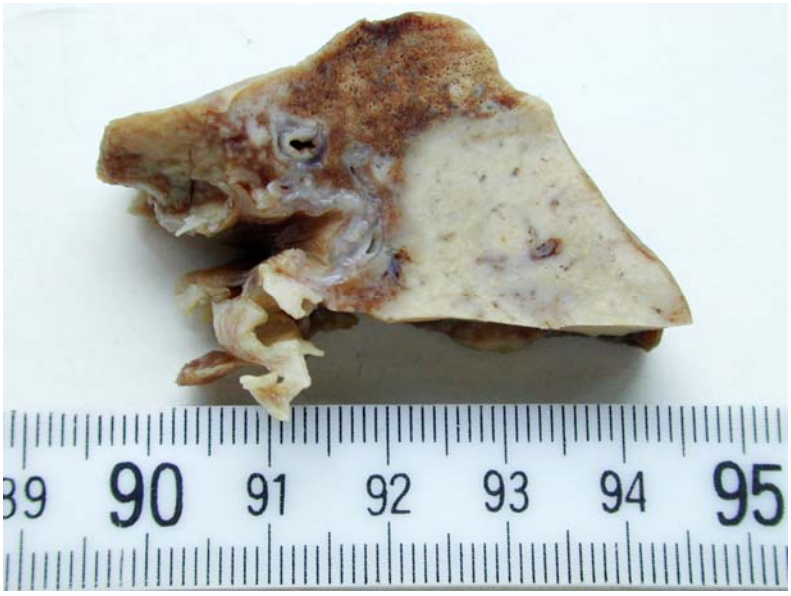


Figure 11. Formalin prepared cut tissue segment of large cell anaplastic carcinoma.

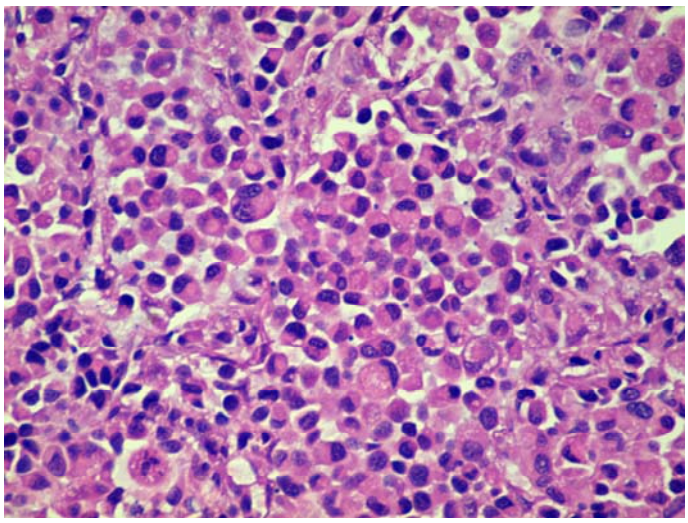


4.1.3 Histiocytic sarcoma

Histiocytic sarcomas are very aggressive tumors that result in excessive proliferation of histiocytic cells. These histiocytic cells that are involved in the malignant transformation are called dendritic antigen presenting cells. The neoplasm can be grouped into two different forms: localized, and disseminated. Out of these two groups, the lung can be primarily affected with the disseminated histiocytic sarcoma and cancerous cell metastasis to regional lymph nodes and to other organs such as the spleen and liver. Under microscopic examination, the cells show quite high of a diversity (Figure 12).

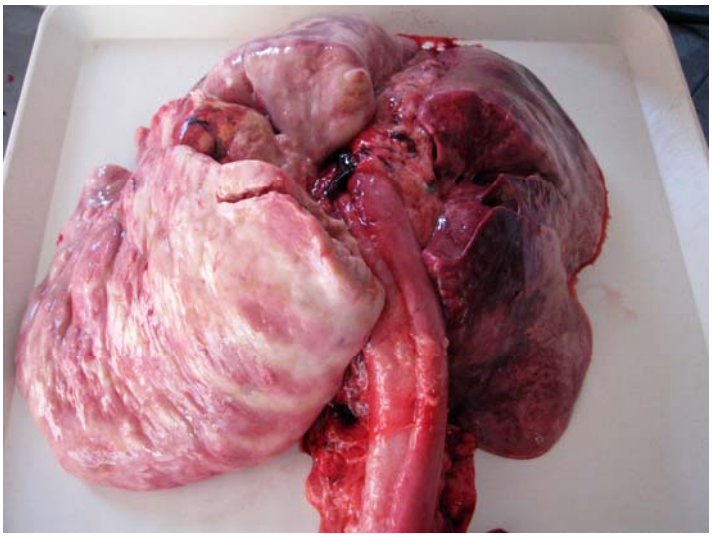
This pleomorphic character can be noted by observing spindle cells, round cells, and giant cells. Vacuolation of the cytoplasm could be noted along with mitotic figures. Similar finding was seen among nineteen cases of histiocytic sarcomas in Pembroke Welsh Corgies when examined histopathologically (Kagawa et al., 2016). The authors noted, that all the neoplastic lesions had common histological features characterized by the proliferation of pleomorphic histiocytic cells combined with various inflammatory cells.

Figure 12. Pleomorphic appearance of histiocytic sarcoma (H&E stain).



On necropsy, more than one lung lobe involvement can hint the efficient intrapulmonary spread. The lesion is different from the firm, large solitary nodules arising from the parenchyma. Instead, the whole lung appears to be uniformly firm on texture (Figure 13).

Figure 13. Gross appearance of histiocytic sarcoma.

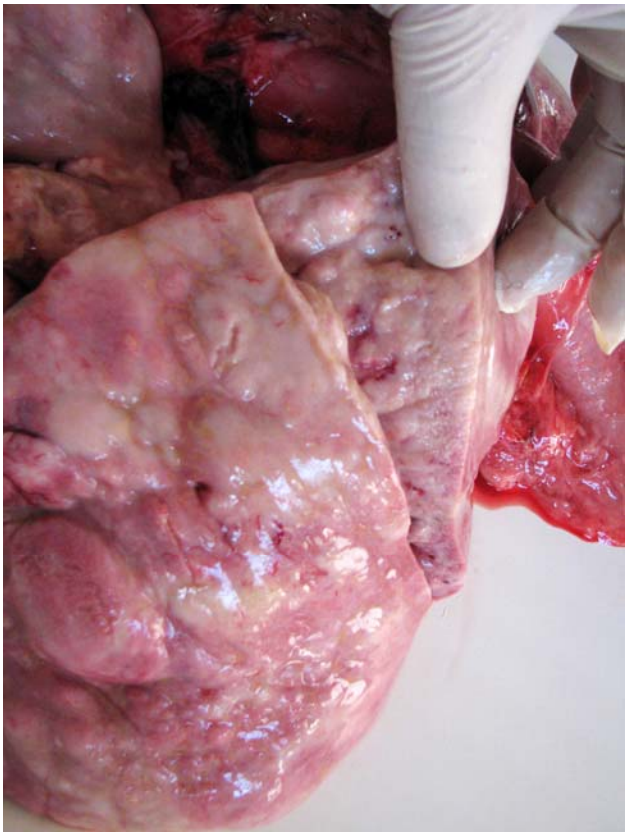


Note the mottled appearance of the right lung lobes with white to pale pink in color.

On closer examination, multifocal raised nodules can be noted with varying shape and size. On the surface of these nodules, the center does not dent inwards. This characteristic of the nodule can help differentiate sarcoma from carcinoma. Sarcomas consist of more stroma as compared to the carcinomas, and therefore the dense cartilage matrix helps hold the shape of the tumor. In contrast, the carcinomas consist of less stroma and therefore the center of the nodule on the surface will have an umbilicated pattern.

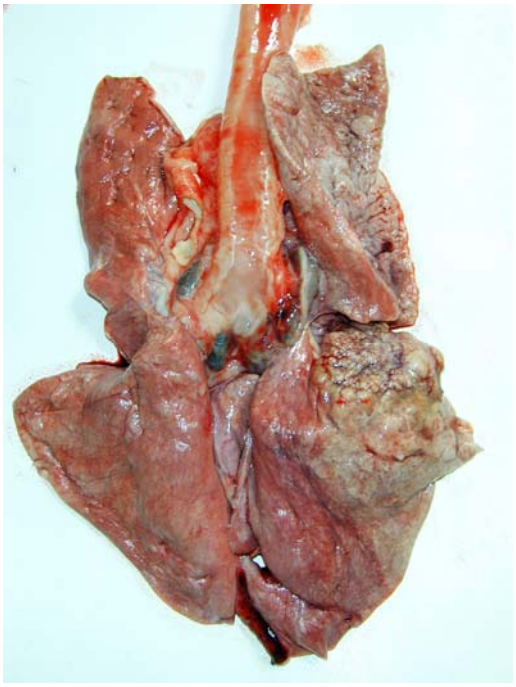
There is no superficial vascularization noted and on the cut surface, the lung parenchyma is necrotized showing complete destruction of healthy lung tissue (Figure 14). Along with the necrotic tissue, hemorrhages could be noted as well. The color of the lesion ranges from being white to light pink.

Figure 14. Cut surface of histiocytic sarcoma.



Note the raised nodules on the surface of the parenchyma.

Figure 15. Tracheo-bronchial lymph node metastasis with non-small cell anaplastic carcinoma.



4.1.4. Metastasis of primary lung neoplasms

Primary lung neoplasms showed the tendency to metastatize from the original place of formation. The frequent locations that metastasis were noted are the following: other parts of the lung lobes, the tracheobronchial lymph nodes as seen with non-small cell anaplastic carcinoma (Figure 15) and the brain.

This metastasis is achieved by intrapulmonary, hemolymhatic, and lymphatic spread of the tumor cells. As mentioned above with the necropsy findings of BADCC, the intrapulmonary spread of cancerous cells were obviously seen with disseminated nodule formations found all along the lung lobes. This type of BADCC can be termed as being diffuse. Such similar case was seen in an eight year old female German wirehaired pointer (Bertazzolo et al., 2002). The author termed this form of BADCC to be unique, because the usual necropsy lesions seen are large neoplastic masses rather than small masses involving the whole lung parenchyma. The next metastasis was seen in the brain. Within the brain, the location of the dark brown , round foci with a size of 0.5 cm in diameter was found to be

in the grey matter (Figure 16). The metastasis to the regional lymph node led to the enlargement of the tissue. This not only leads to the compression of the surrounding airways further restricting breathing, but also to the formation of pleural effusions (Figure 17). As the enlarged tracheobronchial lymph nodes exert pressure on the thoracic duct nearby, lymph fluid start to leak into the thoracic cavity restricting the expansion of the lungs. On necropsy, the hemo-lymph fluid was noted to be light pink in color.

Figure 16. Primary lung neoplasm metastasis to the grey matter.

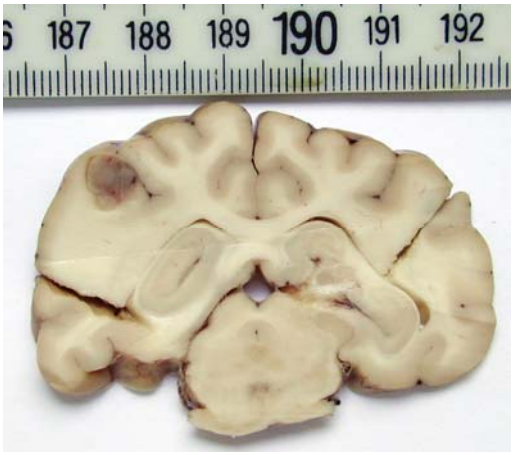
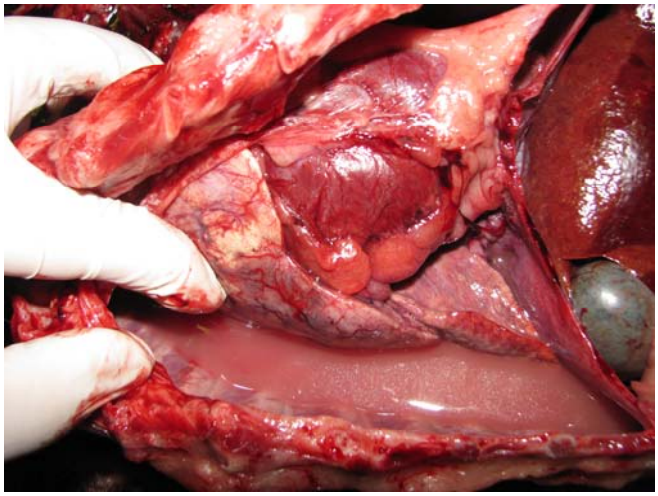


Figure 17. Hemo-lymph fluid found in the thoracic cavity of dog.



4.2 Secondary Lung neoplasm

In the case of the secondary lung neoplasms, the metastasis to the lungs originated from many different organs as seen in Table 3.

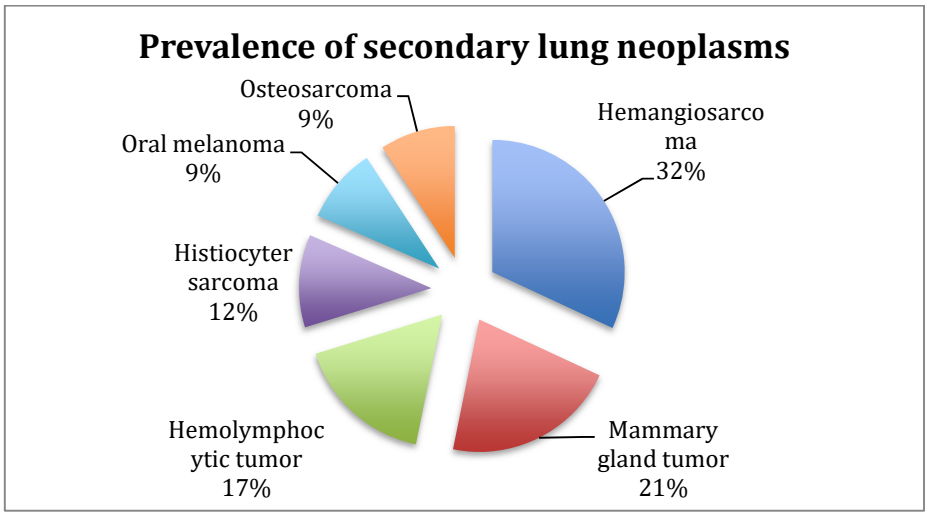
Table 3.

Origin	No. of cases	Diagnosis
Blood vessel	1	Angiomyxosarcoma
Bone	13	Osteosarcoma
Heart	13	Hemangiosarcoma
Hemolymphocytic system	11	Lymphoma
	13	Leukemia
Histiocytic cells	16	Histiocyter sarcoma
Liver	5	Hemangiosarcoma
Mammary gland	17	Simplex carcinoma
	6	Complex carcinoma
	1	Multiplex papilloma
	3	Osteosarcoma
	3	Carcinoma sarcoma
Mouth	13	Melanoma
Spleen	17	Hemangiosarcoma
Skin	4	Hemangiosarcoma
Subserosa	6	Hemangiosarcoma
Thymus	1	Carcinoma
Uroepithelium	12	Carcinoma

The end result for each was the malignant transformation of lung epithelium affecting all lung lobes. The most invasive, and rapidly growing tumor that has caused the most metastasis to the lungs were hemangiosarcomas (Figure 18).

The following are the list of secondary lung neoplasms from the most prevalent to the least prevalent: hemangiosarcomas (45/155=29%), mammary gland tumors (30/155=19.4%), hemolymphocytic tumors (24/155=15.5%), histiocyter sarcoma (16/155=10.3%), oral melanoma (13/155=8.4%) osteosarcoma (13/155=8.4%), uroepithelial carcinoma (12/155=7.7%), soft tissue-angiomyxosarcoma (1/155=0.6%) and endocrine tumors (1/155=0.6%).

Figure 18. Prevalence of secondary lung neoplasms.



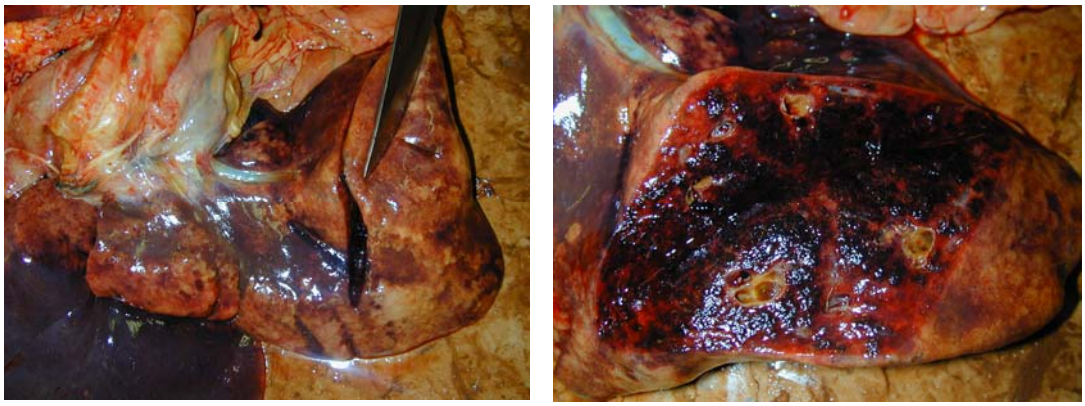
4.2.1 Hemangiosarcoma metastasis

Hemangiosarcomas are malignant tumors of the vascular endothelial cell origin. They can be divided into different groups according to the frequent sites of invasion such as the skin , spleen, liver, right atrium, and subserosal layers. As seen in the pie chart, the hemangiosarcoma from the spleen showed the highest percentage of metastasis to the lungs. One case report however described a rare form of hemangiosarcoma in a 10 year old intact male Norwich terrier dog known as primary peri-aortic hemangiosarcoma (Guinan et al, 2012). Upon analysis of the thoracic radiographs, extrapulmonary masses were detected in the caudodorsal area of the thorax. Under microscopic examination of a section of an aortic

branch, the structure was surrounded by dense cellular and hemorrhagic masses with necrosis.

Splenic hemangiosarcoma metastasis to the lungs affected every lung lobe thus can be termed to be multifocal. The lungs failed to collapse. The color of the lung tissue on the surface appeared to be yellow to dark red areas. On the cut surface, increased amounts of blood clots could be visible and on the full cut surface, hemorrhagic-necrotizing centercould be noted.

Figure 19. Splenic hemangiosarcoma metastasis to the lungs.



The appearance of liver hemangiosarcoma metastasis showed different gross pathological appearance (Figure 20). The lung appeared to be mottled with dark red to purple in color. There are diffuse, round, raised dark purple nodules which are also located at the edge of the lung tissues. A more pronounced nodular appearances of the lungs were seen with hemangiosarcoma originating from the subphrenicus tissues, skin, and the right atrium (Figure 21). In these cases, variable sized, small, dark purple nodules were seen throughout the lung parenchyma. The subphrenicus hemangiosarcoma metastasis gave widespread foci affecting the whole lung surface. These foci are raised, dark-purple nodules of variable size and shape. A sample of lung tissue with skin hemangiosarcoma metastasis was affected with small round, dark purple foci all throughout the lung parenchyma tissue. With right atrial hemangiosarcoma metastasis, the lung showed miliary pattern of numerous round dark-purple foci with variable shape and size.

Figure 20. Gross appearance of liver hemangiosarcoma metastasis (four images).

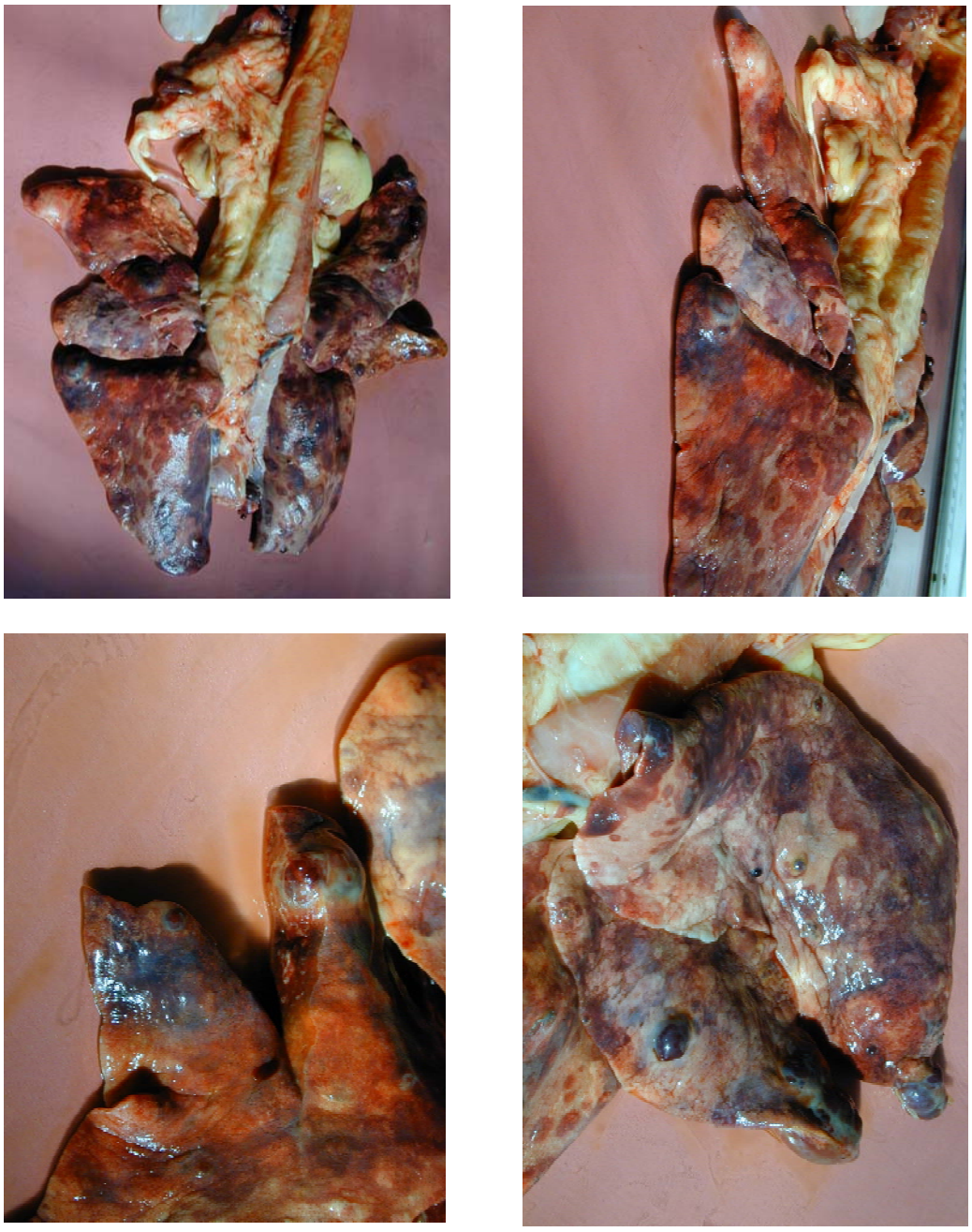
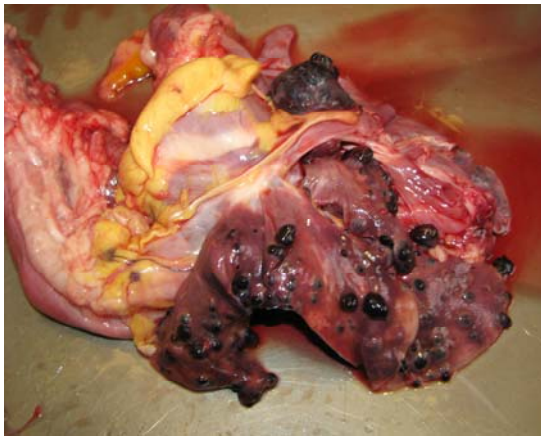
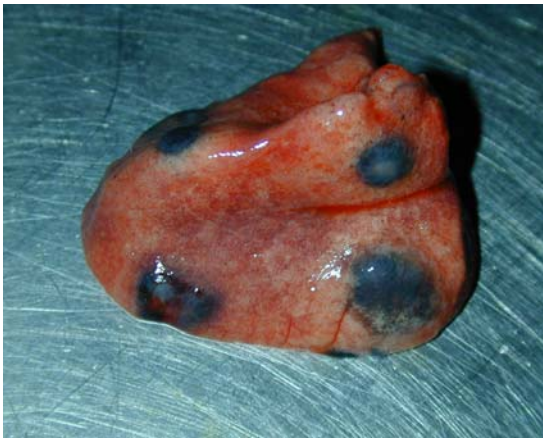


Figure 21. Metastatic nodular masses in the lung parenchym

A: Subphrenical hemangiosarcoma metastasis.

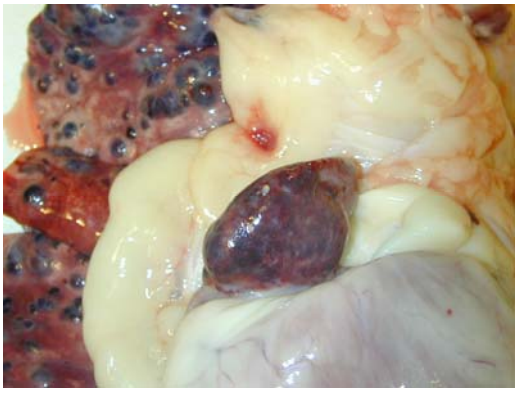


B: Skin hemangiosarcoma metastasis.



C: Right atrial hemangiosarcoma metastasis

D: Right atrial hemangiosarcoma



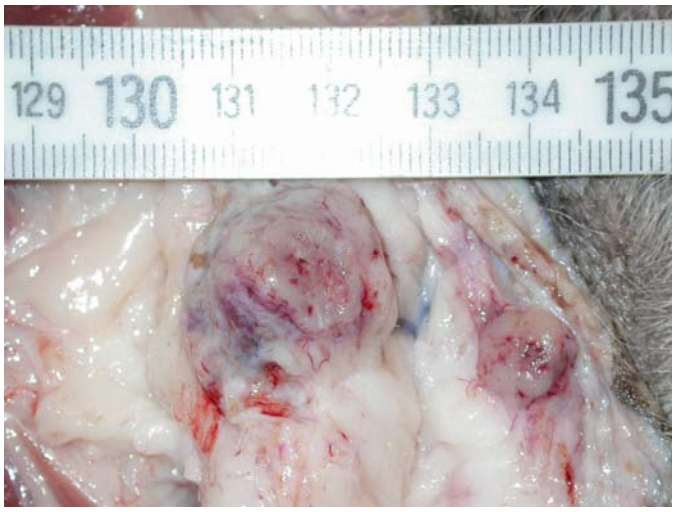
4.2.2 Mammary gland tumor metastasis

The second major tumor that has also shown a high incidence of metastasis to the lungs were the mammary gland tumors. Within the type of tumors, 17 simplex carcinomas out of the total 30 mammary gland tumors have been diagnosed with increased frequency. The simple carcinomas tend to be very aggressive locally and metastatize frequently to the lungs. In contrast, the complex carcinomas are less aggressive and metastatize less frequently to lymph nodes.

The causes of mammary gland tumors are not known exactly in dogs as compared to the mice where a single virus agent called ocornavirus is responsible for the neoplastic transformation of the mammary gland tissue. In dogs, it has been reported that estrogen or progesterone receptors were involved in the mammary gland tumors. The genetic and nutritional effects are not well understood.

Metastasis frequently develops via lymphatic tracts to the axillary and inguinal lymph nodes. The enlargement of the lymph nodes draining the mammary glands were quite evident on dissection (Figure 22).

Figure 22. The lymph node is 2 cm in diameter.



Next, the lymphatic vessels drain into the thoracic cavity facilitating lung metastasis. These lung metastatic lesions can be detected months earlier before clinical signs of mammary tumors can be seen. On gross examination of the lungs with simplex carcinomas, the cancerous lesions showed a diffuse distribution of small nodules thus affecting every lung lobe (Figure 23).

Figure 23. Different macroscopic appearances of simplex mammary gland carcinoma showing diffuse nodular pattern.

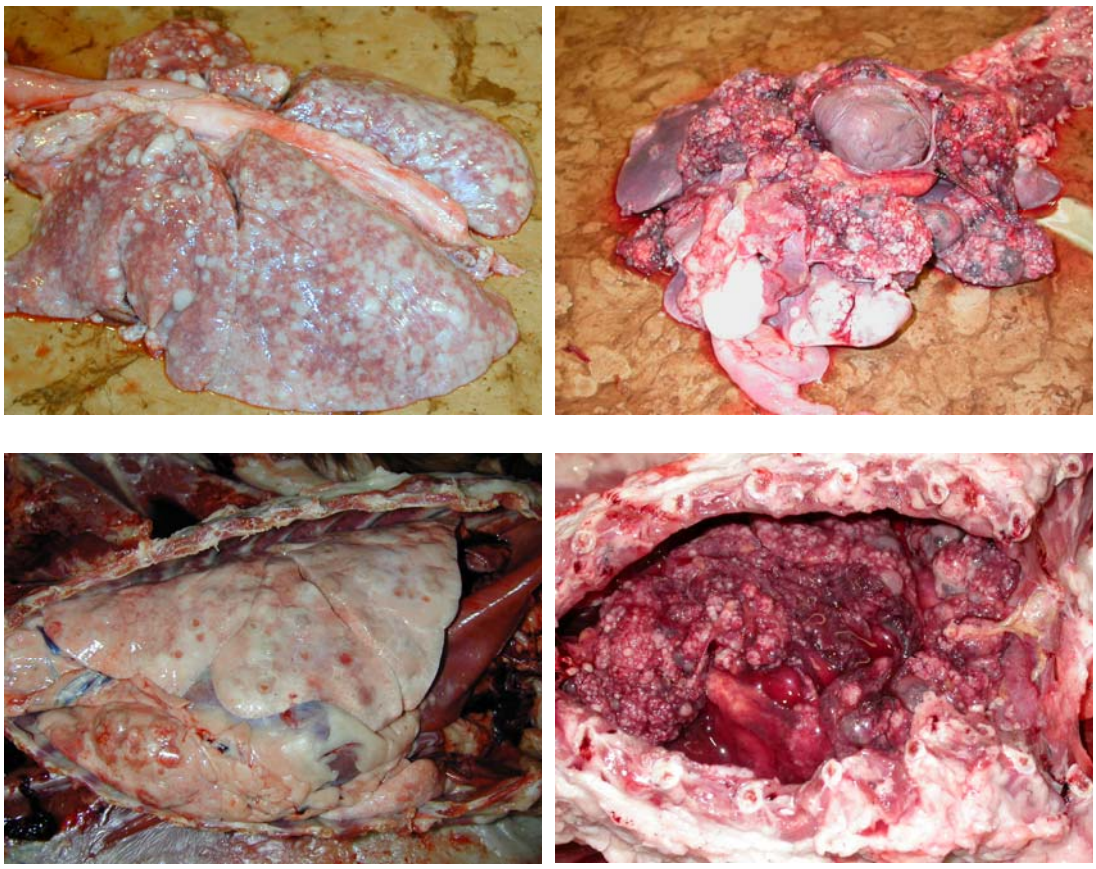
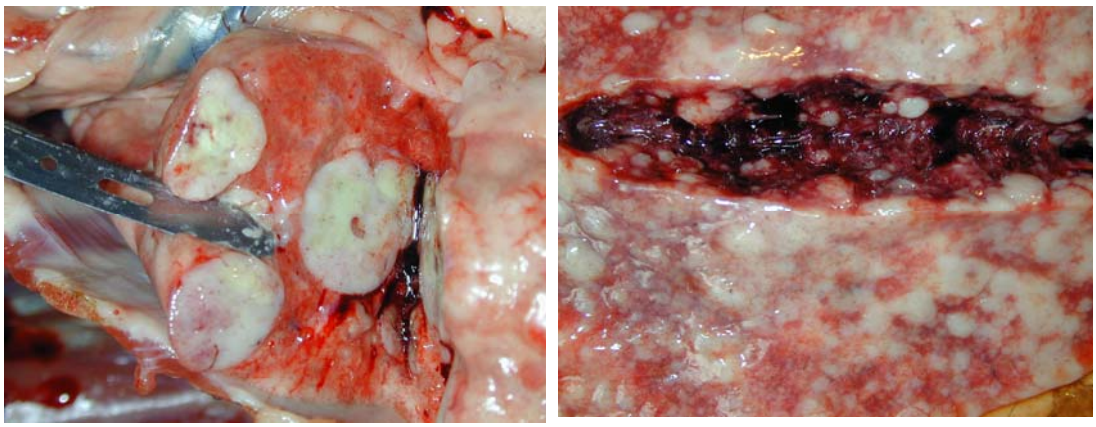
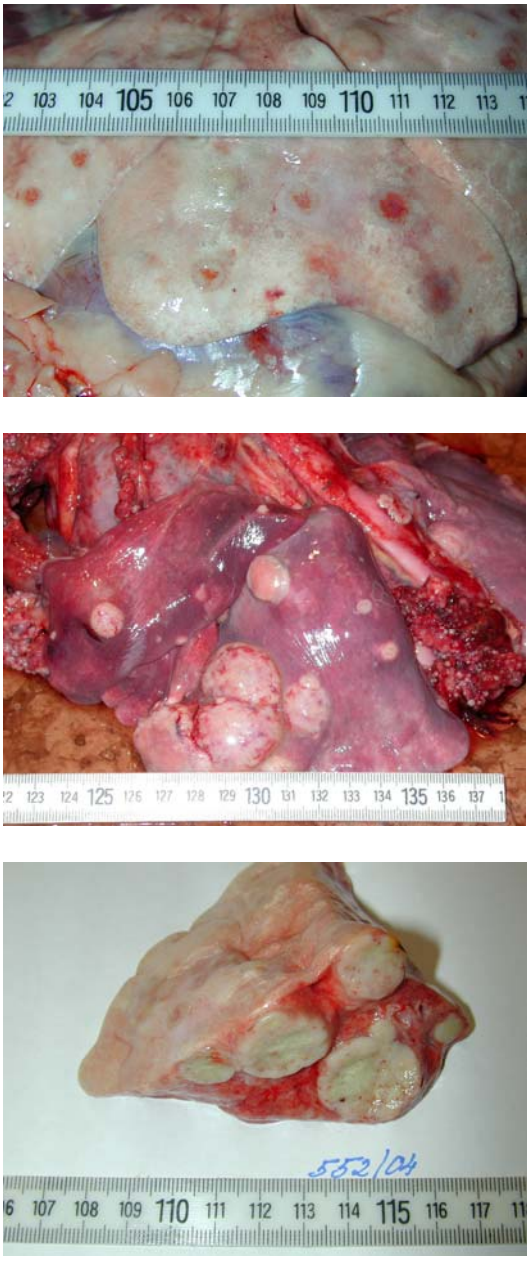


Figure 24. Cut surface of lung tissue with simplex carcinoma depicting the depthness of invasion.



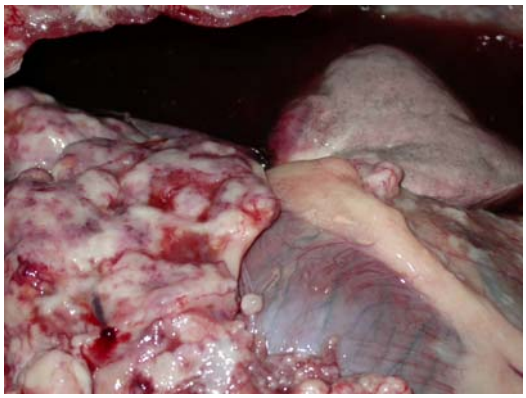
The lesions appeared as firm, white nodules scattered throughout the whole lung surface. Under cut surface examination of the lung tissue, it has been found that the nodules penetrated deep into the parenchyma as well as seen above (Figure 24). The size varied from small nodules (0,5 cm) to more larger ones (5 cm) in diameter (Figure 25).

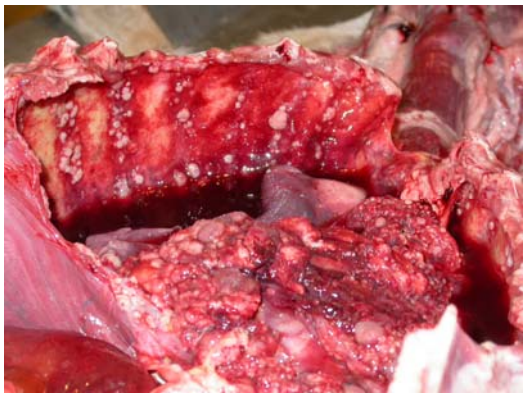
Figure 25. Variable sizes of mammary gland carcinomas present in the lungs.



As was seen with the primary lung neoplasms, the consequence with the invasion of the lungs with the secondary lung neoplasms was the development of exsudative pleuritis (Figure 26). The exudate, which was red in color, appeared in the thoracic cavity. After careful examination, the mediastinum also showed signs of metastatic lesions. These lesions were similar to the lesions found on the lungs: firm, white nodules strongly adhered to the wall of the mediastinum.

Figure 26. The consequence of exsudative pleuritic.





Under microscopic examination, the tumor cells are dominated by tubular epithelial cells which have a low to high mitotic activity and show pleomorphism. The tumor cells are surrounded by lymphocytic cells. Below is the microscopic image of primer mammary carcinoma (Figure 27) and the lung metastasis (Figure 28) depicting invasiveness.

Figure 27. Primary lung carcinoma.

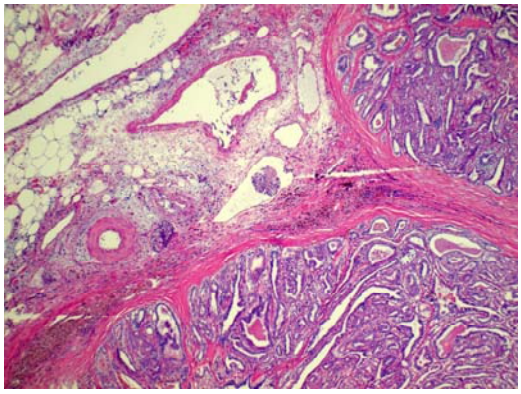
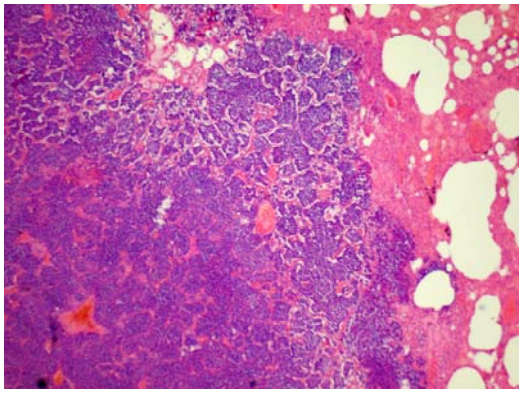


Figure 28. Lung metastasis.



4.3 Age, breed and sex predispositions

The age at which the pulmonary neoplasms occurred were analyzed separately for both primary and secondary lung tumors (Figure 29-30). The mean values were calculated in order to find the average age at which pulmonary neoplasms are more likely seen. Next to the mean value, the median values were additionally calculated as well (Figure 31). This value gives the number at which half the population is underneath that value and the other is above it. The advantage of the median over the mean is that it is not "skewed" so much by extremely small or large values. This was taken into account because the youngest age at which pulmonary neoplasm have been diagnosed was 1 year and the oldest being 16 years.

Figure 29. Ages of 45 primary lung tumor dogs

Years	Frequency	Percentage
0-5	2	4.4
10-Jun	29	64.4
15-Nov	13	28.89
16-20	1	2.2

Figure 30. Ages of 155 secondary lung tumor dogs

Years	Frequency	Percentage
0-5	3	1.9
10-Jun	64	41.3
15-Nov	86	55.5
16-20	2	1.3

Figure 31. Mean and Median age

	Primary lung tumor	Secondary Lung tumor	Lung neoplasms
Mean age	9.2	11.1	10.65
Median age	9	11	11.5

The group being the most affected with primary neoplasms were dogs between the age of 6-10 years. This age range was seen to be younger when compared to the dogs with metastatic lung neoplasm. In this group, the highest percentage was between 11-15 years of age. The overall mean and median values show that pulmonary neoplasms are more seen in older dogs above the age of 10. This result is not far from the results found in previous studies where the older aged population was highly represented as well (Mehlhaff and Mooney, 1985). Specifically, studies showed that primary lung neoplasms occurred between the age of 9 and 11, with the youngest seen at 5 and the oldest seen at the age of 17 (Hahn et al., 1996). As seen in this paper, primary neoplastic can form in earlier than 5 years of age though. This was seen with the 1-year-old female, bernese mountain dog with epithelial bronchial adenocarcinoma. Among the secondary lung neoplasms, the rate of occurance in dogs was seen at the age of 8 to 13 years with hemangiosarcoma.

The breeds being most affected were also compared. Though previous scientific article have found that the boxer is greatly predisposed to primary pulmonary neoplasms, such finding was not seen here (Brodey at al., 1965). Instead, the first two most frequently affected with the overall pulmonary neoplasms, were found to be mix and german shepherd breeds. More specifically, the cause behind why the german shepherd breed was represented was because they have a high breed predisposition to the development of hemangiosarcomas which was the main tumor seen in the secondary lung neoplasm group.

Next to the breed, the sex predilection was lastly compared and found that males seem to be increasingly affected, though with not much difference from the females (Figure 33). The male to female sex ratio was 1.06:0.

Figure 33. Comparison of male and female dogs with pulmonary neoplasms

	Primer lung tumor	Secondary lung tumor	Total
M	22	81	103
F	23	74	97

Though these conclusions have been drawn from the 200 dogs, it is not fully representative of the whole population at risk. A complete data of the dogs should be available regarding the adequate information on antemortem and postmortem findings. The limitation of the collected data are that even though histological diagnosis were obtained from each of the dogs along with the full identification of the animal, the clinical findings and necropsy data were incomplete in some of the cases. In other cases, these two data were present, but the histological diagnosis was not. The end result of this was the complete disregard of those dogs from this report. Therefore, it is important to have properly documented cases to be able to draw conclusions that is representative of the whole population.

5. Clinical Findings

The presence of clinical signs in dogs depends on the tumor size, the location of the tumor and whether there is distant metastasis to neighboring lobes, lymph nodes, pleura or to other organs.

The diagnosis of the lung neoplasms happened at an older age in the dogs when the clinical signs became evident indicating a larger lung surface involvement. These clinical signs included persistent chronic cough, dyspnea, exercise intolerance, and on auscultation the presence of stridor. As mentioned above, once the pleura been invaded, pleural effusions were detected in the thoracic cavity. In another case where the patient had a chylothorax probably due to the obstruction of the thoracic duct by the tumor, the fluid had a milky appearance.

Next to respiratory signs, general signs varied from one animal to the next. Some animals expressed lethargy, loss of appetite where in others, the physical examinations were completely negative. In patients where not just the lungs were affected but also the organs

in the abdominal cavity, than further signs were observed. In the case where the liver has been involved, icterus and anemia were present. As seen in the necropsy, primary lung neoplasms were able to metastatis to the grey matter in the brain. The dog therefore can show central nervous system signs such as ataxia, incoordination, and seizures. Sometimes the clinical signs that were expressed by the dog were not even related to the lung tumor. An example for such case would be the 6 year old Hungarian vizsla who presented with both front and hindlimb lameness. Further examination revealed acrophacia in the metaphysis of the tibia and the radius. Such atypical findings can make the diagnosis of the pulmonary neoplasms difficult by the physicians.

As documented to be part of the paraneoplastic syndrome,hypertrophic osteopathy, hypercalcemia, leukocytosis, and erythrocytosis were not detected (Ogilvie et al., 1989; Watson et al., 1993; Withrow 1996; McNiel et al.,, 1997). Other finding, which was not seen in these case studies, but has been observed in a 2002 case study with diffuse bronchiolo-alveolar carcinoma, was pulmonary hypertension (Bertazzolo et al., 2002). It is said that pulmonary hypertension is more frequent finding in human medicine and less so in veterinary medicine.

6. Diagnostics tools:

The two main diagnostics tools that were used to confirm the presence of pulmonary neoplasms were radiographic imaging and computed tomographic imaging (CT). When comparing the two methods, CT is more sensitive at detecting small nodules than radiographic imaging which can easily miss such lesions and is associated with greater diagnostic accuracy / confidence (Nemanic et al., 2006). CT imaging should also be considered to be taken in dogs in order to reliably stage the disease and to plan an effective therapeutic plan (Nemanic et al., 2006). In the past however CT wasn't used and therefore the most reliable clinical evidence to confirm lung neoplasm among 29 case studies conducted from 1952-1965 was radiographic imaging (Brodey et al., 1965). Regardless of these findings, nowadays pulmonary neoplasms are increasingly diagnosed due to the advancements in diagnostic technologies.

The lung neoplasms appear on the X-ray as radiodense masses. They can be found to form diffuse masses visible throughout the lung surface (Figure 34) or as soliter masses found in one portion of the lungs (Figure 35).

Figure 34. Diffuse nodular appearance of lung neoplasm.

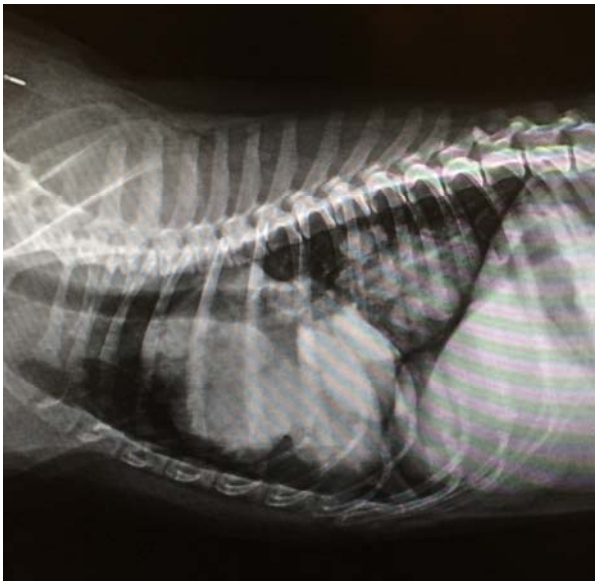
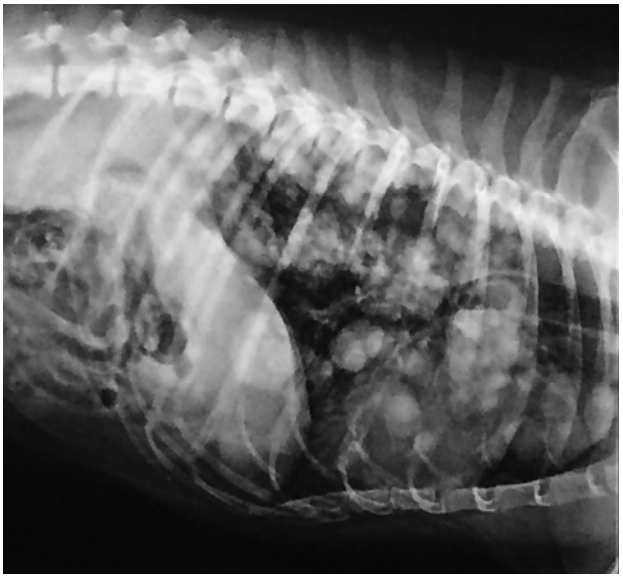


Figure 35. Soliter lung mass visible in the right upper portion of lung with heart involvement.



The main areas that were affected were the left cranial, medial, caudal lobes. The images were taken in three views thus including right lateral, left lateral and a ventro-dorsal view in order to better localize the masses and to plan the best surgical approach for the removal. A recent study went even further and demonstrated the different localization for different types of primary lung tumors (Barrett et al, 2014). They have found that histiocytic sarcomas were mostly found in the left cranial (38% ; 8/21) and right middle lung lobes (43%; 9/21), whereas adenocarcinomas were most likely to be found in the left caudal lung lobe (29%; 9/31).

On the CT, the tumors appeared as radiodense mass or as unhomogen/hypodense areas. Adhesions could be better visualized with either the mediastinum or with the pericardium. The localizations were mainly on the left side affecting the cranial, caudo-ventral, and caudal lobes.

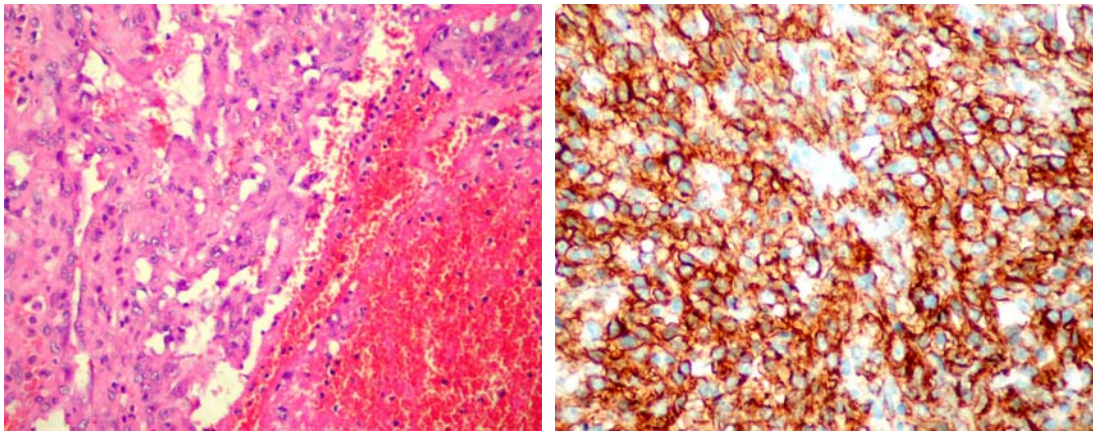
In order to obtain an exact diagnosis of the tumor type, invasive methods have to be used (Roudebush etal., 1981; Teske et al., 1991). These methods include the following: fine needle aspiration, bronchoalveolar lavage, bronchoscopy and thoracotomy. Out of these, the same authors found that fine needle aspiration method is the least invasive type. It is a simple method, which does not require generalized anesthesia, and it is regarded as a safe procedure as well. Severe complications may arise though (hemorrhages, pneuomothorax) but it has been found to be directly related to the dogs age (Teske et al., 1991).

Along with preparing histological slides for diagnosing neoplasms, the use of immunohistochemistry can also aid in the final diagnosis. It is very helpful because it can differentiate whether the neoplasms are malignant or benign and their stage/grade. Most importantly, it can determine the cell of origin and therefore the site of primary neoplasm.

The basis lies on the physiological process of antigen and antibody bindings. The target antigen, which is of interest, binds to the primary antibody being added. Next a secondary antibody is added coupled with a reporter molecule. This complex binds to the primary antibody with high specificity. Than a chemical solution is added that reacts with the reporter molecule creating a color change and this is what is visible under the microscope. The real usefulness of immunohistochemistry can be seen with the study conducted on using Claudin 5 proteins as a differential marker of canine hemangiosarcomas (Jakab et al., 2009). These proteins are found in the tight junctions. It has been found that the proteins are useful in distinguishing hemangiosarcomas from other sarcomas of different origin with hemorrhages

(Figure 36). In addition, using the Claudin 5 protein marker, more canine hemangiosarcomas were diagnosed as compared to using CD31 which is known as cluster of differentiation 31.

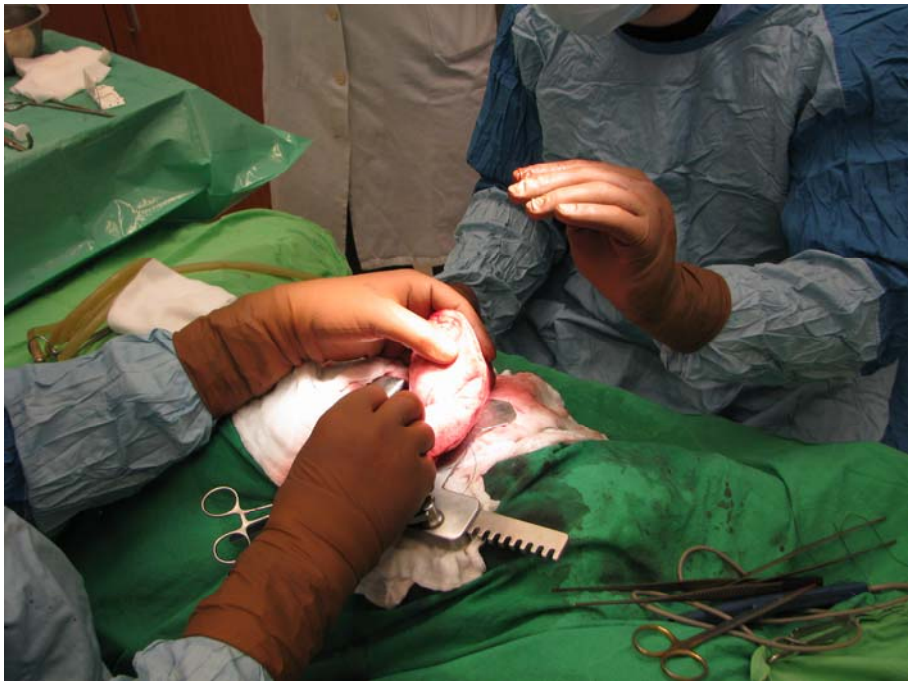
Figure 36. Canine hemangiosarcoma.



Left: H&E stain

Right : claudin 5 immunohistochemistry

Figure 37. Surgical procedure of opening of the thoracic wall (thoracotomy) combined with partial or complete removal of the lung known as lobectomy.



7. Treatment

In most of the cases, the first treatment of choice for pulmonary neoplasms is the surgical excision of the mass via lobectomy (Figure 37). This is accomplished by complete or partial removal of the involved lung lobe. Sometimes along with lobectomy, adhesiolysis were performed due to the spread of the tumor to the mediastinum. Once the thorax is opened and the affected lung lobes removed, visual examination and palpation of the nearby lung tissues and lymph nodes are performed to detect further metastatic lesions. From the removed lung tissues, samples are cut off and placed into a jar with formalin solution to be sent for further histological examination to determine the origin of the mass.

The postoperative time is a critical period ranging from 2-4 days during which the animal is hospitalized and monitored frequently. Complications usually arise from damaging anatomical structures, poor anesthesia control, or due to respiratory failures. The most common complications to monitor for are the formation of atelectesia, bronchospasm and pleural effusions. The placement of a drain into the thorax before closure minimizes the possibility of the third complication to form. The color and the amount is observed and if there is a decreased amount produced and it does not contain blood, than it could be removed. Simultaneously next to the drain management, the animals receive a broad spectrum antibiotic treatment intravenously along with the fluid therapy. Thoracotomy is considered as a painful intervention and animals experience increased amount of pain postoperatively. Therefore proper pain management is crucial. This is achieved by either systemic administration of opiods, NSAID, epidural/intrapleural blocks, or epidural analgesia.

Next to drug administrations, radiographic images are taken in 3 views including left lateral, right lateral and dorsoventral views to look for any postoperative complications such as adhesion formations, pleural effusions, and pneumothorax formation. Once the animals become stable and regain full pulmonary and respiratory functions, the owner at home continued medical treatments. The animals were continued on broad spectrum antibiotic along with painkillers and the order of movement restriction. Than scheduled checkups were made to check the healing of the wounds along the suture line.

The thoracoscopy on the other hand is a procedure that is less invasive than thoracotomy, but is performed on patients with small soliter pulmonary neoplasms. The procedure consists of making a small incision on the thoracic wall and removing the masses

via endoscopy. However, its use remains limited cause it does require special equipment. The advantage is that the recovery time is shorter and there is less amount of pain for the patient postoperatively.

Other possible treatments for pulmonary neoplasms would include chemotherapy and irradiation. The drugs that would be either used as a single or as a multidrug therapy include cisplastin, mitoxantrone, and doxorubicin. Next to the systemic chemotherapy, recent studies have mentioned inhalant chemotherapy with less encouraging results though. Among the irradiation therapy methods, the so called intensity-modulated-radiation therapy is considered as a new method that has been found to be successful among dogs.

There were two cases for which surgery was the initial treatment of choice, but once the spread of tumor has been seen in other organs, the end result was euthanasia with the owner's compliance. Such case was a 9 year old male basset hound in which laparotomy was performed due to the previous diagnosis of a renal tumor via ultrasound and during the surgery it has been noticed that the tumor has spread to the liver and the larger vessels. Through the palpation of the diaphragm, a fist sized mass could be felt on the lungs. Since the prognosis by the surgeon was determined to be grave, the dog was euthanized on the table. The next case was a 9 year old female boxer in which case intraoperatively the primary lung tumor was seen in the medial lung lobe however small metastatic lesions were present in all lobes of the lung along with the lymph nodes.

8. Prognosis

Generally the prognosis of lung tumors is poor, but early detection can increase mean survival time. There are several parameters that play a role in determining the prognosis and thus include the cell type, the size of primary tumor, the location within the lung lobe, presence of clinical signs and the presence of lymph node metastasis. A report mentioned that out of these, the presence of metastasis and the cell type were found to be important (Cheryl et al., 1985). The same report also noted that among primary pulmonary neoplasms, adenocarcinoma had better prognosis (mean 19 months) than compared to squamous cell carcinoma (mean 8 months) due to its diffuse appearance.

The Veterinary Society of Surgical Oncology determines the prognosis for lung neoplasms according to the tumor location, size, lymph node involvement, tumor histology and tumor grade. They reported that the mean survival time for primary neoplasms is 361 days, and for secondary neoplasms 176 days.

In this case study, most of the patients that underwent lobectomy survived the postoperative period and were scheduled in to receive chemotherapy. There was one dog that has died after the surgery due to the loss of approximately 50% of breathing surface. This was a 13 year old, female Transylvanian hound. Once on the surgery table, a large soliter tumor mass was detected in the right medial lung lobe. Further metastasis signs were seen in the pericardium and in the nearby lung lobes. In the end, the middle, caudal and accessory lobes of the right lung had to be resected. The dog did not survive the night.

9. Summary

The incidence of primary and secondary lung tumors in dogs have been observed over a time period from 2002 to 2017. Only histopathologically confirmed cases were taken into consideration when arriving at the conclusion. Out of the total 200 lung neoplasm cases, 45 of them were primary and 155 were of secondary origin. Further examination revealed that among the primary lung neoplasms, bronchioloalveolaris adenocarcinomas (25/45) and among the secondary lung neoplasm, hemangiosarcoma metastasis (45/155) were found to be most prevalent. The overall age group that has been seen to be at increased risk of developing lung neoplasms were above the mean age of 10.65. As regard to the sex predisposition, the males were seen to be greatly represented as females, though with not much of a difference. Among the breeds, the mix and german shepherd breeds were found to be representing most of the lung neoplasm cases. Metastasis of the primary lung neoplasm spread to either other lung lobes, to tracheobronchial lymph nodes, and to the brain.

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12. Appendix

12.1 Tables

12.1.1. Primary lung neoplasms

Epithelial non-small cell carcinoma BADCC			
M	Breed	Age (year)	Sex
1	Staffordshire	8	M
2	Mix	11	M
3	Hungarian vizsla	8	F
4	Cocker spaniel	7	F
5	Mix	11	M
6	Alaskan Malamute	9	F
7	Mix	9	M
8	Mix	7	F
9	Boxer	8	M
10	Fox terrier	7	M
11	Mix	8	F
12	German shepherd	8	M
13	Mix	9	F
14	German shepherd	8	M
15	Mix	10	F
16	Labrador	9	M
17	Mix	8	M
Epithelial small cell carcinoma BADCC			

18	German shepherd	9	M
19	Mixed	7	F (spayed)
Epithelial BADCC			
20	Cocker spaniel	8	F
21	Gordon Setter	13	M
22	Mixed	12	F
23	Mixed	16	M
24	Bernese Mountain Dog	1	F
25	Mixed	9	M
26	Canary Mastiff	8	F
27	Mixed	11	M
28	Hungarian vizsla	6	F
29	Transylvanian Hound	14	F
30	Beagle	4	M
31	Hungarian vizsla	14	F
32	West Highland Terrier	12	F
33	Large Schnauzer	10	M
34	Mixed	10	M
35	Beagle	10	F (spayed)
36	English Cocker Spaniel	8	F
37	Transylvanian Hound	13	F (spayed)

38	Mixed	12	F (spayed)
39	Mixed	14	M
40	Mixed	10	M
41	West Highland Terrier	10	M
42	Mixed	13	M
43	Mixed	9	F(spayed)
44	Mixed	13	F (spayed)
Bronchiolar-alveolar adenoma			
45	Mixed	9	F

12.1.2 Secondary lung neoplasms

Skin s.c hemangiosarcoma			
1	Mix	7	F
2	Hungarian vizsla	11	M
3	Argentine Dog	9	F
4	Hungarian vizsla	11	M

Spleen hemangiosarcoma			
5	Mix	12	M
6	Rottweiler	10	M

7	Daschund	13	M
8	Mix	11	F
9	Irish Setter	12	F
10	Mix	9	F
11	German Shepherd	12	M
12	German Shepherd	10	F
13	Mix	14	M
14	German Shepherd	11	M
15	Mix	15	F
16	Rottweiler	8	F
17	Alaskan Malamute	11	M
18	German Shepherd	8	M
19	BerneseMountain Dog	4	M
20	Puli	11	M
21	Mix	7	M

Right Atrial Hemangiosarcoma			
22	Mix	11	M
23	German Shepherd	9	F
24	German Shepherd	11	M
25	German Shepherd	9	M

26.	Mix	12	M
27	German Shepherd	13	F
28	Boxer	9	M
29	German Shepherd	10	M
30	German Shepherd	11	M
31	German Shepherd	15	M
32	Kuvasz	12	F
33	Mix	10	M
34	Mix	11	M

Liver Hemangiosarcoma			
35	Mix	12	F
36	German Shepherd	9	F
37	Miniature Schnauzer	12	F
38	Mix	12	F
39	German Shepherd	8	F

Subserosal hemangiosarcoma			
40	German Shepherd	11	F
41	Mix	12	F
42	Mix	9	F
43	Mix	12	F
44	Mix	11	F
45	Mix	8	M

Mammary gland simplex carcinoma			
46	Mix	13	F
47	Rough Collie	9	F

48	Boxer	10	F
49	Mix	11	F
50	Mix	14	F
51	Daschund	15	F
52	Caucasian Shepherd Dog	12	F
53	Mix	12	F
54	Mix	11	F
55	Mix	13	F
56	Puli	14	F
57	Mix	14	F
58	Mix	11	F
59	Daschund	15	F
60	Mix	16	F
61	Mix	11	F
62	Daschund	13	F

Mammary gland multiplex papilloma			
63	Mixed	13	F

Mammary gland complex carcinoma			
64	Mix	14	F
65	Husky	11	F
66	Mix	11	F
67	Boxer	10	F
68	Puli	14	F
69	Mix	12	F

Mammary gland osteosarcoma			
70	Mix	12	F
71	Mix	12	F

72	German Shepherd	11	F

Mammary gland carcinoma sarcoma			
73	German Shepherd	12	F
74	Mix	14	F
75	Central Asian Shepherd Dog	10	F

Histiocyter Sarcoma			
76	Bernese Mountain Dog	12	F
77	Mix	13	M
78	Rottweiler	12	M
79	Bernese Mountain Dog	11	M
80	Bernese Mountain Dog	12	M
81	Beagle	12	M
82	Mix	11	M
83	Mops	7	F
84	Mix	12	M
85	Bullmastiff	9	M
86	German Shepherd	11	M
87	Labrador Retriever	9	M
88	Mixed	10	F(spayed)
89	Basset Hound	11	F (spayed)
90	Sharpei	10	M
91	Mixed	12	M

Oral melanoma			
92	Cocker Spaniel	11	M

93	West Highland Terrier	12	M
94	West Highland Terrier	10	M
95	Mix	11	M
96	Mix	10	M
97	Beagle	11	F
98	Miniature Schnauzer	9	F
99	Mix	14	M
100	Rottweiler	11	M
101	Hannover Hound	11	M
102	Poodle	15	F
103	Miniature schnauzer	11	M
104	Rottweiler	12	M

Hemolymphocytic tumors- Lymphoma			
105	Cocker spaniel	13	M
106	Cocker spaniel	3	F
107	Mix	9	M
108	mIX	8	M
109	Puli	11	F
110	German shepherd	7	F
111	Mix	11	M
112	Cocker Spaniel	9	F
113	German Shepherd	10	M
114	English Mastiff	8	F
115	Bernese Mountain Dog	12	F

Hemolymphocytic tumors-Leukemia			
116	Mix	13	M

117	Mix	8	F
118	German Shepherd	11	F
119	Mix	9	F
120	Mix	10	M
121	Staffordshire	8	M
122	Alaskan Malamute	8	M
123	Staffordshire	6	M
124	German Shepherd	8	M
125	English Bulldog	2	M
126	Dog	8	M
127	German Shepherd	6	M
128	Cocker Spaniel	8	M

Bone Osteosarcoma			
129	Labrador Retriever	8	M
130	Rottweiler	9	M
131	Mix	11	M
132	Great Pyrenees	7	M
133	Dog	8	F
134	Mix	7	M
135	Puli	9	M
136	Labrador retriever	8	M
137	Mix	8	F
138	Mix	8	M
139	Moscow Watchdog	8	M
140	Central Asian shepherd dog	7	M
141	Cane Corso	9	M

Endocrine tumors-Thymus carcinoma			
142	Mix	16	F

Uroepithelial cell carcinoma			
143	Mix	8	M
144	Mix	8	M
145	Beagle	8	M
146	Border Collie	12	M
147	Hungarian vizsla	12	F
148	Pointer	14	M
149	Hungarian vizsla	13	F
150	Puli	12	F(spayed)
151	Mix	10	F
152	Beagle	10	M
153	Mix	11	M
154	Basset Hound	9	M

Soft tissue neoplasm-Angiomyxosarcoma			
155	French Bulldog	8	M

12.1.3 A summary of case histories of dogs with Pulmonary Neoplasms

Case # Breed	Age (yr) Sex	Clinical signs	-Location (lung lobe) -Sample	Origin	Diagnosis	Treatment
1. Cocker spaniel	8 F	Lethargiclo ss of appetite	- -Lung	Primary	Bronchial adenocarcinoma	-
2. Hungarian vizsla	6 F	Lameness Normal physical examinatin	-Right caudal lobe -Lung	Primary	Bronchiolo-alveolar carcinoma (tibia/radius metaphysis acropachia	lobectomy
3. Gordon setter	13 M	Dyspnoe, cough	-Caudal lobe -Lung	Primary	Bronchial Adenocarcinoma	-
4. Mixed (spayed)	10 F	-	- -Lung, Adrenal glands	Secondary	Histiocytaer sarcoma	-
5. Mixed	12 F	Cough,dysp noe	-Right cranial lobe -Lung	Primary	Mucoid type bronchiolo-alveolar adenocarcinoma Sentinel lnn metastasis Intrapulmonary metastasis chylothorax	-
6. Basset hound (spayed)	11 F	Icterus, Enlarged lnn lethargy	-Multiplex masses -Lung, Pancreas, liver	Secondary	Lnn generalized metastasis, aggressive histiocyter sarcoma Pancreas/liver enlarged	-
7. German shepherd	8 F	Lateral recumbency Weak vomitus	- -Lung, Liver	Secondary	Hepatocellular carcinoma metastasis to lung and lnn.	-
8. German shepherd	9 M	Cough, Inspiratory dyspnoe	- -Lung	Primary	Mixed small cell size adenocarcinoma/carcin oma	-
9. Mixed (spayed)	7 F	Lethargy Lateral recombecny	- -Lung	Primary	Small cell BAC Metastasis to kidney, pancreas,spleen	-
10.	4	Lethargy, anemia	-Multiplex masses	Secondary	Hemangiosarcoma metastasis to lung	-

Bernese Mountain dog	M		-Lung			
11. **Shar-pei**	10 M	Stridor lethargy	-Right diaphragmatic lobe -Lung, Liver and Kidney	Primary	Malignant histiocytosis metastasis Lung: primer BAC?!	Euthanasia
12. **Boxer**	10 F	-	-Right caudal lobe -Lung, Mammary gland and Kidney	Primary	Lung: Primer BAC Mammary gland: complex carcinoma Kidney: metastatic carcinoma	-
13. **Bernese Mountain dog**	12 F	Icterus	-Right middle lobe -Lung, spleen, heart	Secondary	Multicentric malignant lymphoma	-
14. **Transylvanian hound**	14 F	Icterus	-Right /left caudal lobe -Lung	Primary	BAC	-
15. **Rottweiler**	12 M	Submandibular region enlarged	- -Skin, Thorax fluid cytology	Secondary	Oral malignant melanoma Due to cell morphology: sarcoma in lung	-
16. **Mixed**	12 M	-	- -Lung Thymus	Secondary	Disseminated histiocyter sarcoma	-
17. **Mixed**	13 F	-	- -Lung, Mammary gland	Secondary	Mammary gland multiplex papilloma metastasis	
18. **Puli**	14 F	-	- - Mammary gland, Lung, Liver	Secondary	Mammary gland carcinoma metastasis to liver and lung	-

19. **Beagle**	4 M	-	- -Lung	Primary	BAC	-
20 **Mixed**	11 M	-	- -Lung	Primary	Bronchus gland carcinoma	-
21 **Puli**	11 M	-	- -Lung	Secondary	Hemangiosarcoma metastasis to lung	
22. **Mixed**	16 M	-	- -Lung	Primary	Bronchiolo-alveolar adenocarcinoma	-
23. **Mixed**	12 F	Enlarged superficial lnn. Enlarged mammary glands	- - Mammary gland, Lung	Secondary	Mammary gland invasive tubulopapillaris carcinoma metastasis to the lung	-
24 **Mixed**	7 M	-	- -Lung, liver	Secondary	Hemangiosarcoma multiplex metastasis from spleen	-
25. **Basset hound**	9 M	Regular, rhythmic breathing General condition normal	- -Lung, Kidney	Secondary	High grade anaplastic tumor with widespread necrosis	Right sided nephrectomy Laparotomy: metastatic spread of tumor to liver/large vessels, through diaphragm fist sized lung tumor felt Euthanasia
26. **Hungarian vizsla** **(spayed)**	14 F	General condition normal Cough, stridor	- -Lung	Primary	Bronchiolar-alveolar carcinoma	Lobectomy
27. **w.h.w terrier**	12 F	Cough	-Left cran. Lobe -Lung	Primary	Bronchiolar-alveolar carcinoma	Lobectomy
28. **Mixed**	9 F	-	- -Lung, Liver	Primary	Multifocalis bronchiolar-alveolaris adenoma with anthracosis in lnn.	-

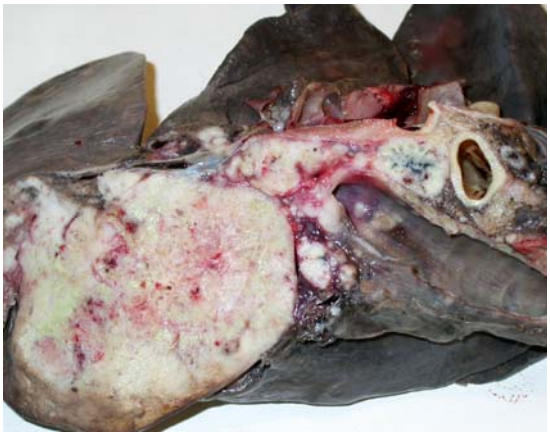
					Fibrotic lung, anthracosis in lnn. Related to liver parenchyma atrophy, lipidosis with cholastasis	
29. **Large schnauzer**	10 M	Physical exam: neg. Breathing normal	-Left cran. Pars caudalis lobe -Lung	Primary	High grade bronchiolar-alveolar carcinoma Lnn. metastasis	Lobectomy
30. **Mixed**	10 M	Elevated WBC	- - Lung	Primary	Carcinoma metastasis, non-mucoid	-
31. **Beagle** **(spayed)**	10 F	Cough	-Left caudal lobe -Lung	Primary	Soliter Bronchiolar-alveolar carcinoma	Lobectomy
32. **English cocker spaniel**	F	-	-Left cran. Lobe -Lung	Primary	Mucinus, soliter Bronchiolar-alveolar carcinoma	Lobectomy
33. **Transylvanian** **Hound** **(spayed)**	13 F	Physical exam neg. Normal breathing	-Right middle lobe Spread to caudal lobe and pericardium -Lung	Primary	Non-mucoid, soliter Bronchiolar-alveolar carcinoma	Lobectomy-worsened condition-death
34. **Mixed** **(spayed)**	12 F	Cough, pulmonary edema	-Right caud. Lobe -Lung	Primary	Mucinous Bronchiolar-alveolar carcinoma	Lobectomy-enlarged tracheobronchial lnn
35. **Bernese Mountain Dog**	1 F	-	-Right diaphragmatic lobe, Metastasis to cran + middle lobes -lung	Primary	Adenocarcinoma	Lobectomy
36. **Mixed**	14 M	-	-Right, middle lobe	Primary	Bronchiolar-alveolar carcinoma , papillaris	-

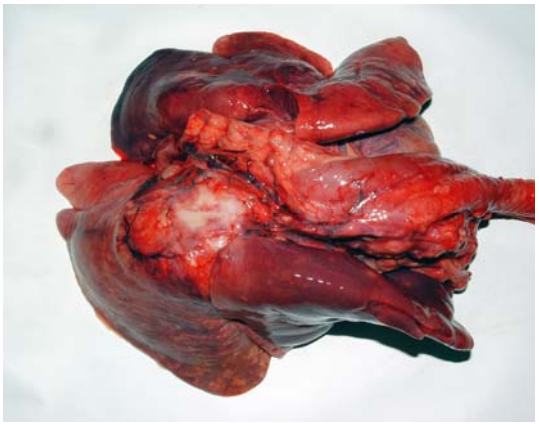
			-Lung			
37. **Mixed**	10 M	Cough Dyspnea	- -Lung	Primary	Bronchiolar-alveolar carcinoma	-
38. **Mixed**	9 M	-	-Left diaphragmatic lobe -Lung	Primary	Bronchioalveolaris adenocarcinoma	Lobectomy
39. **Canary Mastiff**	8 F	-	-Multiplex -Lung	Primary	BAAC	-
40. **w.h.w terrier**	10 M	Physical exam neg. Breathing normal	-Left cran. Lobe Adhesion to mediastinum -Lung	Primary	High grade malignant , non-mucoid bronchiolar-alveolar carcinoma	Lobectomy Adhesiolysis
41. **Cane corso** **(Neutered)**	9 M	Physical exam neg.	-Right caudal lobe -lung	Primary	High grade osteosarcoma	Lobectomy
42. **Mixed** **(spayed)**	13 F	Physical exam neg.	-Left cran. Lobe Metastatized to cran. Mediastinum -Lung	Primary	Desmoplasticus pulmonalis carcinoma	Lobectomy Adhesiolysis
43. **Mixed**	13 M	Cough	- -Lung	Primary	Non-mucoid Bronchiolar-alveolar carcinoma	Euthanasia
44. **French bulldog**	8 M	Lethargy after exercise	- -Lung	Secondary	Angiomyxoma with lung metastasis	-
45. **Mixed** **(spayed)**	9 F	Physical exam – At rest: normal breathing	--Right middle lung lobe -Lung	Primary	Bronchiolo-alveolar carcinoma	Lobectomy

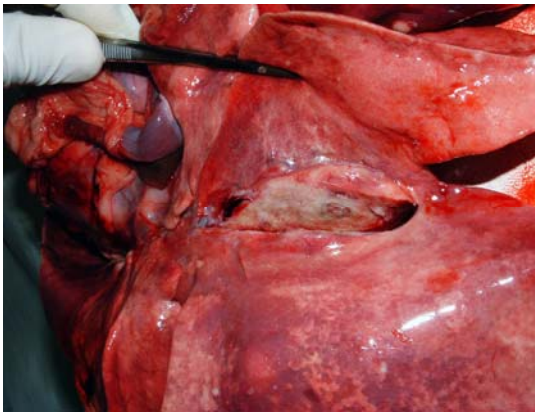
12.2 Collection of Images

11.2.1 Figure. Mucinosus bronchiolar-alveolar carcinoma

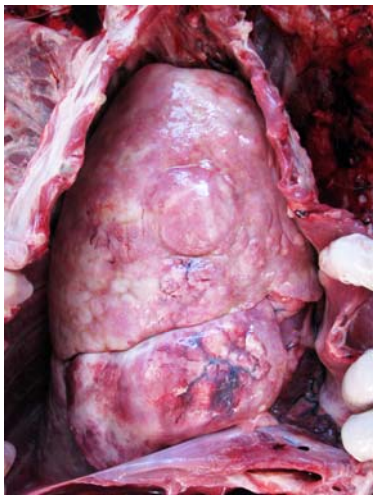
11.2.2 Figure. Anaplastic large cell carcinoma

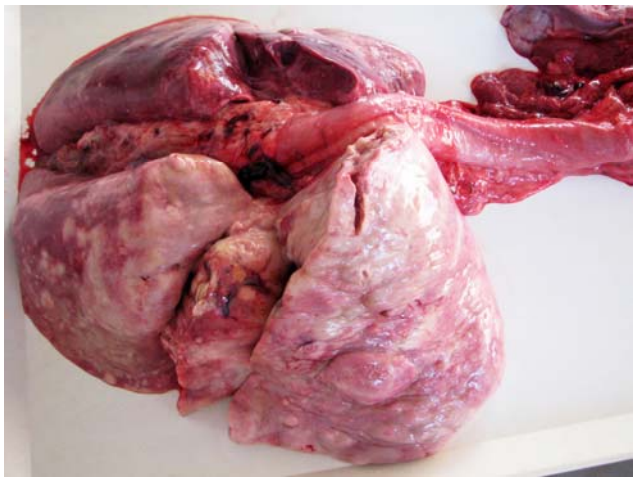




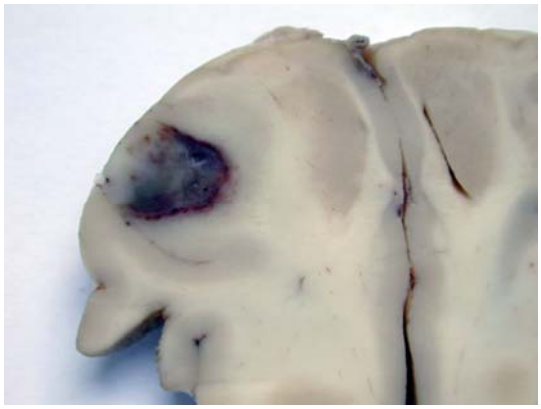


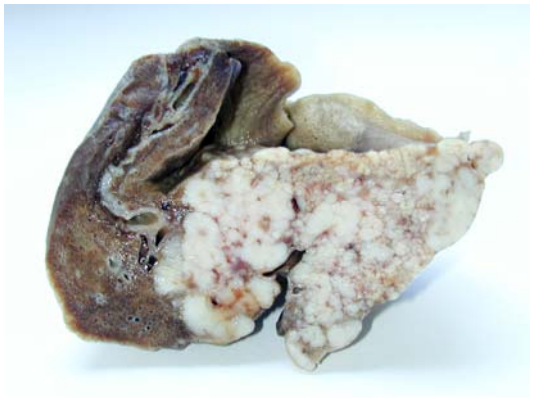
1.2.3 Histiocytic sarcoma

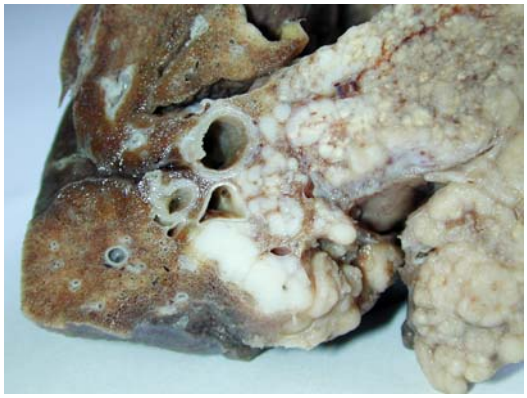




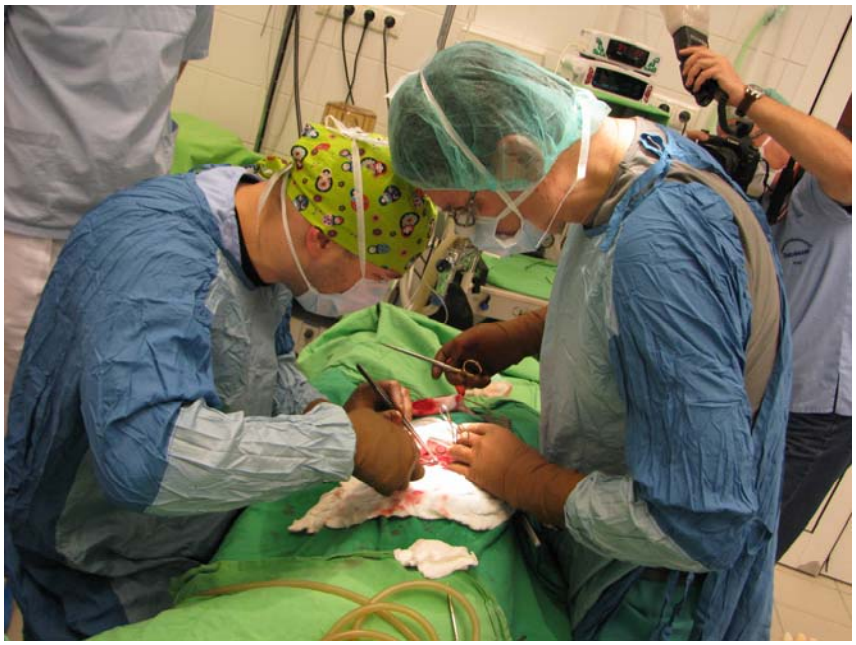
11.2.4 Brain metastasis of primary lung neoplasms

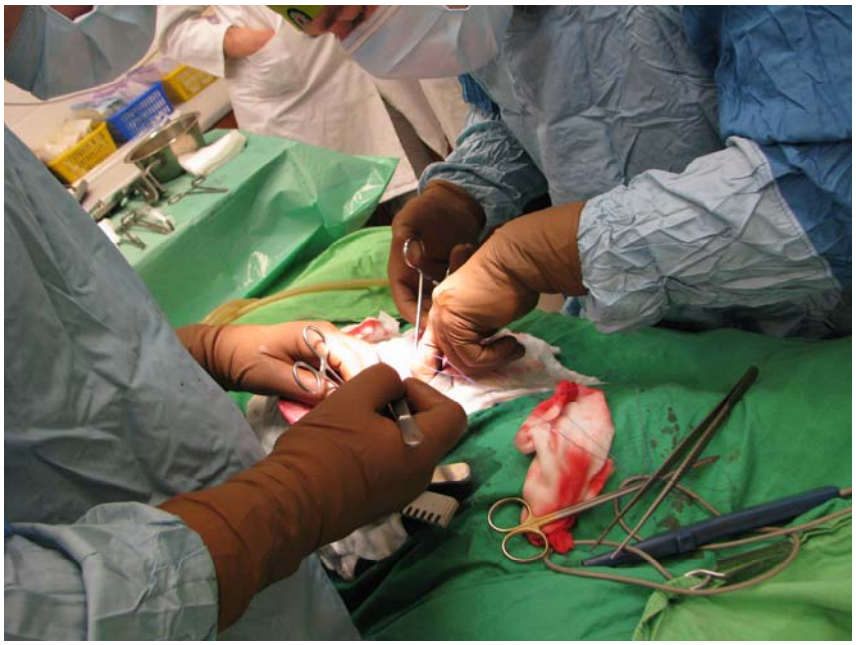






11.2.5 Lobectomy





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I hereby confirm that I am familiar with the content of the thesis entitled ..... **The incidence of pulmonary neoplasms in dogs** .....)

.....

written by ..... **Zsófia Bezdek** ..... (student name)

which I deem suitable for submission and defence.

Date: Budapest, ...day.....month .....year

Dr. Csaba Jakab

.....

Supervisor's name and signature

Department of Pathology

.....

.....

Department

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Publication data of document: 2017

Number of files submitted: One

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